Neurosurgery for Mental Disorders (NMD) in the 21st Century

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Neurosurgery for Mental Disorders (NMD) in the 21st Century

Current NMD encompasses:

- Ablative NMD (ANMD) includes:
  - Bilateral anterior capsulotomy (BACA) and
  - Bilateral anterior cingulotomy (BACI).
- Deep brain stimulation NMD (DBS-NMD) includes;
  - Bilateral Stimulation of anterior capsule
  - Bilateral stimulation of the subgenu cingulum.
- Vagus nerve stimulation (VNS-NMD).

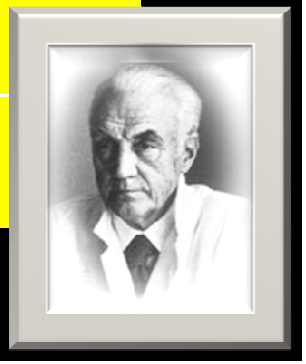
Mental disorders carry heavy burden and come second to cardiovascular disease by selected illness categories:

Illness / Condition	% Disability adjusted life year
All cardiovascular diseases	18.6
Mental disorders **Depression alone**	15.4 6.8
All cancers	15
All respiratory diseases excluding lung cancer	4.8
All alcohol related disorders	4.7
All infections and parasites	2.8
All drug usage related disorders	1.5

*Disability-adjusted life year (DALY) is a measure that expresses years of life lost to premature death and years lived with a disability of specified severity and duration

NMD has a long history and goes as far back as 1948

Procedure	Year	Developed by
Orbital Undercutting	1948	William Scoville
Anterior cingulotomy	1962	Foltz and White
Subcaudate tractotomy	1964	Geoffrey Knight
Anterior capsulotomy	1972	Jean Talairach (1949) Lars Leksell
Limbic Leucotomy	1973	Desmond Kelly



Neurosurgery for Mental Disorders is regulated by law

Mental Health Act -England (1983), Section 57 states that a patient could be treated by NMD if he/she fulfils the following two criteria:

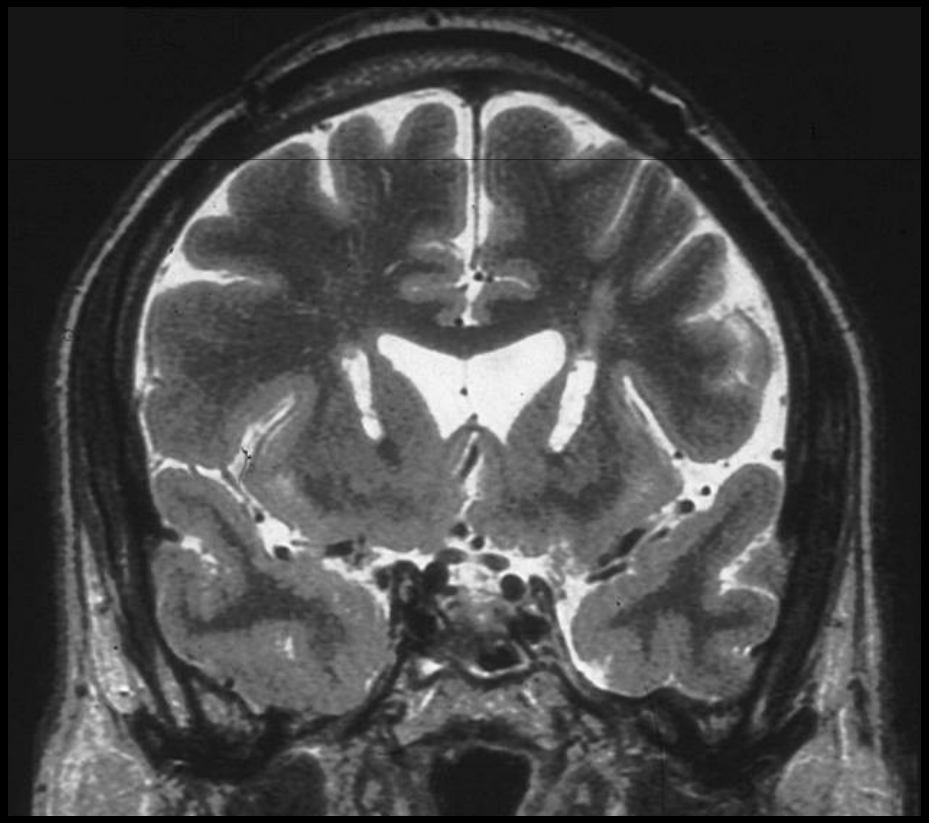
1. All other appropriate treatment exhausted

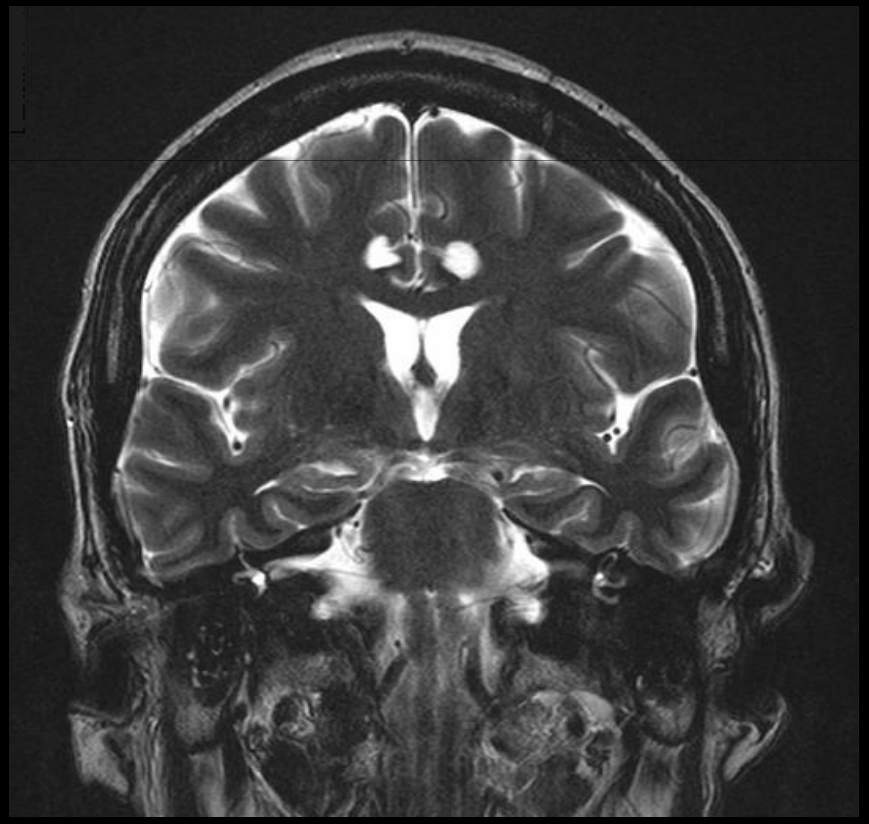
2. Free, informed consent

Why we need NMD?

NMD was born because treatment-refractory patients with mental disorders who failed all other treatments had no other option at the time except to be incarcerated indefinitely in asylum institutions, this lecture aims to demonstrate that NMD in selected patients and performed by appropriate MDT is safe and effective alternative to continuing morbidity and mortality of mental disorders.

Stereotactic ablative NMD (ANMD) in 21st century is totally different from lobotomy: these two MRI scans demonstrate examples of current practice: Rt bilateral ant capsulotomy and Lt bilateral ant cingulotomy





NMD is Safe:

Temporary and transient side effects are not uncommon, serious adverse events are uncommon in my experience.

1. **Seizures can occur after NMD in the same way as in stereotactic surgery for movement disorders (1-3%).**
2. **Urinary problems can occur in up to 5-10% and usually transient.**
3. **Weight gain can occur in patients after treatment, this may reflect return to normal weight as some patients may have lost weight as a result of their illness.**
4. **Haemorrhage can occur in the same way as in stereotactic surgery for other conditions (0-5%).**
5. **Infection in 1-3%.**
6. **Memory problems can be seen after bilateral ant capsulotomy.**

Safety in DBS surgery for NMD is not dissimilar:

L. Gabriëls, P. Cosyns, B. Nuttin, H. Demeulemeester, J. Gybels. *Acta Psychiatrica Scandinavica* 2003; 107: 275-282.

Nuttin B, Gabriëls L., Cosyns P, et al., *Neurosurgery* 52: 2, 2003.

Complications :

Battery runs empty in few months.

Hypomania with too high amplitude.

2 / 8 underwent anterior capsulotomy later

2 DBS leads broke.

2 extension leads broke.

Weight gain.

Fatigue.

Sometimes uncontrolled urinary loss in 2 patients.

Safe: DBS hardware failure is expected to be not dissimilar from DBS in movement disorders though the neurological complications would probably be less as these patients a much younger group.

Series	Starr & Sillay 2008	Lyones et al 2001	Peak et al 2008	Tir wt al 2007	Total / average
Number of patients	637	206	53	100	996
Hemorrage	6.7%	12%	5.7%	5%	5-12%
Neurolog deficit	1.4%		1.9%	3%	1.4-3%
Seizures	1.7%	3%	3.8%		1.7-3.8%
Infection	4.8%	6%	1.9%	7%	1.9-7%
Hardware problems	5.6%	23%		12%	5.6-23%
DVT/PE/ Pneumonia	1.6%			2%	1.6-2%

Beric et al Stereo Funct Neurosurg 2001; 77:73-78

It has been argued that DBS-NMD for mental disorders might be safer than ANMD, there has been no direct comparison and these suggestions were speculations based upon the following RCT in tremor

A Comparison of Continuous Thalamic Stimulation and Thalamotomy for Suppression of Severe Tremor

P. Richard Schuurman et al NEJM 342:461-468.

thalamic stimulation was associated with significantly fewer adverse effects than thalamotomy.

However, one have to point out that patients in this trial are different from those undergoing NMD (NMD patients are much younger and fitter) and the target of NMD is more forgiving than the basal ganglia.

Incidence of Adverse Effects Immediately after Surgery and at the Six-Month Follow-up Visit

TABLE 4. INCIDENCE OF ADVERSE EFFECTS IMMEDIATELY AFTER SURGERY AND AT THE SIX-MONTH FOLLOW-UP VISIT.*

ADVERSE EFFECT	THALAMOTOMY (N=34)		THALAMIC STIMULATION (N=34)	
	AFTER SURGERY	AT 6 MONTHS	AFTER SURGERY	AT 6 MONTHS
	number of patients			
Somnolence	3	—	—	—
Cognitive deterioration	3	3 (2 with Parkinson's disease, 1 with essential tremor)	—	—
Dysarthria†				
Mild	8	3 (2 with Parkinson's disease, 1 with essential tremor)	1	2 (1 with Parkinson's disease, 1 with multiple sclerosis)
Severe	3	3 (with Parkinson's disease)	2	2 (1 with Parkinson's disease, 1 with multiple sclerosis)
Dystonia	—	—	2	—
Impaired eye movement	—	—	1	—
Mild facial paresis	6	—	1	—
Mild arm paresis	3	—	2	—
Hypesthesia	2	1 (with Parkinson's disease)	1	—
Gait or balance disturbance‡				
Mild	11	4 (3 with Parkinson's disease, 1 with essential tremor)	2	1 (with essential tremor)
Severe	6	6 (4 with Parkinson's disease, 2 with multiple sclerosis)	1 (with multiple sclerosis)	1 (with multiple sclerosis)
Arm ataxia	6	1 (with Parkinson's disease)	2	1 (with multiple sclerosis)
Death related to surgery	—	—	1 (with Parkinson's disease)	—
Equipment-related effect				
Hematoma near pulse generator	—	—	1	—
Infection of pulse generator	—	—	1	—
Total no. of patients	28	16 (11 with Parkinson's disease, 3 with essential tremor, 2 with multiple sclerosis)	7	6 (2 with Parkinson's disease, 1 with essential tremor, 3 with multiple sclerosis)

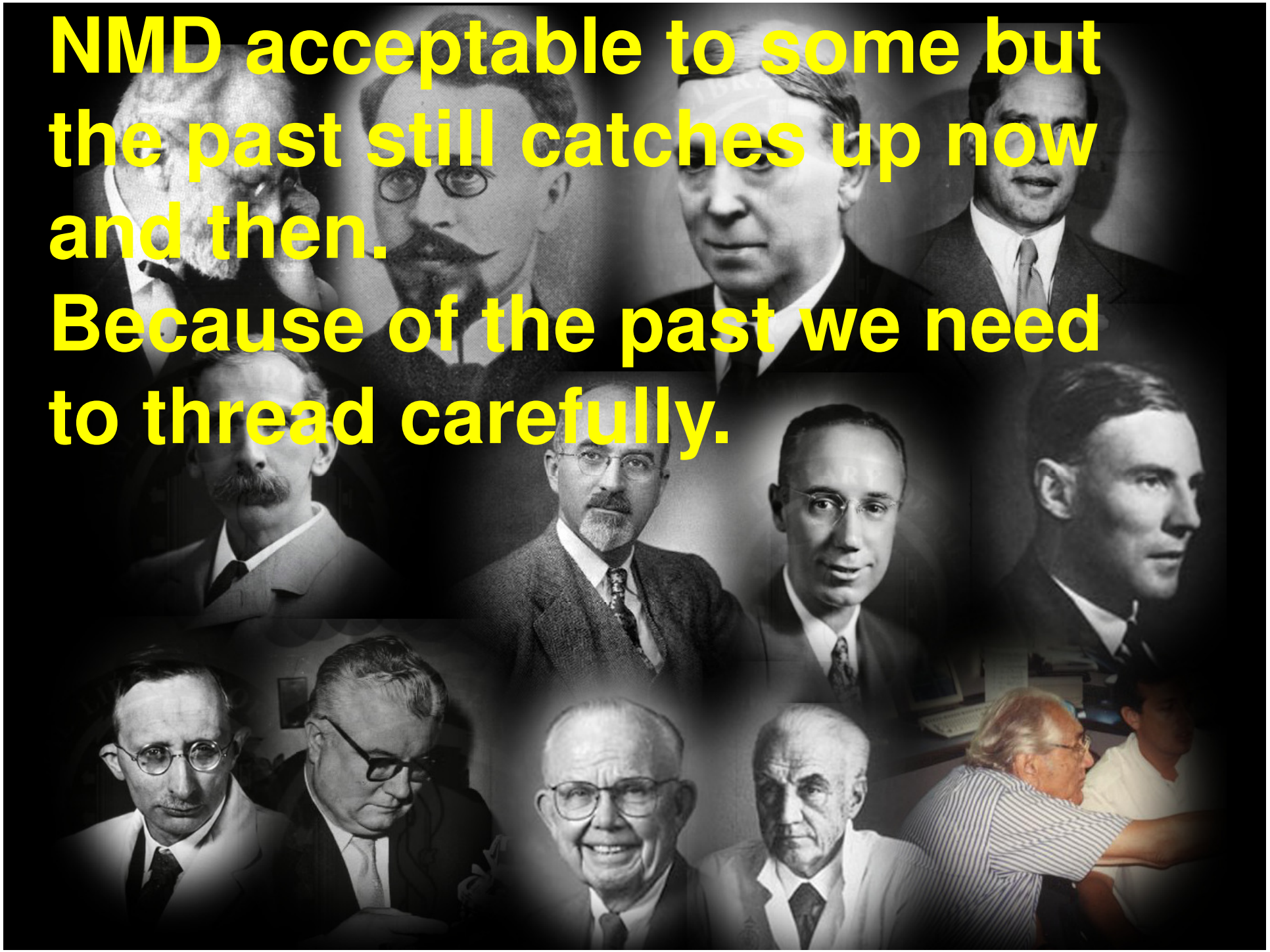
*Some patients had more than one adverse effect.

†Patients with mild dysarthria had no difficulty being understood, and patients with severe dysarthria had a speech disturbance that, at a minimum, led to their sometimes being asked to repeat statements.

‡Patients with a mild disturbance of gait or balance had mild difficulty walking, and in some cases required a cane; patients with a severe disturbance could not walk without a walker or were wheelchair-bound.

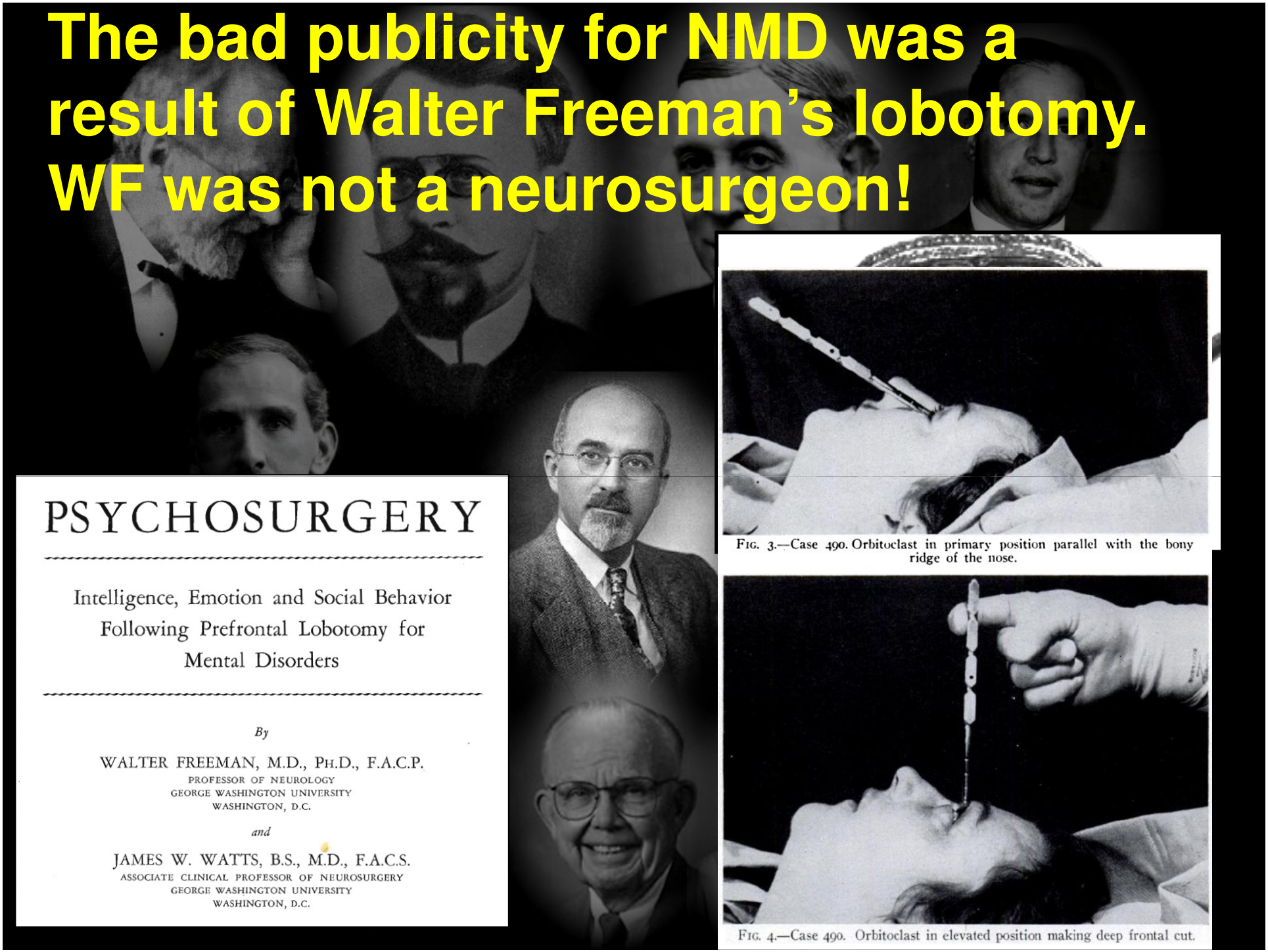
Schuurman P et al. N Engl J Med 2000;342:461-468

The NEW ENGLAND JOURNAL of MEDICINE


NMD acceptable to some but the past still catches up now and then.
Because of the past we need to thread carefully.


STOP
PSYCHIATRY
TO LET
PSYCHIATRY
KILLS

The bad publicity for NMD was a result of Walter Freeman's lobotomy. WF was not a neurosurgeon!



PSYCHOSURGERY

Intelligence, Emotion and Social Behavior Following Prefrontal Lobotomy for Mental Disorders

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FIG. 3.—Case 490. Orbitoclast in primary position parallel with the bony ridge of the nose.

FIG. 4.—Case 490. Orbitoclast in elevated position making deep frontal cut.

Flexibility of NMD:

- DBS-NMD avoids reoperation in these patients but reoperation in DBS-NMD is inevitable for battery replacement.
- Ablative NMD on the other hand if successful is one off procedure and avoids readjustments and programming.

Effectiveness of NMD:

- Ablative neurosurgery for mental disorders (ANMD).
- Vagus nerve stimulation (VNS-NMD)
- Deep brain stimulation (DBS-NMD)

- **Ablative neurosurgery for mental disorders (ANMD).**
  - **Bilateral Ant Capsulotomy (BACA).**
  - **Bilateral Ant Cingulotomy (BACI).**

You have to remember that NMD patients are at the end of their tether and had failed all other treatments, typically they have the following features which we observed in our cohort :

Age	43 (SD 9.8) years	Very young patients
Gender	73 % females	Majority are females.
Marital status	1/3 still married at the time, 1/3 single	1/5 are divorced.
Employment	100% unemployed	All patients either did not work or could not work.
Residence	43.3% were hospitalised	Most patients are hospitalised or very closely supervised.
Age of onset	27.8 years	Range 13.6 to 48.4 years.
Duration recent attack -Total duration - Number of episodes	393.5 weeks 545.6 weeks 1.9 episodes	135.7 – 1296.3 weeks 184.6 – 1311.6 weeks 1-6 episodes
No hospital admission Total duration in	6.5 times 130.6 weeks	1-15 hospitalisations 5.6 – 468.9 weeks

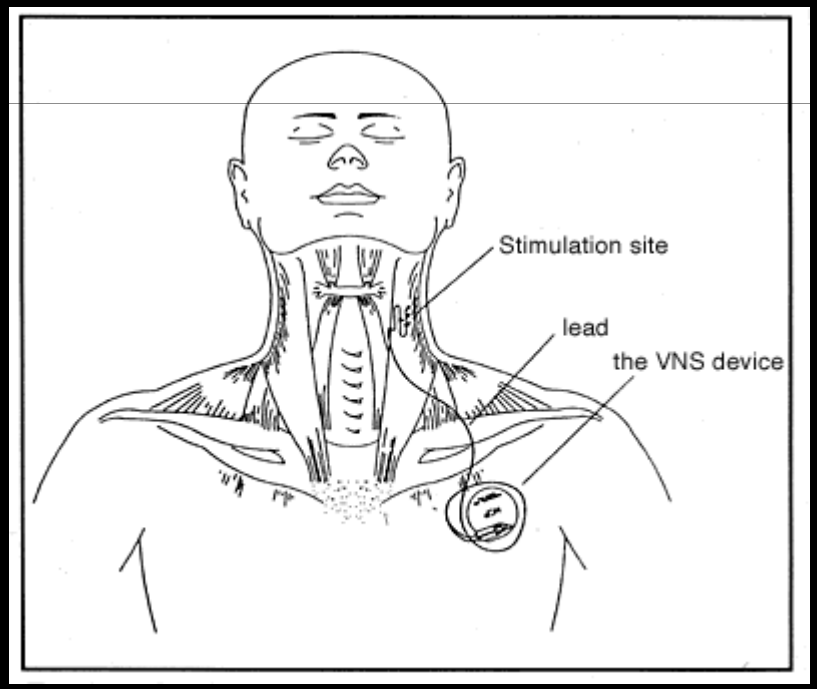
All patients had several adequate treatments but failed these trials, these patients are truly refractory :

All scores are mean ± S.D.	All participants (N=21)	ACAPS (N=16)	ACING (N=5)
Number of adequate treatment trials on the ATHF (includes ECT)	**9.1 ± 3.2**	**8.0 ± 2.7**	**12.4 ± 2.7**
Number of adequate treatment trials from different classes (includes ECT)	4.6 ± 1.1	4.3 ± 1.1	5.6 ± 0.5
Number of adequate trials of SSRIs	2.0 ± 1.0	2.0 ± 1.1	1.8 ± 0.4
Number of adequate trials of TCAs	1.6 ± 0.9	1.4 ± 0.9	2.4 ± 0.5
Number of adequate trials of MAOIs	0.6 ± 0.7	0.6 ± 0.8	0.6 ± 0.5
Number of adequate trials of Other Antidepressants	1.1 ± 1.2	0.6 ± 0.8	2.8 ± 0.4
Number of augmentation trials	1.2 ± 0.9	0.9 ± 0.7	2.2 ± 0.8
Number of adequate courses of ECT	2.6 ± 1.3	2.6 ± 1.3	2.6 ± 1.5
Mean Thase & Rush score (TR-S) (Range)	4.71 (3 – 5)	4.63 (3 – 5)	5.00 (N/A)
Mean Massachusetts General Hospital Staging (MGH-S) score (Range)	13.7 (9.5 – 17.5)	13.0 (9.5 – 17.5)	15.8 (14.5 – 17.0)

Categorical outcomes for Depression (unipolar and bipolar)

	12-months	Long-term follow-up
Response (≥ 50% reduction in baseline score on the $HRSD_{17}$ OR MADRS OR Rating of 1 (Very much improved) or 2 (Much improved) on the CGI-I)		
Bilateral anterior capsulotomy (N=20)	5 (25.0%)	10 (50.0%)
Bilateral anterior cingulotomy (N=5)	3 (60.0%)	2 (40.0%)
Remission (Score ≤ 7 on the $HRSD_{17}$ OR Score ≤ 10 on the MADRS)		
Bilateral anterior capsulotomy (N=20)	**2 (10.0%)**	**8 (40.0%)**
Bilateral anterior cingulotomy (N=5)	**1 (20.0%)**	**2 (40.0%)**

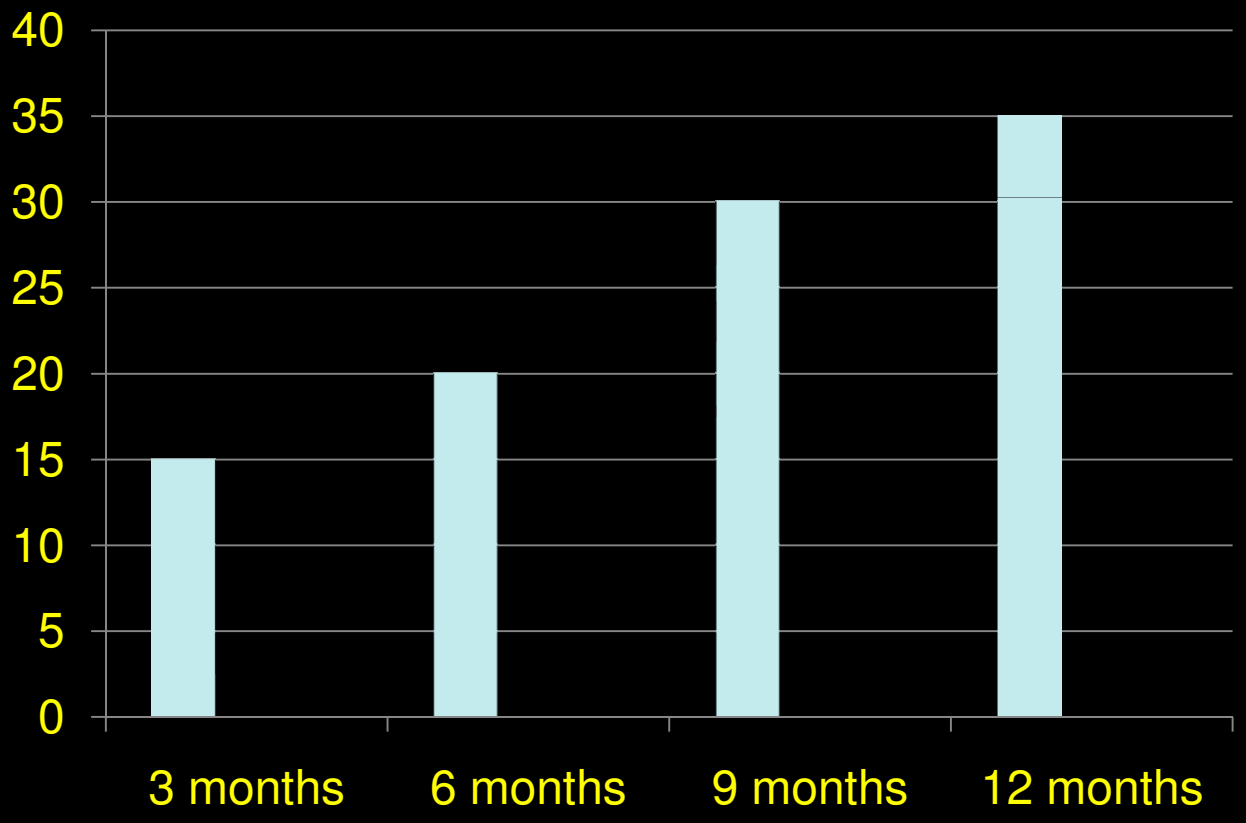
- **Vagus nerve stimulation - NMD (VNS-NMD)**



• VNS-NMD: These are the studies published so far on VNS_NMD

Study	*N*	Design	Study	Duration	Response rates	Remission rates
Rush *et al* (2000)	30	Open Study	D-01	10 weeks	40%	17%
Marangell *et al* (2002)	30	Open Study	D-01	12 months	46%	29%
Sackeim *et al* (2001)	60	Open Study	D-01	10 weeks	30.5%	15.3%
Nahas *et al* (2005)	59	Open Study	D-01	2 years	42%	22%
Rush *et al* (2005)	235	RCT	D-02	10 weeks	15.2% (Active) 10% (Sham)	N/A
George *et al* (2005)	329	VNS + TAU (N=205)	D-02	12 months	27% (VNS)	15% (VNS)
		vs TAU (N=124)			13% (TAU)	3.6% (TAU)
Rush *et al* (2005)	202	Open Study	D-02	12 months	27.2%	15.8%
Corcoran *et al* (2006)	11	Open Study	D-03	12 months	55%	27%
Schlaepfer *et al* (2008)	60	Open Study	D-03	12 months	53%	33%
Bajbouj *et al* (2010)	49	Open Study	D-03	24 months	53%	39%
Total/ Mean	355		at 12 m		42%	25.7%
			at 24 m		47.5%	30%

Within the constraints of interpreting studies with an open-label design, response to VNS appears to be cumulative. On average, studies suggest that



Contra-indications for VNS:

1- Significant cardiac disease.
2- Pacemaker.
3- Chronic obstructive airway disease.
4- Previous vagus injury.

Complications of VNS:

1- Infection 3-6%.

2- Recurrent laryngeal injury.

3- Cardiac arrythemia rare.

4- Diarrhoea uncommon.

Stimulation related side effects of VNS (Reversible by stopping stimulation):

1- Tickly cough.

2- Voice change.

Adverse Event	3 months	6 months	9 months	12 months
Headache	5%	4%	4%	4%
Neck pain	16%	11%	14%	13%
Dysphagia	13%	8%	7%	4%
Nausea	6%	2%	2%	2%
Increased cough	24%	9%	7%	6%
Dyspnoea	14%	16%	15%	16%
Voice alteration	58%	60%	57%	54%
Worsening depression	5.2%	6.7%	4.6%	5.7%
Mania	1%	<1%	0%	0%
Suicide	1%	1%	<1%	<1%

NO RCT: we set up a RCT but we could not recruit patients

- NMD, VNS, DBS 2003 √
- Ethical approval √

Doctor if you are able to help me I want a permanent solution.

Doctor you are not touching my brain, I want a VNS.

Prospective comparison of three cohorts of 5 patients each	Response ($HAMD_{17}$)	Response (CGI-I)	Recovery (HAMD/ MADRS)
ACAPS (N=5)	2 (40%)	2 (40%)	2 (40%)
ACING (N=5)	3 (60%)	3 (60%)	1 (20%)
VNS (N=5)	0 (0%)	1 (20%)	0 (0%)

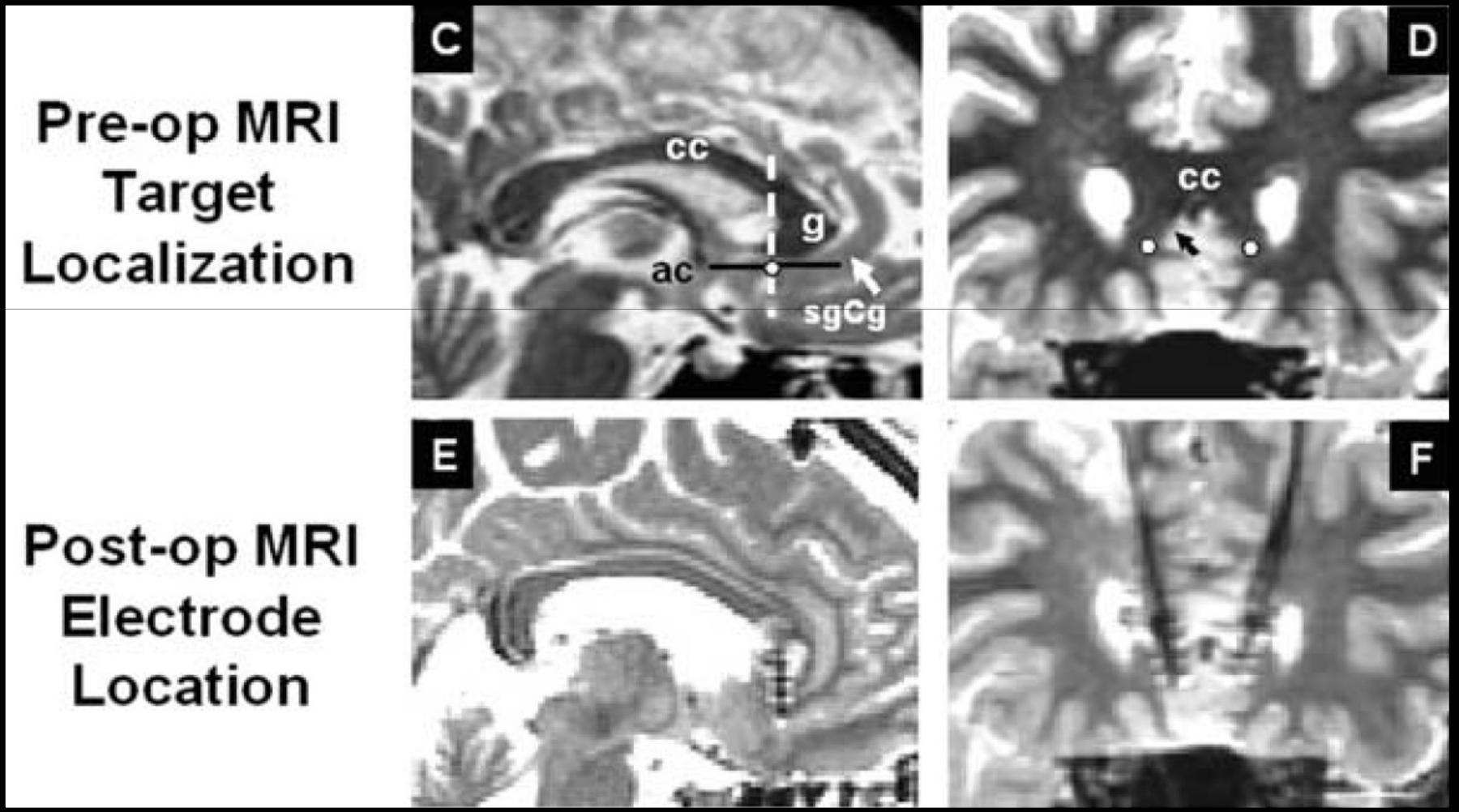
Response ($HAMD_{17}$) = ≥ 50% improvement in baseline Hamilton Depression Rating Scale
Response (CGI-I) = Score of 1 or 2 on the Clinical Global Impression – Improvement Scale
Recovery (HAMD/ MADRS) = Score of ≤ 7 on HAM-D or score of ≤ 10 on MADRS

DBS in NMD:

Nuttin et al 1999 – DBS for OCD.
Meyberg et al 2005 – DBS for TRD.

Possible mechanisms of action:
1- Inhibition.
2- Excitation of some circuits.
3- Modulation.

DBS Target site (Mayberg, 2005)



Results (Mayberg, 2005)

- 4 responders (66%); 2 of which (33%) remitted Adverse effects: infection (2)

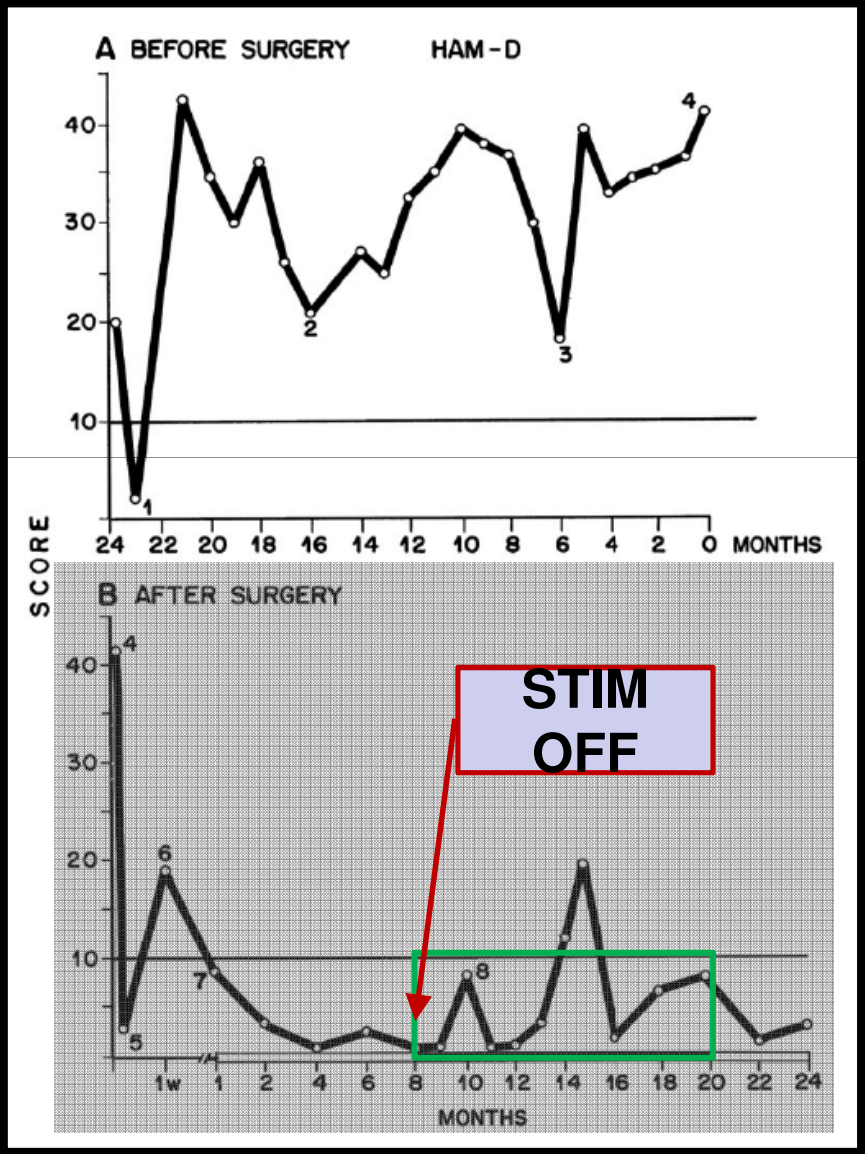
Table 2. Hamilton Depression Rating Scale, HDRS-17, Scores over Time for Each Subject

Time	Hamilton Score[a]					
	Pt 1[b]	Pt 2[c]	Pt 3[b]	Pt 4[c]	Pt 5[b]	Pt 6[b]
Preop baseline	29	22	29	24	26	25
1 week postop (acute stimulation)	5	10	12	18	17	12
2 weeks postop (DBS off)	9	13	23	18	22	n/a
1 month	10	14	17	20	22	12
2 months	13	11	12	18	10	12
3 months	2	15	14	25	7	14
4 months	4	9	12	24	6	12
5 months	5	18	7	23	8	n/a
6 months	5	15	9	23	6	12

[a] Clinical response: decrease HDRS score >50%. Clinical remission: absolute HDRS score <8.
[b] Clinical responders.
[c] Clinical nonresponders.

Mayberg, H. S., Lozano, A. M., Voon, V., et al (2005) Deep Brain Stimulation for Treatment-Resistant Depression. *Neuron*, 45, 651-660.

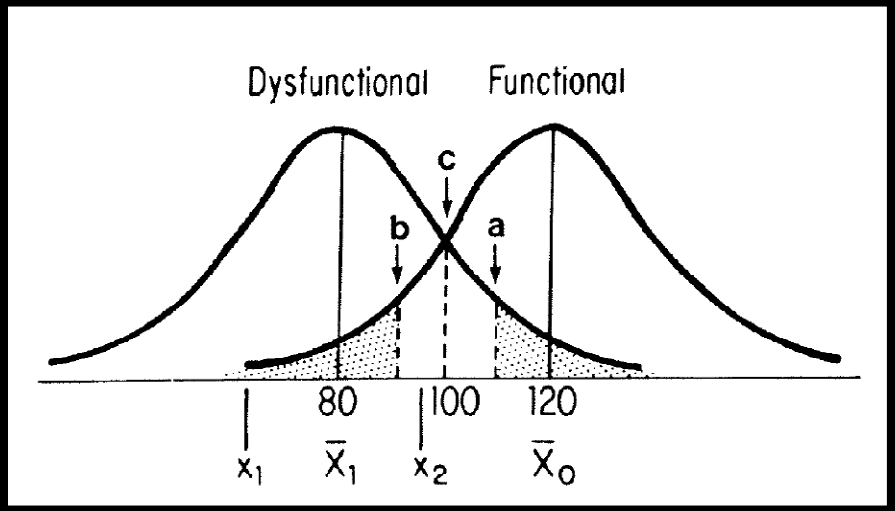
Results (Jiminez, 2005)



Jimenez, F., Velasco, F., Salin-Pascual, R., et al (2005) A patient with a resistant major depression disorder treated with deep brain stimulation in the inferior thalamic peduncle. *Neurosurgery*, 57, 585-592.

It is important to report clinically Significant Change rather than mere improvements of YBOCS or MADRAS scales

- Change may be statistically significant, but it may not be clinically significant
- Attempts to determine how many individuals move from the 'dysfunctional' to 'functional' populations



Jacobson, N. S. & Truax, P. (1991) Clinical significance: A statistical approach to defining meaningful change in psychotherapy research. *Journal of Consulting and Clinical Psychology*, **59**, 12-19.

Lancet, 1999

Electrical stimulation in anterior limbs of internal capsules in patients with obsessive-compulsive disorder

Bart Nuttin, Paul Cosyns, Hilde Demeulemeester, Jan Gybels, Björn Meyerson

Chronic electrical stimulation instead of bilateral capsulotomy was done in four selected patients with long-standing treatment-resistant obsessive-compulsive disorder. In three of them beneficial effects were observed.

2003

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LONG-TERM ELECTRICAL CAPSULAR STIMULATION IN PATIENTS WITH OBSESSIVE-COMPULSIVE DISORDER

OBJECTIVE: Because of the irreversibility of lesioning procedures and their possible side effects, we studied the efficacy of replacing bilateral anterior capsulotomy with chronic electrical capsular stimulation in patients with severe, long-standing,

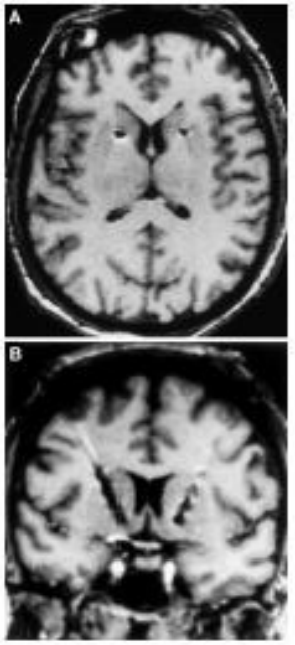


FIGURE 1. *Axial (A) and coronal (B) T1-weighted MRI studies of Patient 3 showing the stimulating electrodes in the anterior limbs of the internal capsules.*

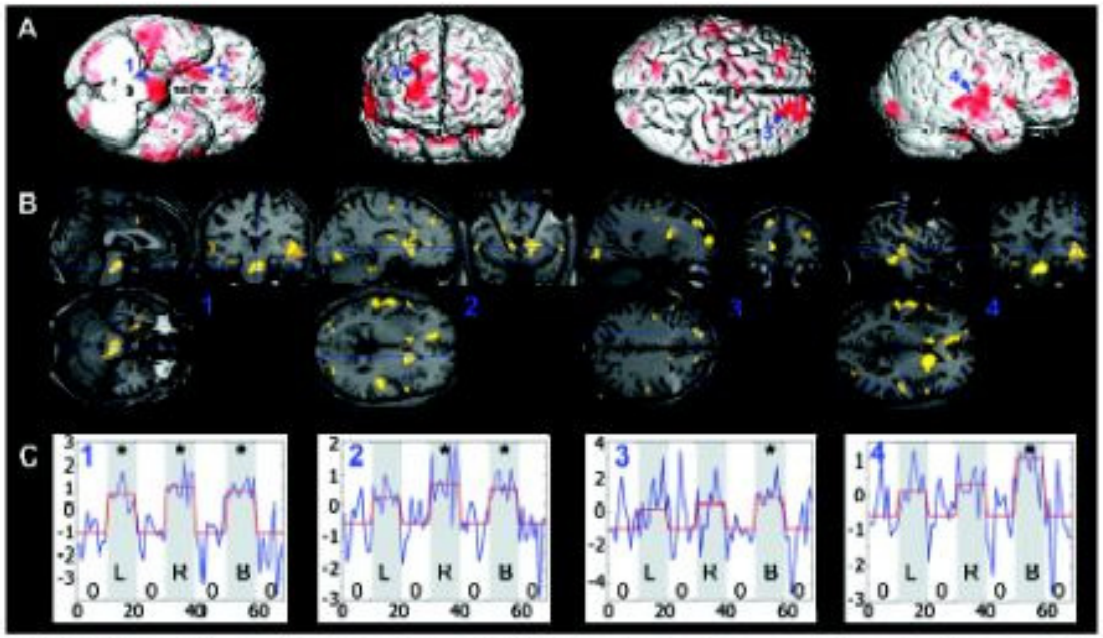
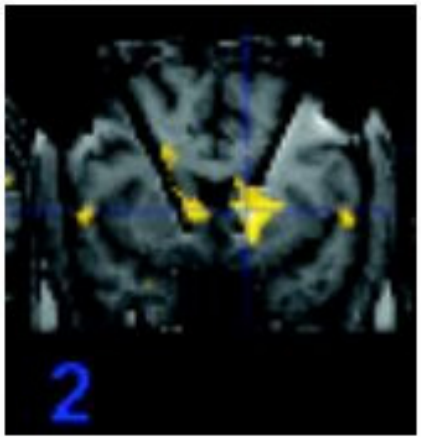
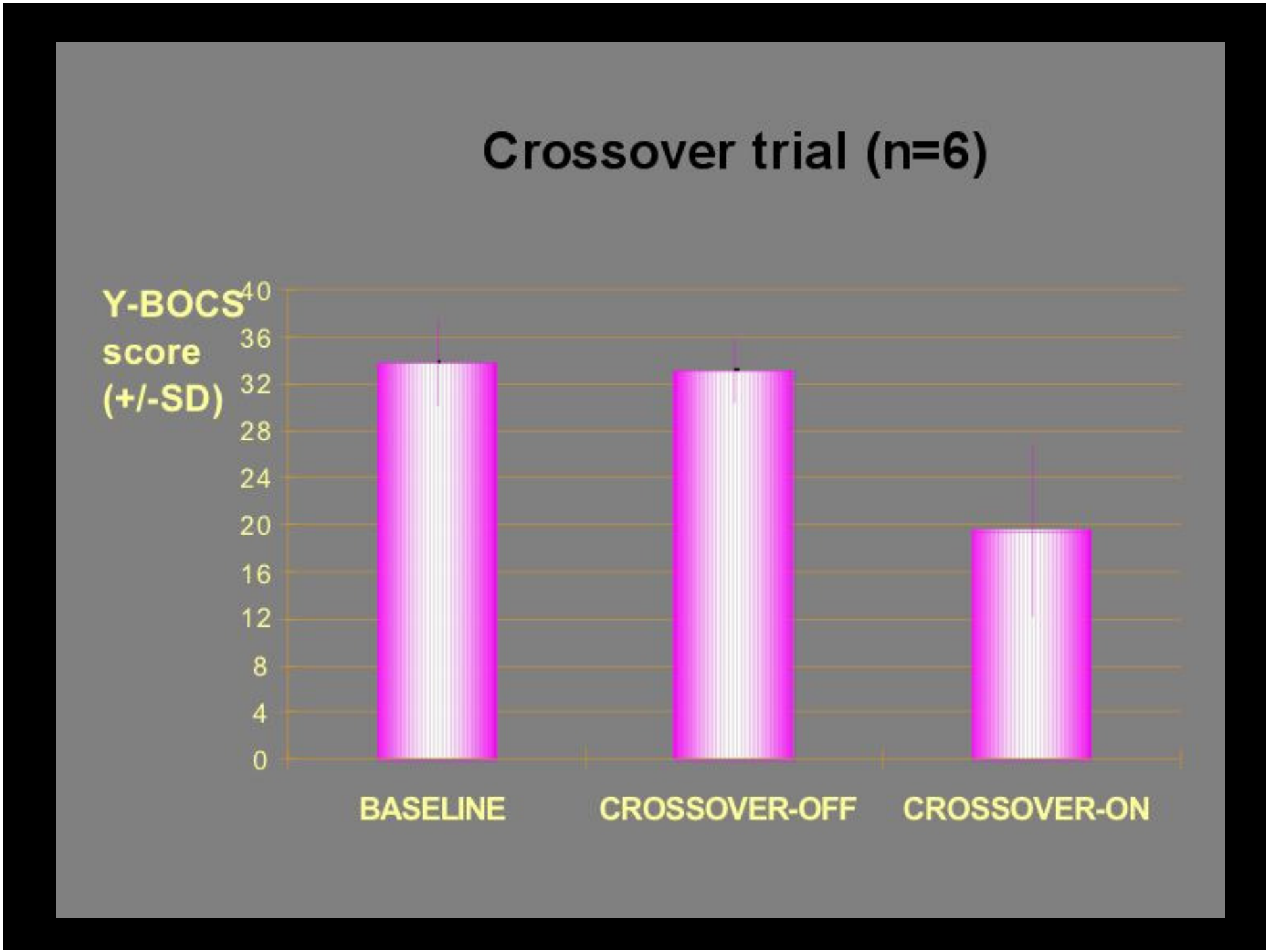


FIGURE 3. *FMRI studies showing cortical and subcortical activation in Patient 4 when brain activity is subtracted during the stimulation-off condition from brain activity shown during the stimulation-on condition, superimposed onto surface reconstructions (A) and sections (B) of the patient's brain. Regions are labeled as follows: the midline focus in the pons (1), the striatum (2), the focus in the right frontal cortex (3), and the left superior temporal gyrus (4). In the brain sections, the left hemisphere is shown on the right or at the bottom. C, percentage fMRI signal change (blue line) and statistically modeled signal change (red line) during left (L), right (R), simultaneous (B) and no stimulation (0) in the four labeled regions. Conditions for which stimulation versus no stimulation was significant ($P < 0.05$ corrected for multiple comparisons) are indicated by asterisks.*




Crossover trial (n=6)
Y-BOCS score (+/-SD)
40
36
32
28
24
20
16
12
8
4
0
BASELINE
CROSSOVER-OFF
CROSSOVER-ON

Okun MS, Bowers D, Springer U, Shapira NA, Malone D, Rezai AR, Nuttin B, Heilman KM, Morecraft RJ, Rasmussen SA, Greenberg BD, Foote KD, Goodman WK:

What's in a "smile?" Intra-operative observations of contralateral smiles induced by deep brain stimulation.

Neurocase. 2004;10:271-9.

METHODS: A single patient with intractable OCD had electrode arrays placed in the right and left anterior limbs of the internal capsule and region of the nucleus accumbens.

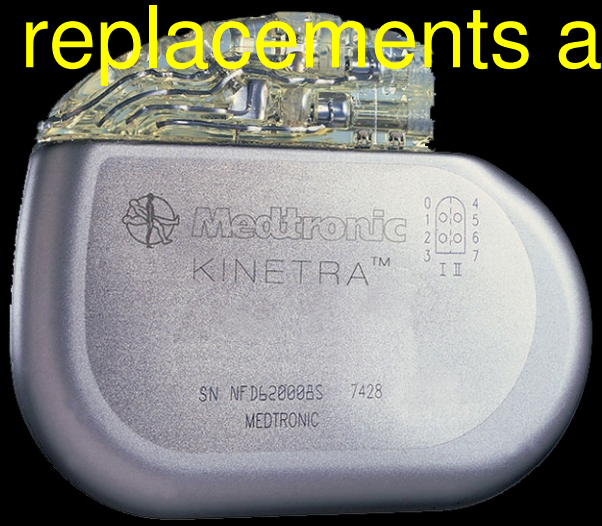
RESULTS: During stimulation on both the right and left side, the patient consistently developed a half smile on the side of the face contralateral to the stimulating electrode, and also became euphoric..

CONCLUSIONS: …This observation suggests that DBS may be useful as a therapy for mood disorders.

Published data on DBS-NMD still in its infancy and the number of patients treated is accumulating:

Study	N	Target	Follow-up (months)	Response
Jiménez *et al* (2005)	1	Inf. Thalamic peduncle	24	N/A
Kosel *et al* (2007)	1	GPi	18	N/A
Mayberg *et al* (2005)	6	CG25	6	4/6 (66%)
Lozano *et al* (2008)	20	CG25	12	55%
Neimat *et al* (2008)	1	CG25	30 months	Yes
Schlaepfer *et al* (2008)	3	NAcc	5-22 weeks	2/3 (66%)
Malone et al (2009)	15	VC/VS	12	53.3%
Bewernick *et al* (2010)	10	NAcc	12	50%
Total	**48**			

Is DBS-NMD affordable when battery replacements are needed every 8-12 months?



DBS-NMD:

Although DBS-NMD is in its infancy and the number of patients treated is accumulating, it is promising therapeutic option which might resolve some issues that bugged NMD for decades, e.g. It might make NMD more acceptable as DBS-NMD is perceived as non-destructive in nature. However, DBS-NMD introduces new issues e.g. What happens when the battery is depleted and symptoms return. The target of DBS-NMD needs refinement to preserve battery life, rechargeable batteries will reduce the number of operations required for battery replacement and reduces the cost significantly. However, the burden of recharging on daily or less frequently basis should not be under-estimated. Hardware failure in the long run is not small and should be considered carefully.

In my opinion it would make sense to try DBS-NMD in suitable patients who comply with all the indications and country –specific regulations before embarking on ANMD. The reason being if the patient was not responsive to DBS-NMD, the system can be removed and no irreversible damage had occurred. Responders to DBS-NMD should be offered a more permanent solution such as ANMD to avoid the need of long term maintenance of DBS systems.

In summary and conclusions:

1- NMD in the form of ablative, VNS or DBS is safe treatment option.

2- Patients had to be selected carefully and assessed by MDT team consisting mainly of experienced psychiatrists.

3- There is no room for sole operators in this area of neurosurgery as the diagnosis, patient selection, rehabilitation and follow up are complex and governed by stringent legal requirements.

4- NMD seems to be effective in 40-60% of patients who otherwise deemed untreatable and unresponsive.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