Brain Stimulation Therapies for Treatment Resistant Depression

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IN DEO SPERAMUS

Disclosures

Consultant:	**Cephalon; GlaxoSmithKline; Johnson & Johnson; Sepracor; Wyeth, Bristol Myers Squibb, Medtronic Pfizer Inc**
Full-time Employee:	**None**
Grant/Research Support:	**Cephalon; Corcept Therapeutics; Cyberonics; Medtronic; Merck Co. & Inc; National Institutes of Health (NIH); Pfizer Inc; UCB Pharma; US Dept of the Interior**
Speakers' Bureau/ Lecture Honoraria:	**AstraZeneca; Cyberonics; Merck & Co., Inc.; Pfizer Inc; Wyeth Pharmaceuticals Inc.**
Major Stockholder:	**None**
Other Financial/ Material Interest:	**None**

Overview

- Neurotherapeutics - Definitions
- Electroconvulsive Therapy (ECT)
- Repetitive Transcranial Magnetic Stimulation (rTMS)
- Magnetic Seizure Therapy (MST)
- Vagus Nerve Stimulation (VNS)
- Deep Brain Stimulation (DBS)

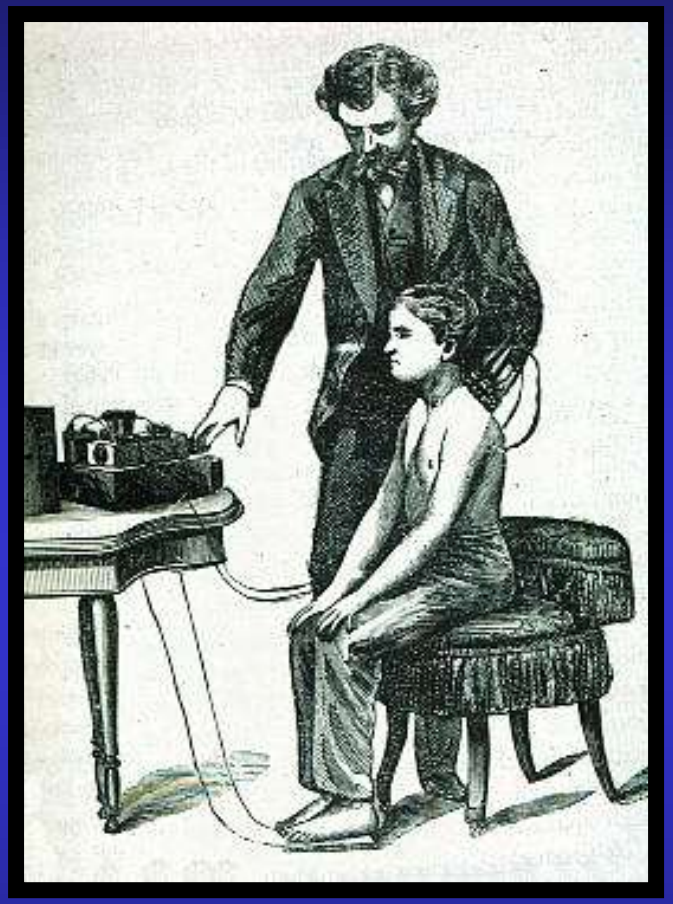
Definitions

Neurotherapeutics

- Treatments for nervous system diseases and disorders
- Pharmacological and other modalities

Neuromodulation

- Therapeutic alteration of nerve activity
- Central, peripheral or autonomic nervous systems
- Electrically or pharmacologically
- Implanted devices
- Pain, movement disorders, spasticity, epilepsy, sensory deprivation, urinary incontinence, gastric dysfunction, pancreatitis/visceral disorders

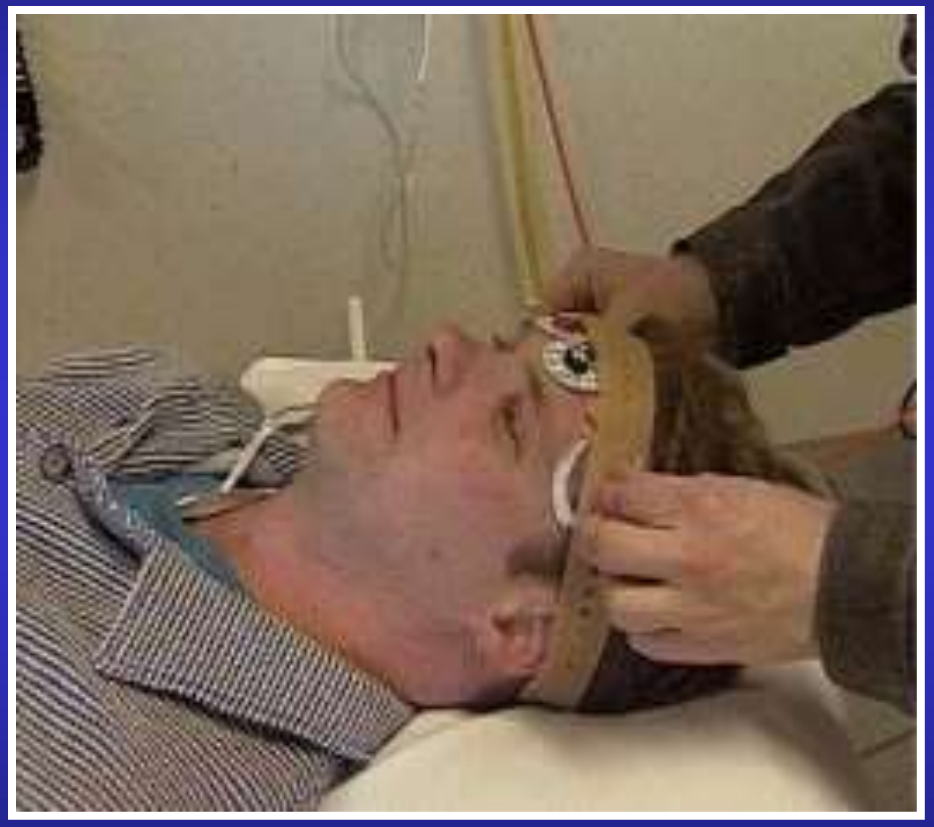


Neurostimulation

- Typically refers to implantable devices with power source, lead wires, electrodes and programming components

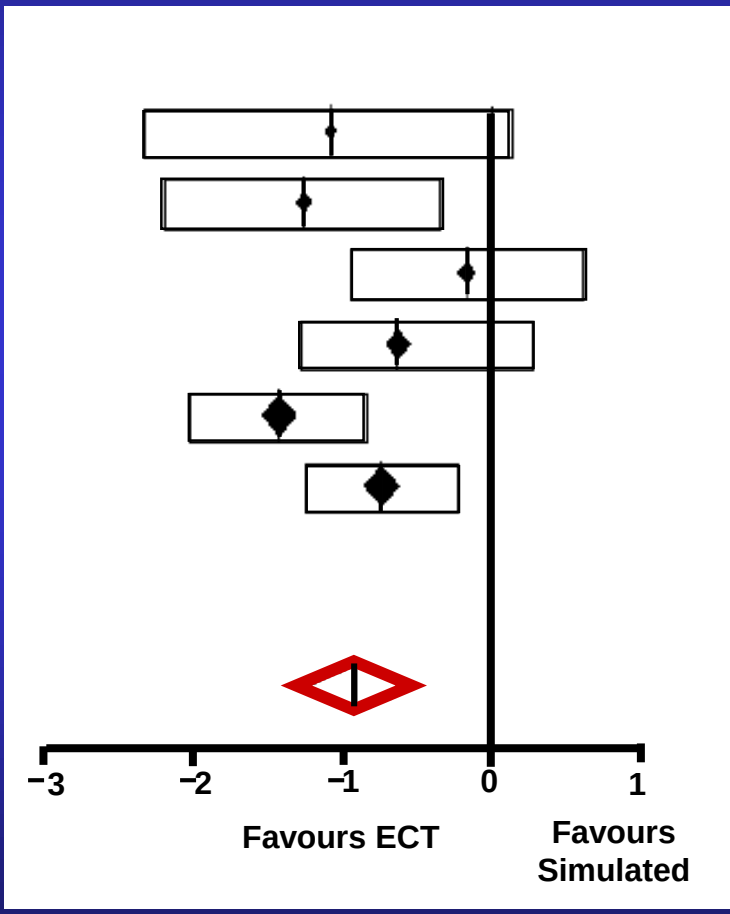
Electroconvulsive Therapy (ECT)

- Developed in 1930s
- FDA- Approved Device in 1979 (grand-fathered)
- Brief electrical pulse passed through scalp
- Patient under anesthesia
- Produce seizure on EEG
- Muscle paralysis prevents convulsive movement
- Bilateral or unilateral
- 6 - 12 treatments
- 2 - 3 treatments per week



Electroconvulsive Therapy: Effect of ECT versus SHAM

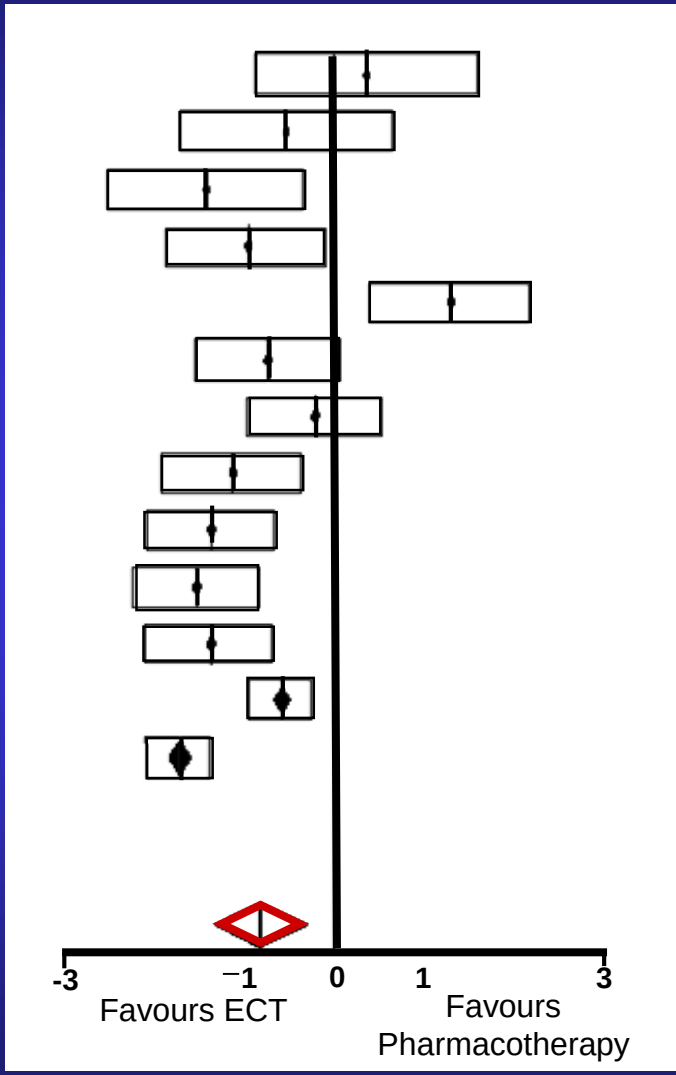
Trial	# of Participants	Standard Effect Size (95%CI)
Wilson 1963	12	-1.078 (-2.289 to 0.133)
West 1981	25	-1.255 (-2.170 to -0.341)
Lambourn 1978	40	-0.170 (-0.940 to 0.600)
Freeman 1978	40	-0.629 (-1.264 to 0.006)
Gregory 1985	69	-1.418 (-2.012 to -0.824)
Johnstone 1980	70	-0.739 (-1.253 to -0.224)
Pooled Fixed Effects		-0.911 (-1.180 to -0.645)
Pooled Random Effects		-0.908 (-1.270 to -0.537)



UK ECT Review Group, *Lancet* 2003; 361: 799-808

Effect of ECT versus Pharmacotherapy

Trial*	# of Participants	Standard Effect Size (95%CI)
Steiner 1978	12	0.369 (-0.840 to 1.578)
Wilson 1963	12	-0.513 (-1.663 to 0.637)
Davidson 1978	19	-1.389 (-2.449 to -0.328)
McDonald 1966	22	-0.930 (-1.813 to -0.047)
Gangadhar 1982	32	1.287 (0.406 to 2.169)
MacSweeney 1975	27	-0.714 (-1.492 to 0.065)
Dinan 1989	30	-0.196 (-0.926 to 0.534)
Janakiramaiah 2000	30	-1.095 (-1.863 to -0.328)
Folkerts 1997	40	-1.336 (-2.032 to -0.640)
Herrington 1974	43	-1.497 (-2.174 to -0.821)
Stanley 1962	47	-1.342 (-2.047 to -0.638)
Medical Research Council 1965	204	-0.559 (-0.883 to -0.234)
Greenblatt 1964	242	-1.683 (-2.020 to -1.346)
Pooled Fixed Effects		-1.010 (-1.170 to -0.856)
Pooled Random Effects		-0.802 (-1.290 to -0.289)



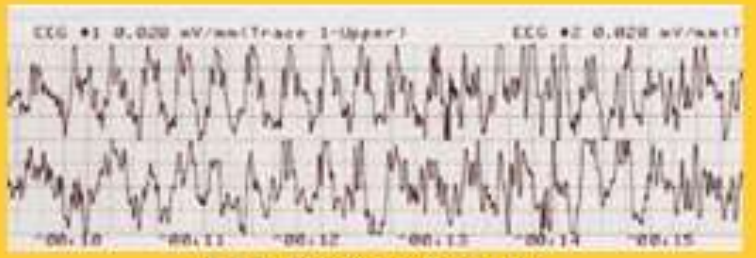
*Other trials are not included: Kendrick 1965, Bruce 1960, Bagadia 1981, Hutchinson 1963, Robin 1962

UK ECT Review Group, *Lancet* 2003; 361: 799-808

Electroconvulsive Therapy (ECT)

Limitations:

- **Headache, muscle aches**
- **Cognitive Side Effects: Memory**
- **Access: Hospital, Often Inpatient**
- **Stigma**
- **Anesthesia Risks**
- **Cost**
- **Maintenance: ECT v. meds**

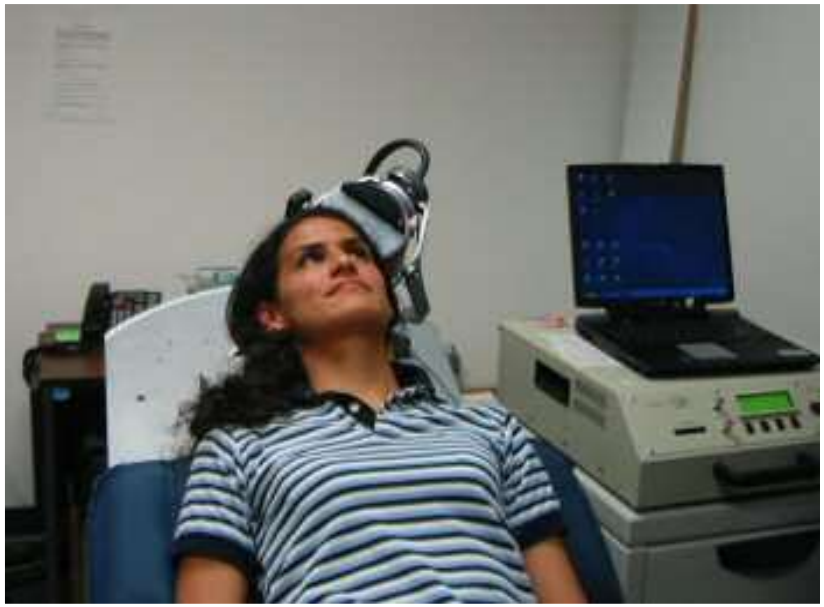


EEG Seizure Activity

EEG Seizure Termination

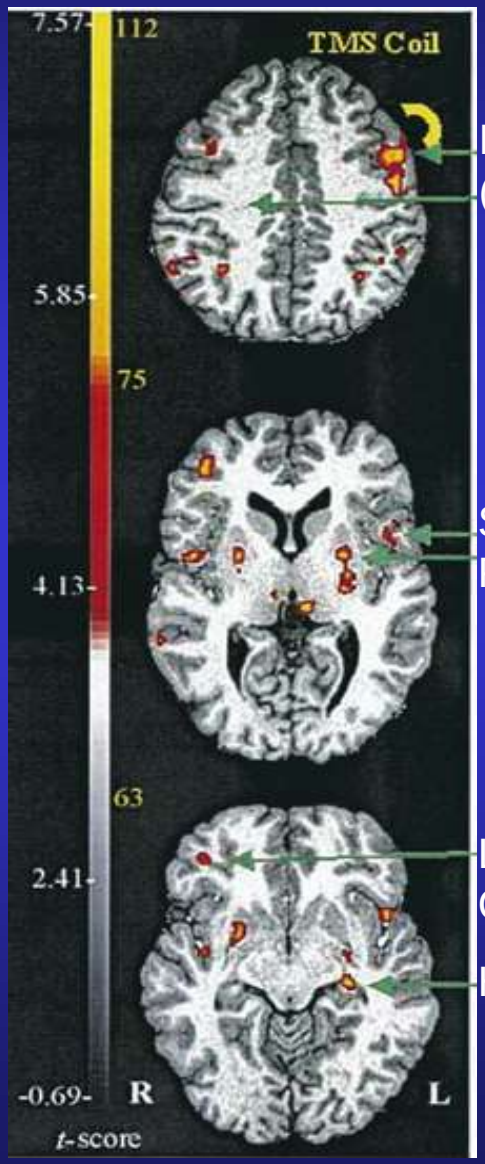
Repetitive Transcranial Magnetic Stimulation (rTMS)

- Non-invasive technique
- USA: Investigational
- Approved: Canada and Israel
- Strong, pulsed (e.g., 2/28 sec) magnetic fields pass through skull unimpeded
- Coil placed on head in awake patient
- Induces electrical current in cortex which depolarizes neurons
- Greater control over site and intensity of stimulation (e.g, left DLPFC)



This information concerns a use that has not been approved by the U.S. Food and Drug Administration

Left PFC rTMS Immediately Activates Frontal-Subcortical Neuronal Circuits

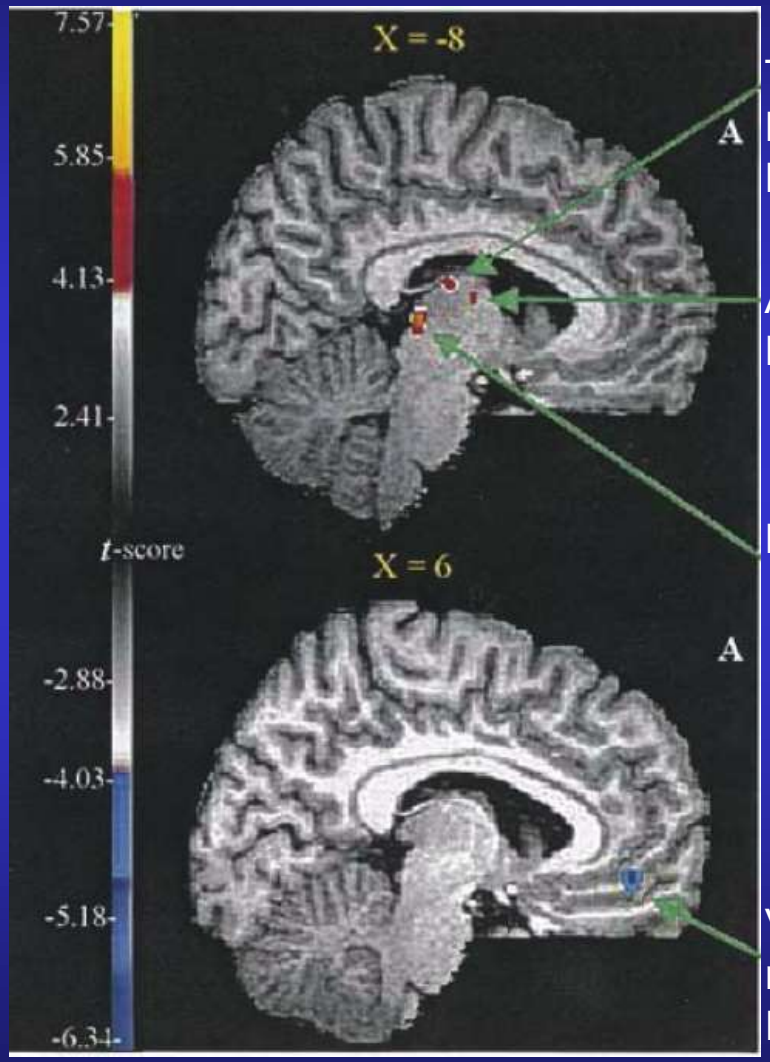


Middle Frontal Cortex (Noise)

Sup Temporal Gyrus
Putamen

Lat Orbitofrontal Cortex

Hippocampus



Thalamus MD Nucleus

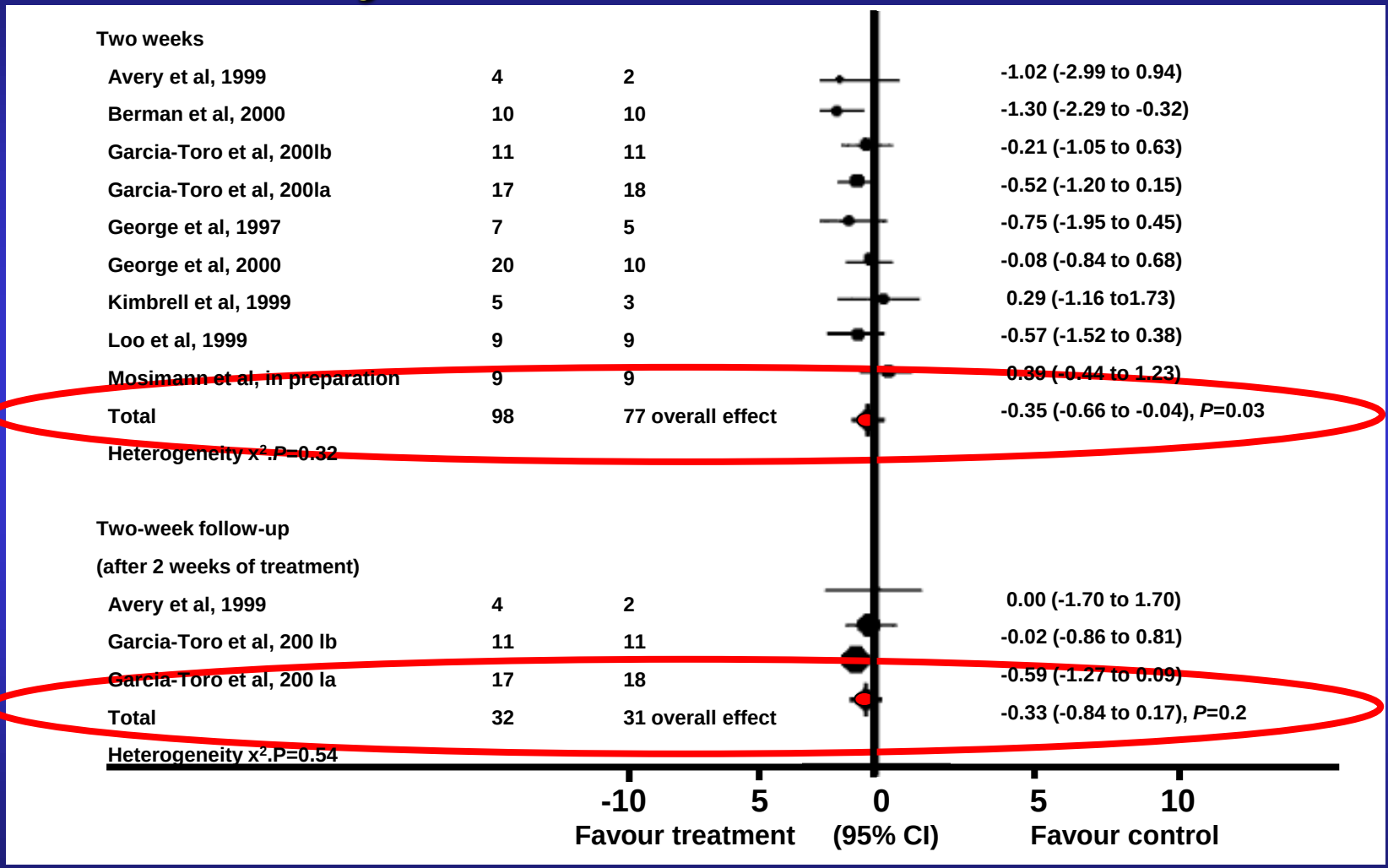
Anterior Nucleus

Pulvinar

Ventro-medial PFC

Li X et al. *Biol Psychiatry*. 2004.

TMS Efficacy Yet to Be Established: Meta-analysis of 14 Controlled Trials



Martin JLR et al. *Br J Psychiatry.* (2003), 182, 480-491.

This information concerns a use that has not been approved by the U.S. Food and Drug Administration

rTMS

Limitations:

- **Need more controlled trials for efficacy/maintenance data**
- **Higher intensity stimulation leads to higher risk of motor convulsion**
- **Best stimulation parameters not known**
- **Noisy; high-freq clicking**
- **Neuronal depolarization only extends 2 cm blow scalp - effects limited to cortex**

This information concerns a use that has not been approved by the U.S. Food and Drug Administration

Magnetic Seizure Therapy (MST)

- **Investigational**
- **Magnet-induced stimulus (like rTMS)**
- **High Intensity**
- **Target “antidepressant regions”**
- **Fewer side effects**
- **3 sessions/week**
- **Same as ECT**
  - **Anesthesia**
  - **Tonic clonic seizure**
  - **Monitor EEG, vitals**

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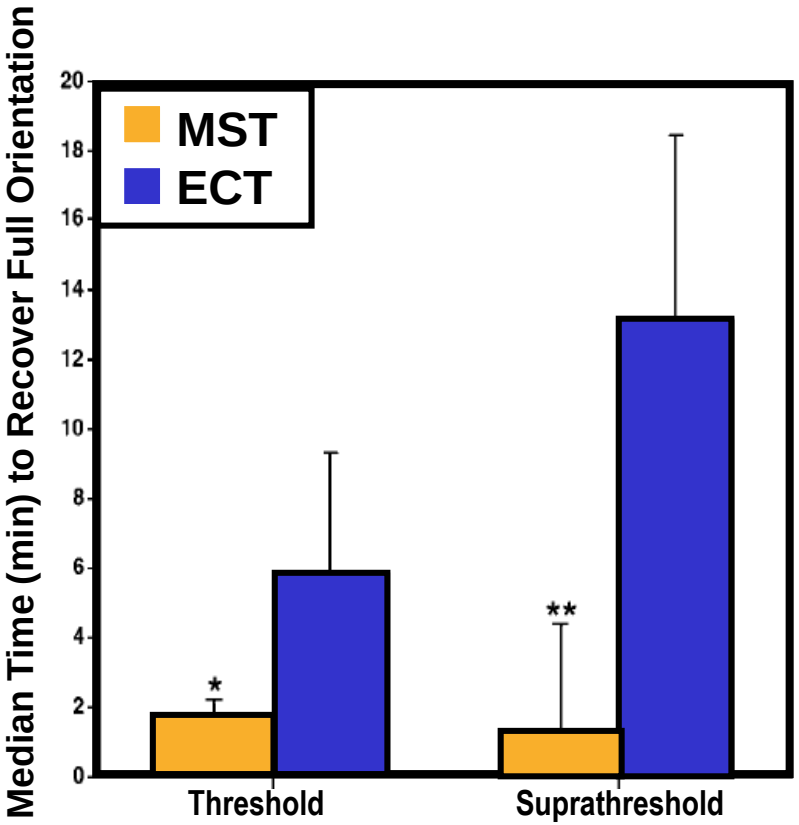
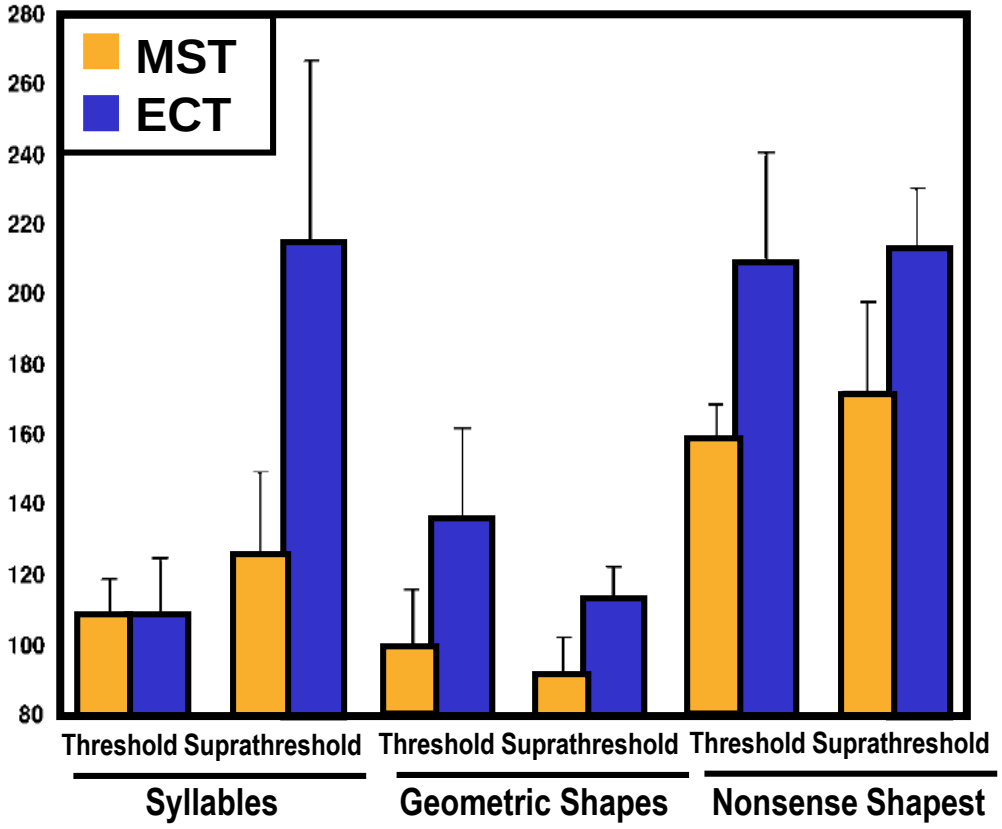
MST: Shorter Period of Post-Ictal Disorientation and Inattention



*Threshold MST v.ECT, p<.004



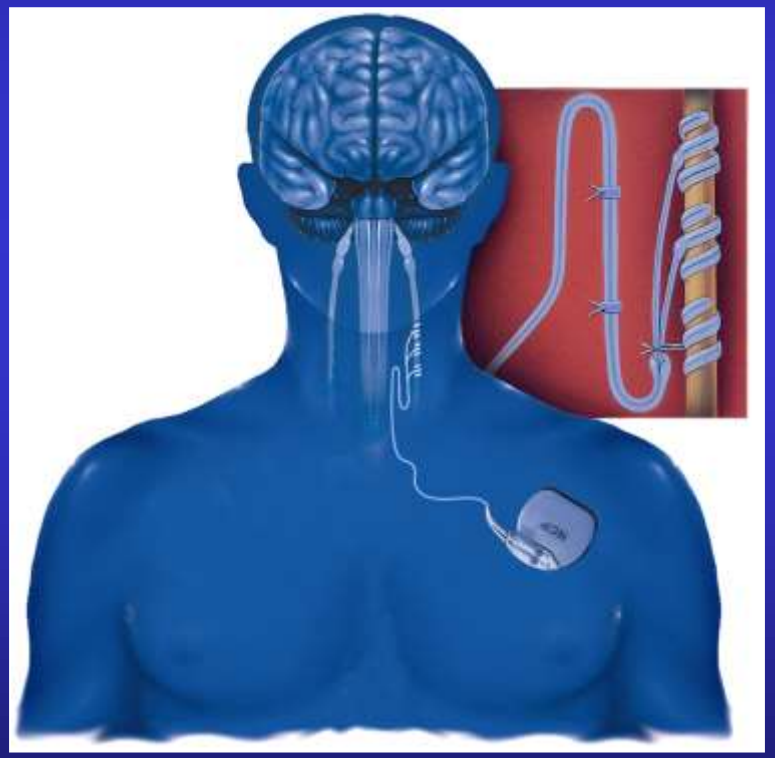
Faster following MST, p<.01

Lisanby SH et al. *Neuropsychopharmacology.* 2003.

This information concerns a use that has not been approved by the U.S. Food and Drug Administration

Vagus Nerve Stimulation (VNS)

- FDA approved for epilepsy; FDA approved for TRD July, 2005
- Implanted in over 30,000 patients worldwide (over 79,000 patient years)
- Pulse generator implanted in left chest wall area, connected to leads attached to left vagus nerve
- Mild electrical pulses applied to CN X for transmission to the brain



Vagus Nerve Stimulation (VNS)

Intermittent stimulation

- **30 sec on/5 min off**
- **24/7 continuous cycles**

Magnetic empowerment

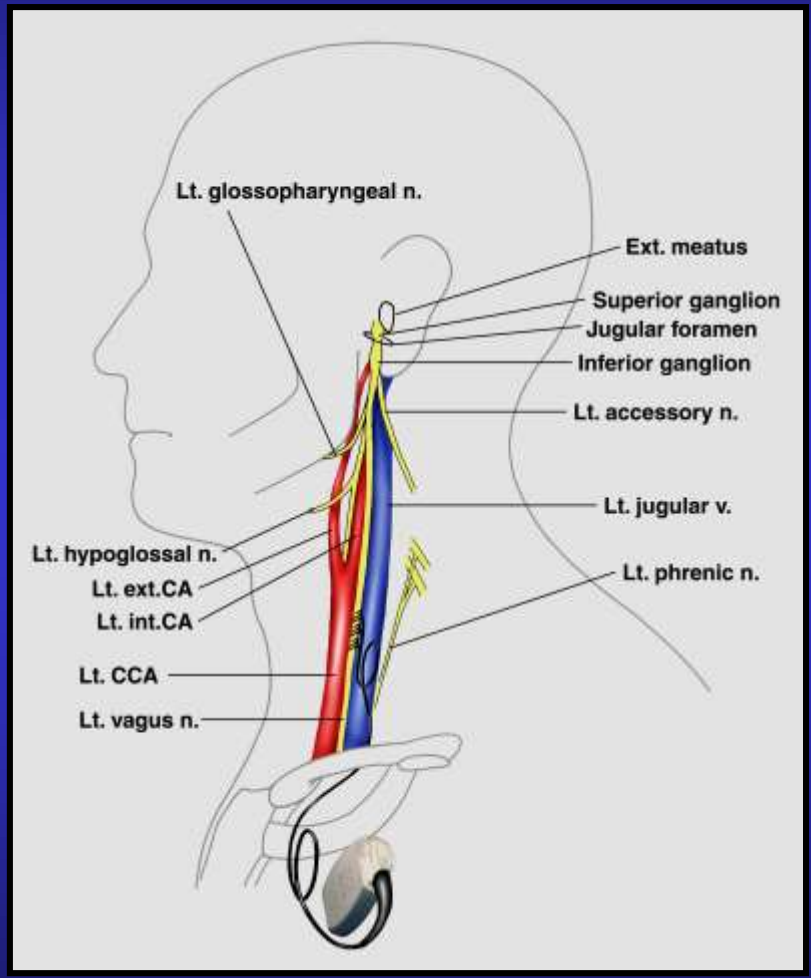
Simple in-office programming (dosing) by treating physician

Assured compliance

No known interactions with medications

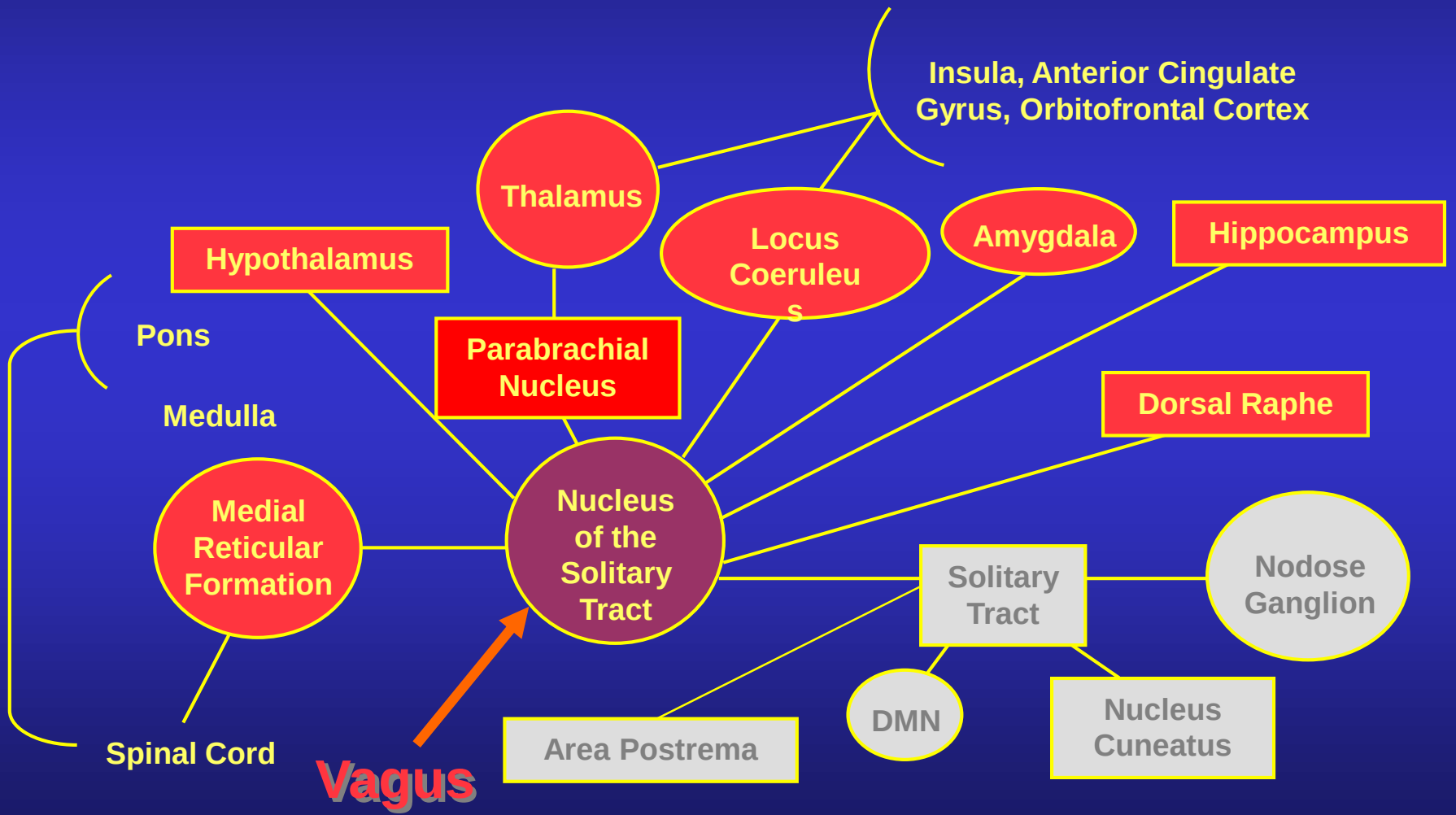
Cervical Vagus Nerve Anatomy

- ~80% afferent fibers, mostly unmyelinated
- ~20% efferent fibers, mostly unmyelinated parasympathetic fibers to thoracoabdominal viscera
- Some myelinated fibers to striated muscles of the pharynx and larynx



Henry TR. *Neurology.* 2002;59(suppl 4):S3-S14.

VNS: Afferent Pathway to the Brain



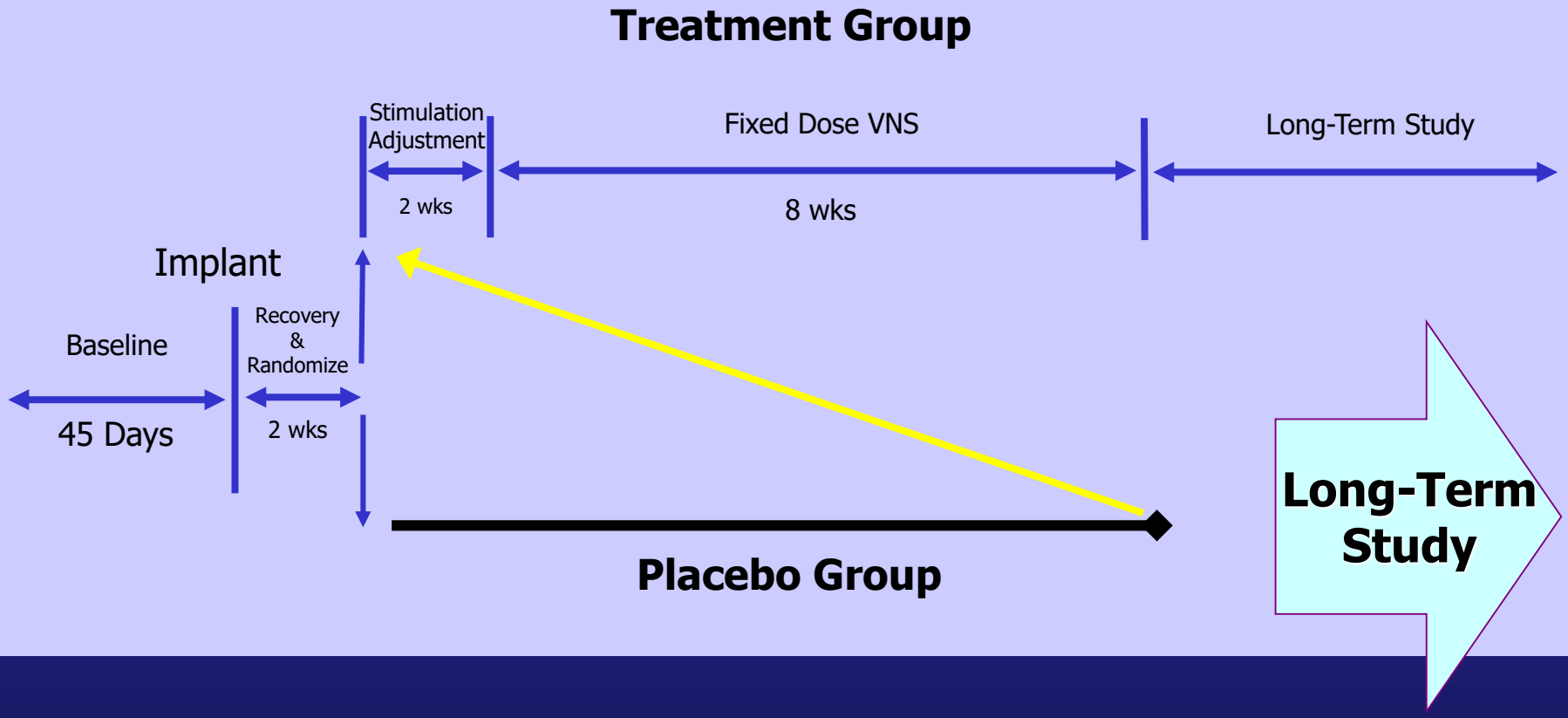
Animal Research: VNS Neurochemical and Monoamine Data

- Vagus nerve stimulation is associated with
  - LC involvement[1]
    - VNS demonstrated an anticonvulsant effect in rats given electroshock
    - Chronic and acute chemical lesioning of the LC was then performed
    - After LC lesioning, VNS was no longer effective
  - NTS involvement[2]
    - Examined influence of GABAergic and glutamatergic transmission in the NTS on chemically induced seizures in rats
    - Increased GABA and decreased glutamate in the NTS reduced susceptibility to chemically induced seizures[2]

1. Krahl SE, et al. *Epilepsia.* 1998;39:709-714. 2. Walker BR, et al. *Epilepsia.* 1999;40:1051-1057.

D-02 Study Design

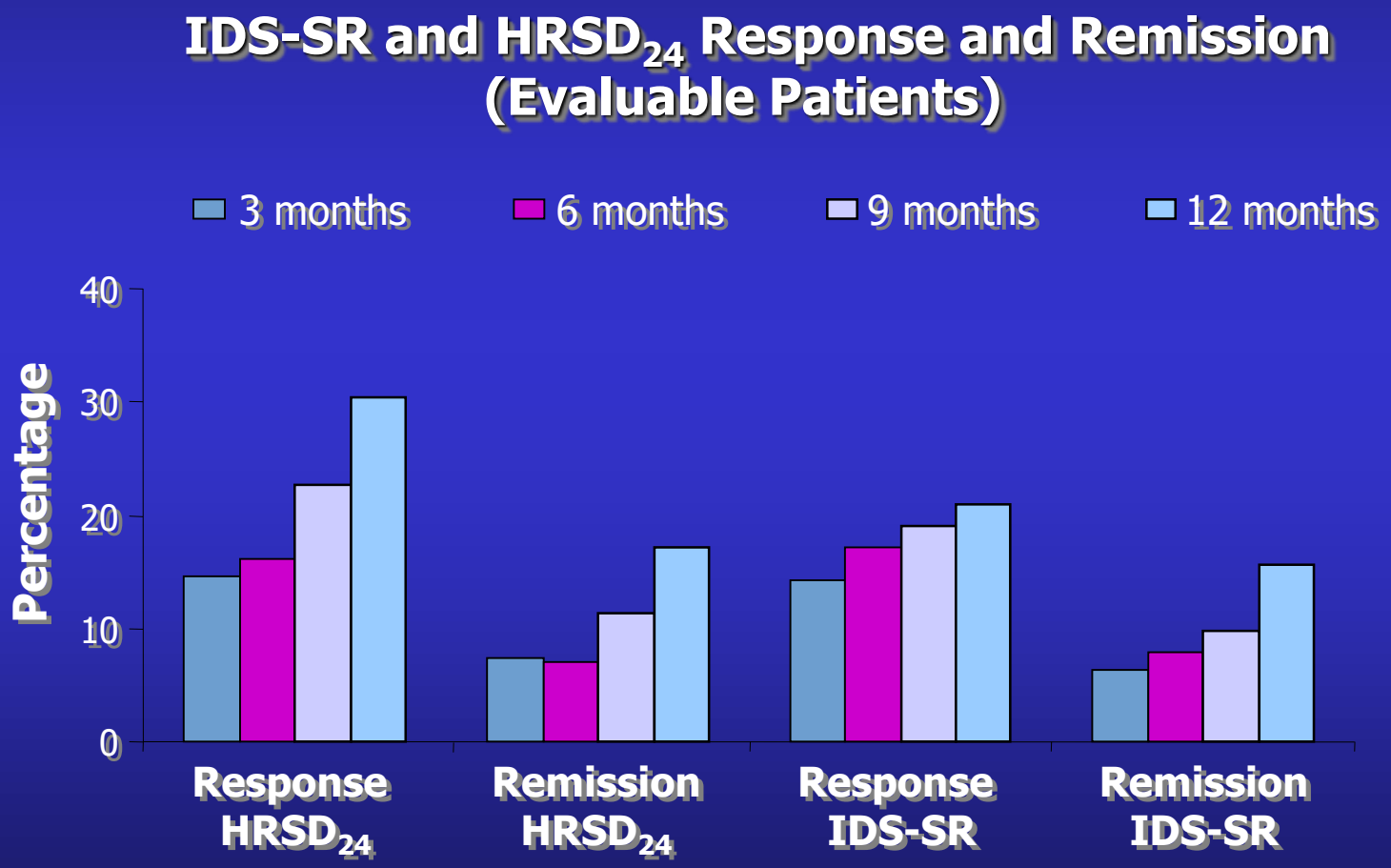
10 weeks of VNS (8 weeks fixed dose stimulation)



Summary of Major Acute Study Outcomes (D-02)

	Treatment (n=112)	**Control (n=110)**	***P*-value**
$HRSD_{24}$ Responders	15%	10%	.251
$IDS\text{-}SR_{30}$ Responders	17%	8%	.045
CGI-I Responders	14%	12%	.648
MADRS Responders	15%	11%	.378

Long-Term Outcomes (D-02)

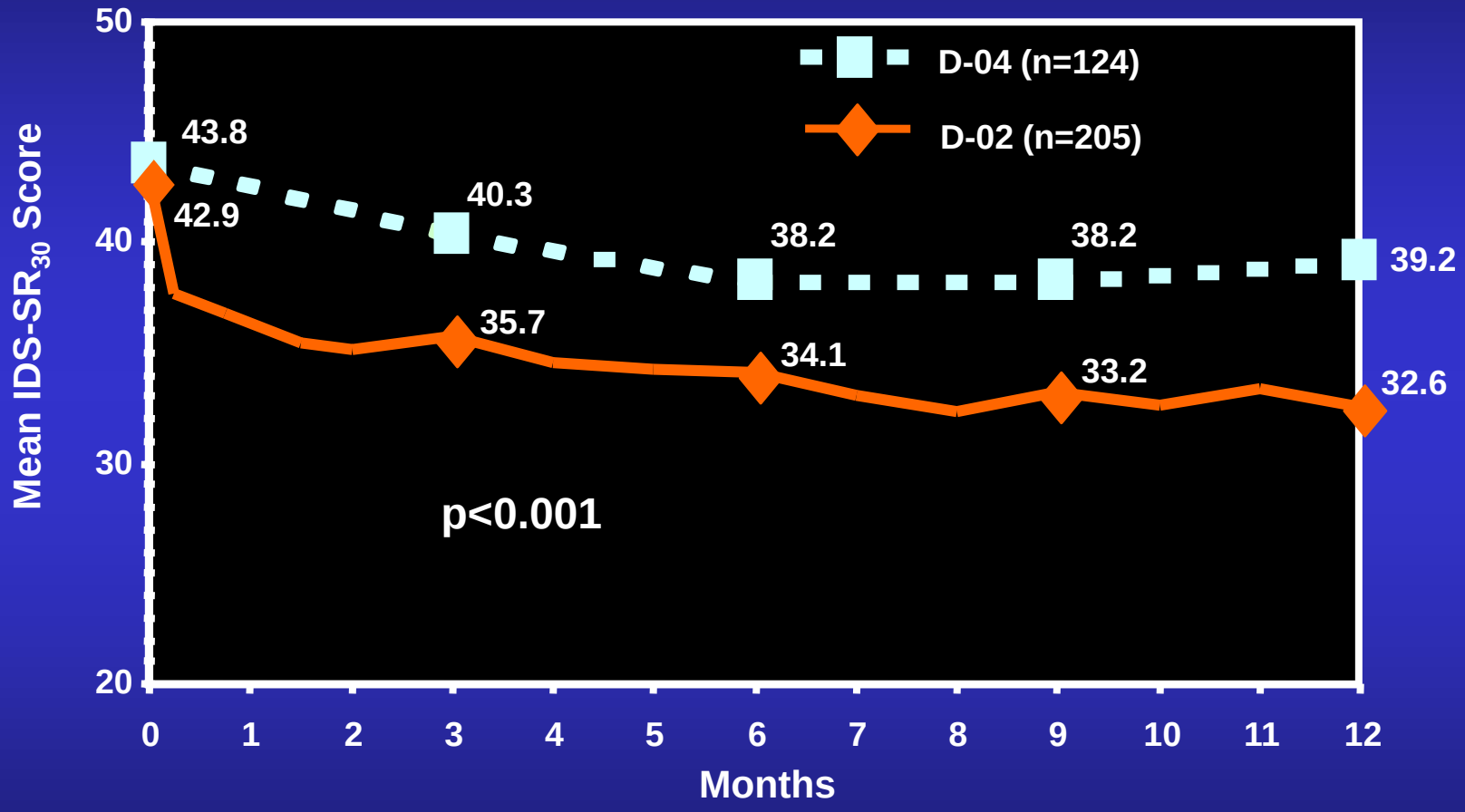


D-02 vs. D-04: Comparison of Patient Populations

Patient Characteristic	D-02 (n=205) Evaluable Population	D-04 (n=124)
Average Age (yrs.)	46	46
% Female	64%	69%
Baseline HRSD-24*	27.9	27.8
Avg Duration Lifetime Illness (yrs)	25	26
Avg Duration, Current Episode (yrs)	4.2	5.8
% Treated W/ ECT, Current Episode	35%	12%
Avg # Failed Adequate Treatments, Current MDE (ATHF)	4	4

*For patients W/ 12-month assessment

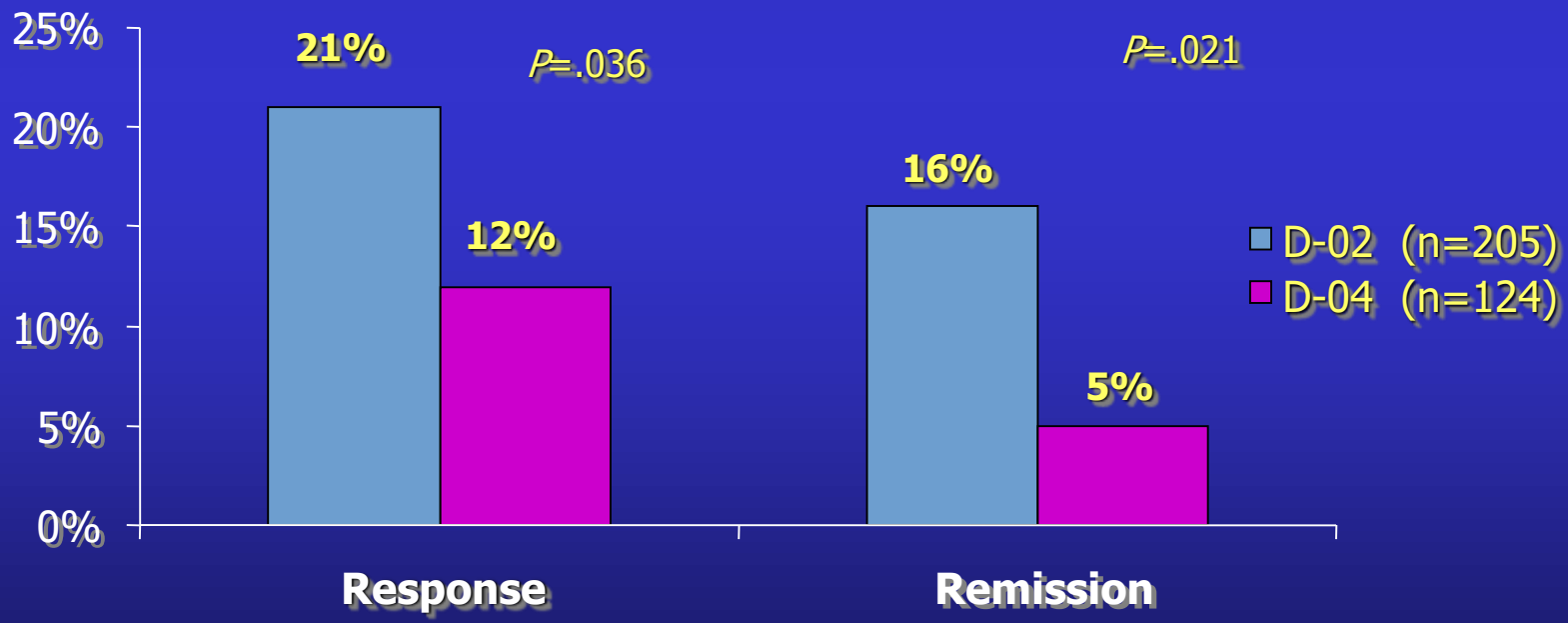
Adjunctive VNS (D-02) Superior to Naturalistic Treatment (D-04) Over 1 Year



Data on File, Cyberonics; PMA-S Submission, October 2003

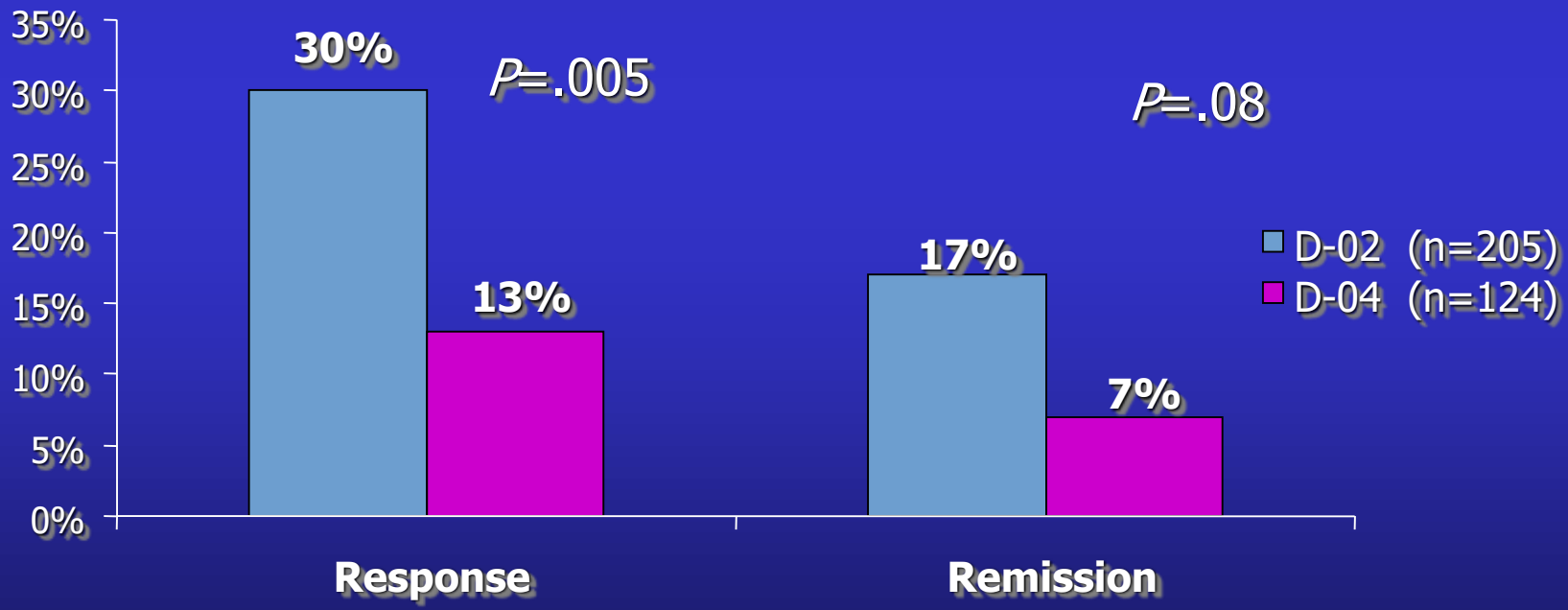
D-02 vs D-04: 12-Month IDS-SR$_{30}$

12-Month IDS-SR$_{30}$ Response and Remission Rates (Evaluable Patient Population; Observed Data)



D-02 vs D-04: 12-Month $HRSD_{24}$

12-Month $HRSD_{24}$ Response and Remission Rates (Evaluable Patient Population; Observed Data)

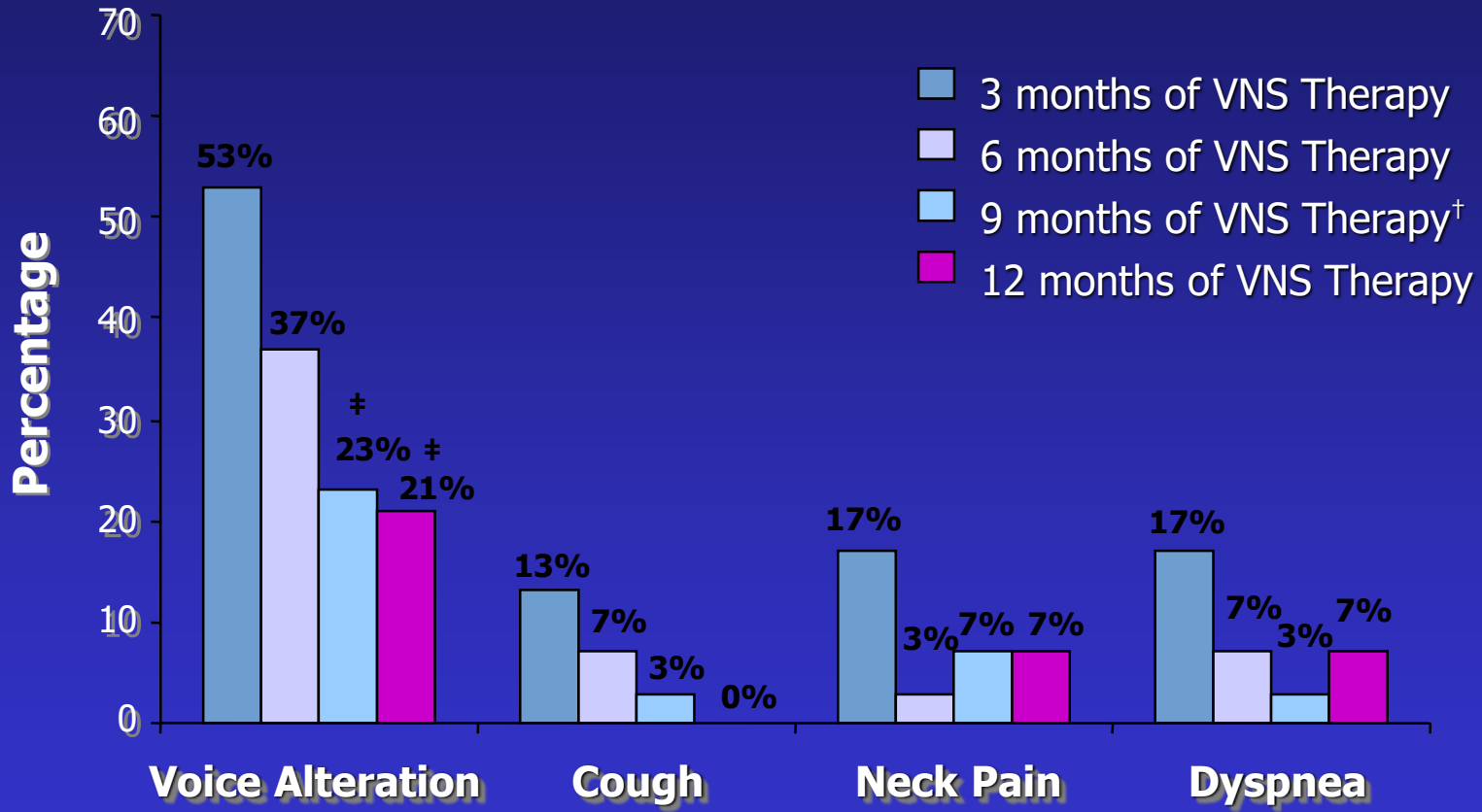


D-02 Acute Adverse Events

Adverse Event	Treatment Group, % (n=109)	Sham Control Group, % (n=110)
Neck pain	21 %	10 %
Wound infection	8 %	2 %
Dyspepsia	10 %	5 %
Vomiting	11 %	5 %
Cough increased	29 %	9 %
Laryngismus	11 %	2 %
Voice alteration*	68 %	38 %
Dyspnea*	23 %	14 %
Paresthesia*	16 %	10 %
Dysphagia*	21 %	11 %

*AEs occurring at ≥5% and 1.5 × Sham Control Group.

Longer-Term Adverse Events at >5% (Observed Cases)*

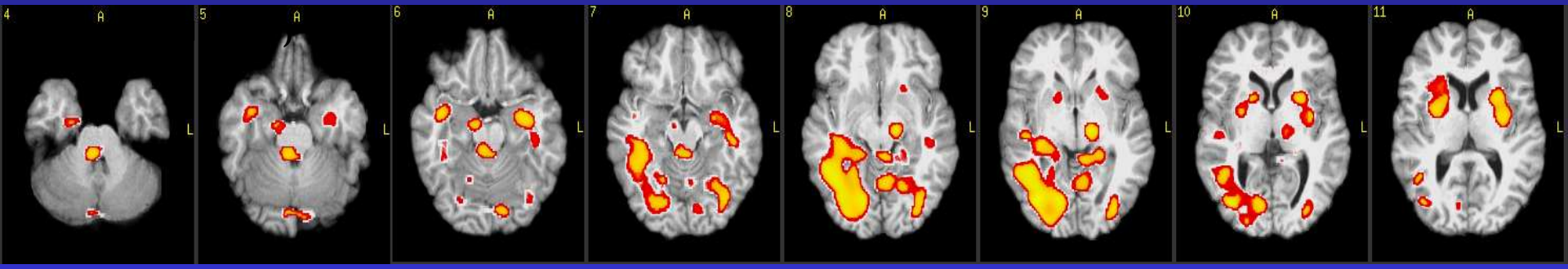


*AEs are possibly, probably, or definitely related to stimulation based on observed cases.
†9-month follow-up corresponds to 1 year postimplant.
‡Statistically significant improvement from 3 months ($P \leq .01$).

Marangell LB, et al. *Biol Psychiatry.* 2002;51:280-287.

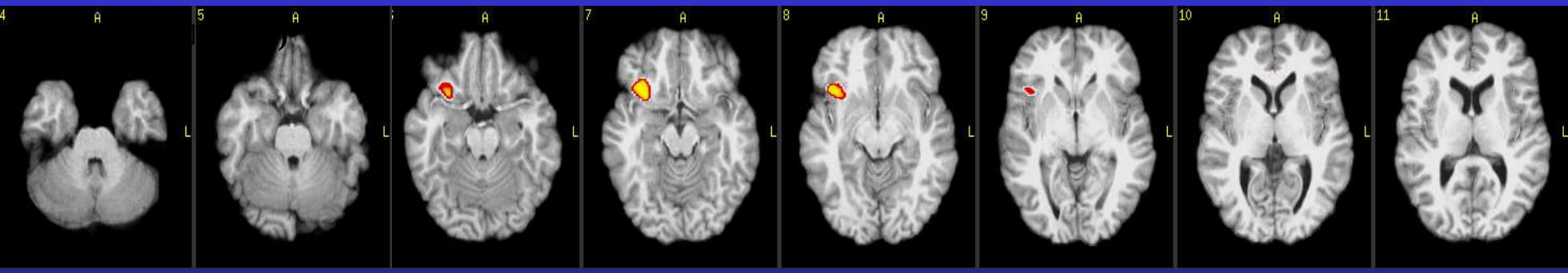
SPECT studies: 10 weeks of VNS

Increased rCBF



Decreased rCBF

Devous, M 2002



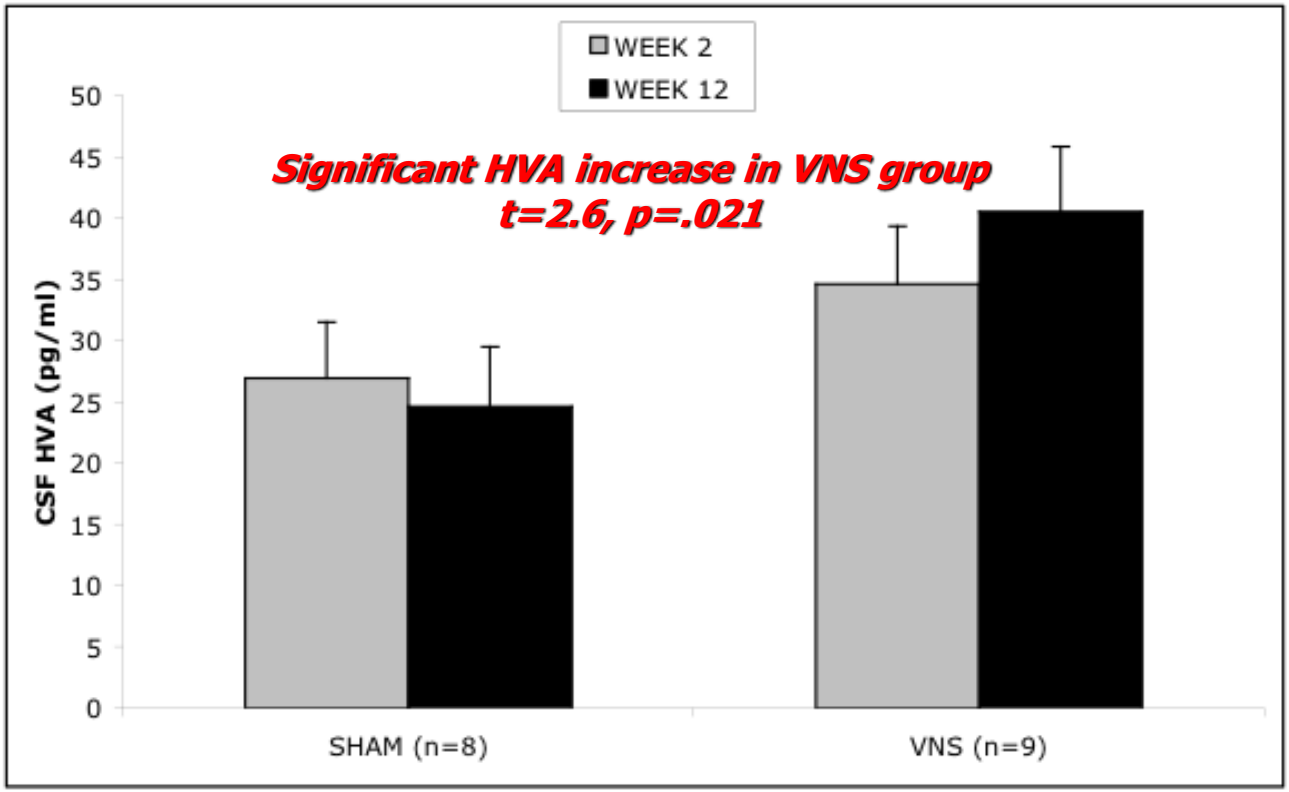
Treatment resistant MDD shows classic pre-op ↓ rCBF; deficits appear to resolve w/ VNS treatment

VNS responders show rCBF changes that include limbic system components

Effective VNS therapy is associated with remodeling of resting rCBF patterns; areas of remodeling relate to changes in symptom state

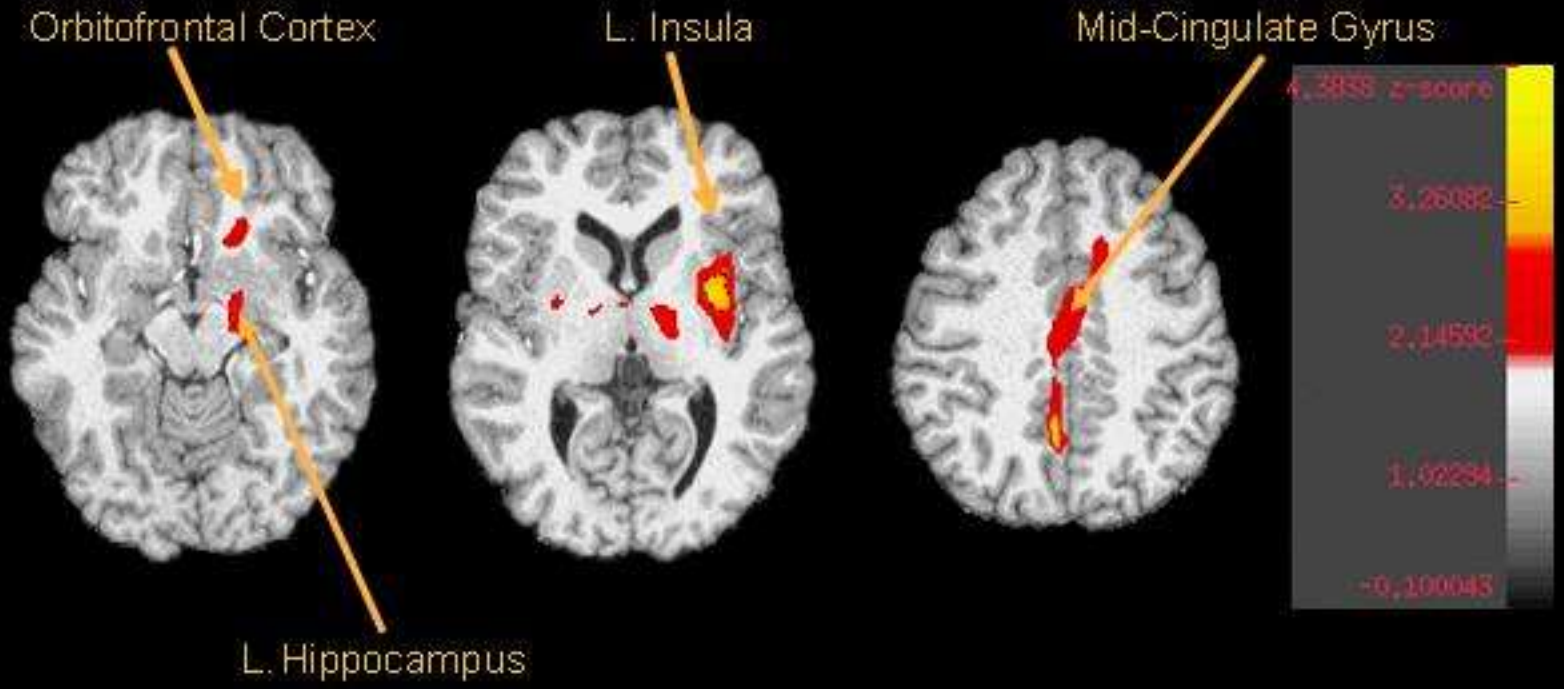
Acute Study Results: Active VNS vs. SHAM

CSF HVA



Carpenter et al, 2004

PET Shows Increased Limbic Activity in Brains of Patients with TRD After 3 Months of VNS Therapy

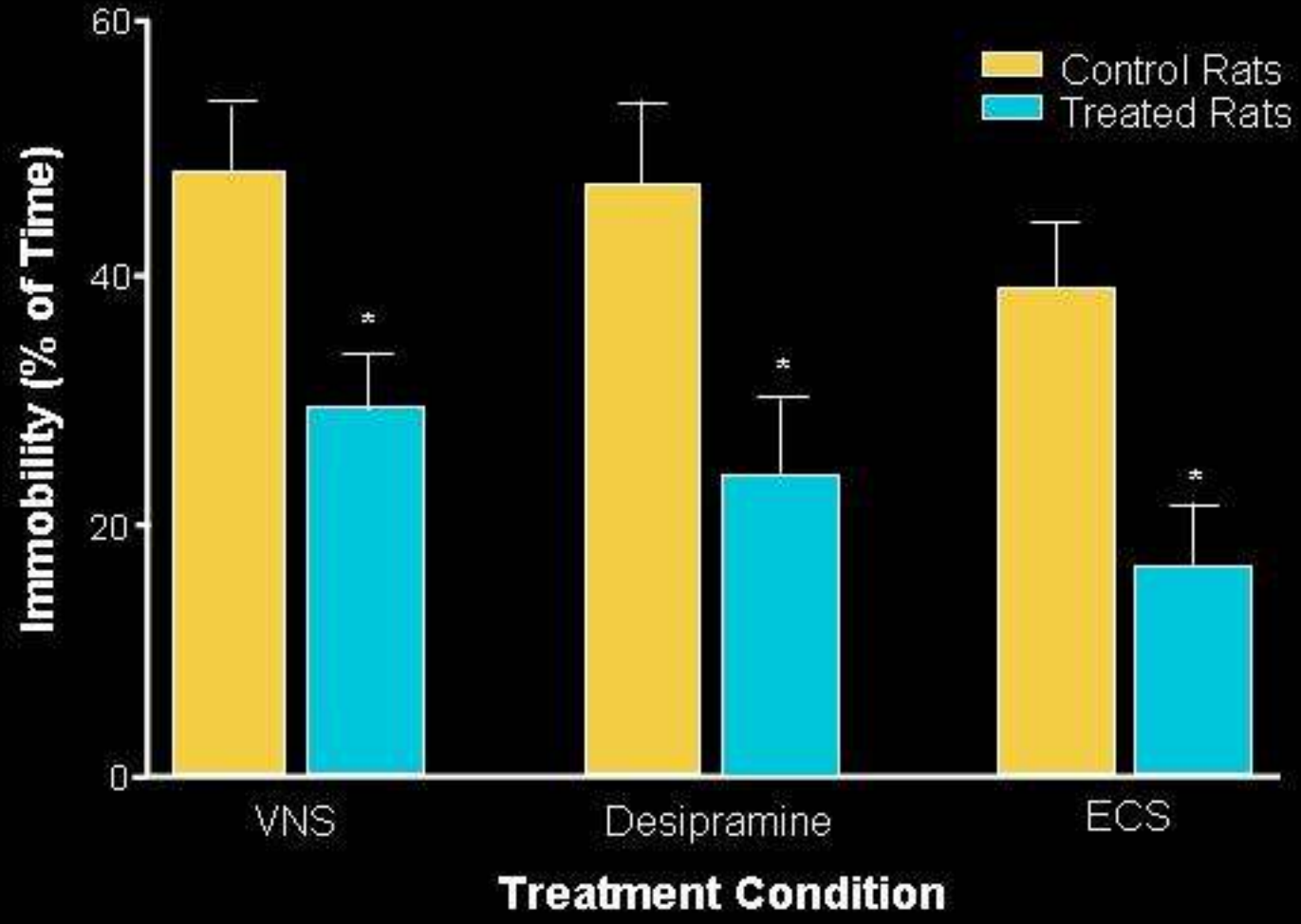


Data acquired from Saint Louis University, analyzed by MUSC CAIR.

P<0.05 for display; no significant decreases.

MUSC CAIR = Medical University of South Carolina Center for Advanced Imaging Research.
Data on file. Cyberonics, Inc.

VNS Is Effective in an Established Animal Model of Depression: Forced Swim Test



*$p<0.05$ vs control.

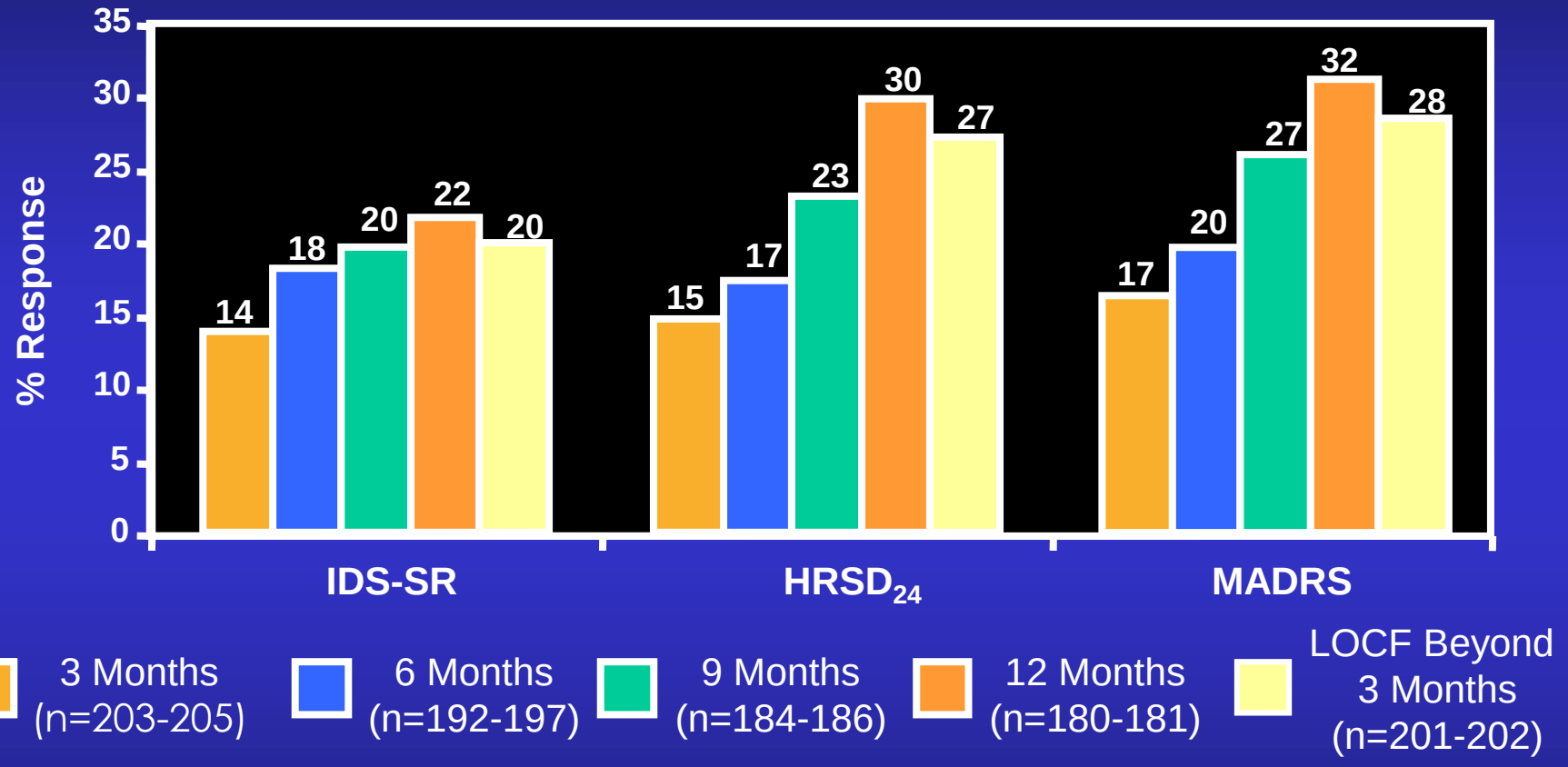
Krahl SE, et al. *J Psychiatr Res.* 2004;38:237-240.

Summary: Rationale for VNS Therapy in Depression

- Anatomical projections of vagus nerve into areas of brain known to be implicated in depression[1]
- Evidence of mood improvement in epilepsy studies, irrespective of seizure control[2]
- Use of anticonvulsants as mood stabilizers/augmentation has established history in psychiatry[1]
- Neuroimaging data have demonstrated that VNS Therapy affects many areas of the brain implicated in neuropsychiatric disorders[1]
- Effects on neurotransmitters implicated in depression[1,3-6]
- Activity in animal antidepressant model (FST)

1. George MS, et al. *Biol Psychiatry.* 2000;47:287-295; 2. Harden CL, et al. *Epilepsy Behav.* 2000;1:93-99; 3. Ben-Menachem E, et al. *Epilepsy Res.* 1995;20:221-227; 4. Krahl SE, et al. *Epilepsia.* 1998;39:709-714; 5. Walker BR, et al. *Epilepsia.* 1999;40:1051-1057; 6. Krahl SE, et al. *J Psychiatr Res.* 2004;38:237-240.

Response Rates Over Time During Adjunctive VNS Therapy



Response defined as ≥50% reduction in $HRSD_{24}$, MADRS, $IDS\text{-}SR_{30}$ compared with pre-stimulation baseline

Rush et al, 2005

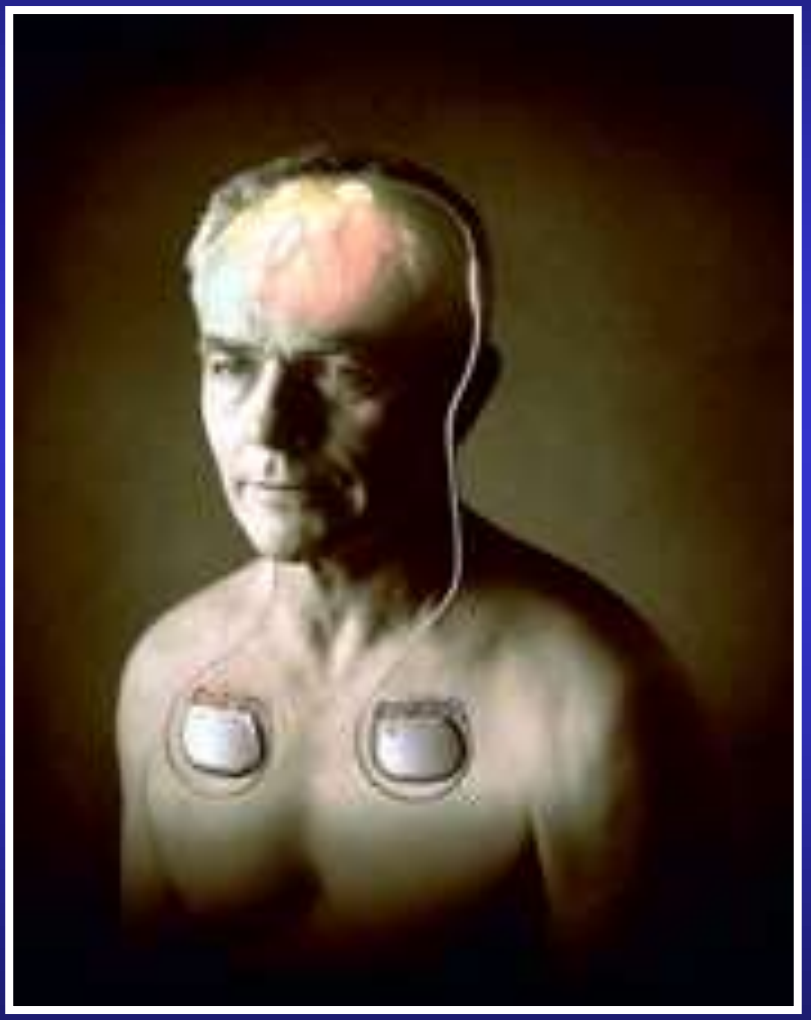
Vagus Nerve Stimulation (VNS)

Limitations

- Efficacy data from nonrandomized study
- Surgical procedure
- Cosmesis
- Limited acute antidepressant effect
- MRI contraindication
- Battery Life (3- 8 yrs)

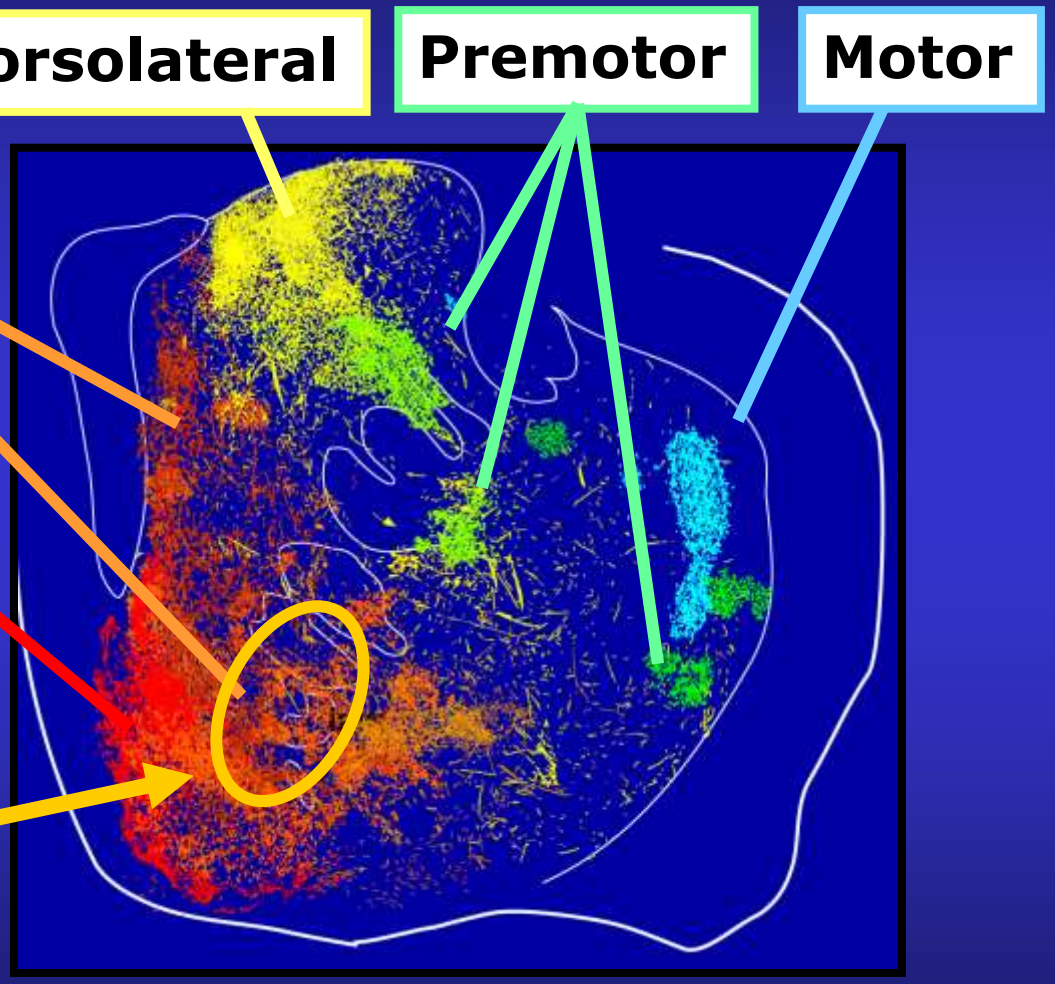
Deep Brain Stimulation (DBS)

- **FDA Approved for Parkinson's and Tremor**
- **Investigational for OCD, TRD**
- **Stereotactic Target from MRI**
- **Two chest-wall Internal Pulse Generators**
- **Burr holes in skull for electrode placement**
- **Stimulation parameters programmed by computer, through "wand"**



This information concerns a use that has not been approved by the U.S Food and Drug Administration

Brown DBS Target: Ventral Anterior Limb Internal Capsule/Ventral Striatum

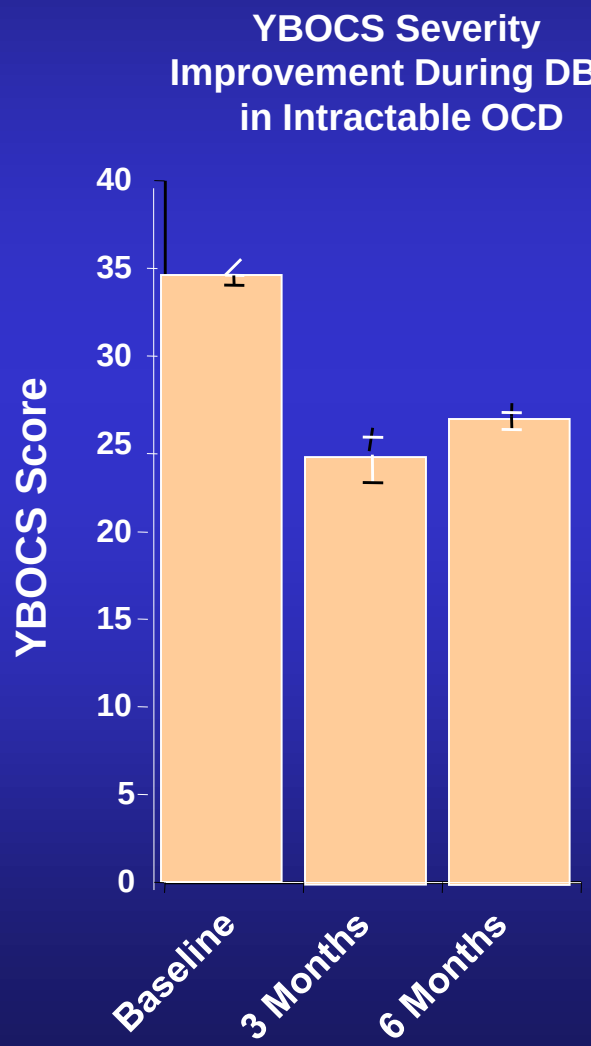


Haber SB et al. *J of Neuroscience*. 1995.

Fronto-Basal Projections to Striatum in Primate

This information concerns a use that has not been approved by the U.S Food and Drug Administration

Brown Experience with DBS for OCD (n=10)

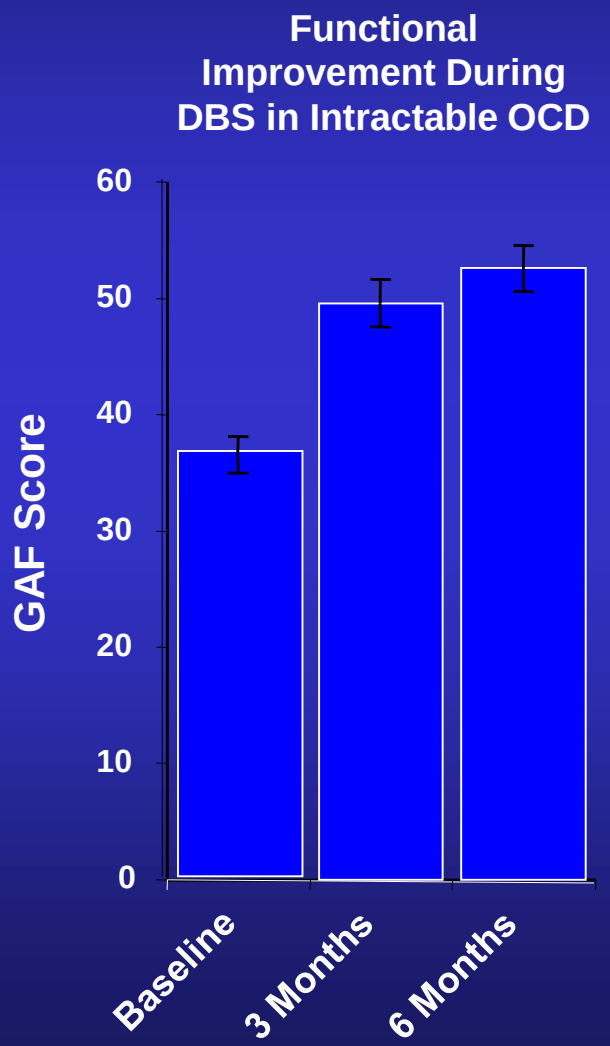


35% ⇓ YBOCS

3/10 (6 months)

25% ⇓ YBOCS

5/10 (6 months)



DBS for OCD: Adverse Effects

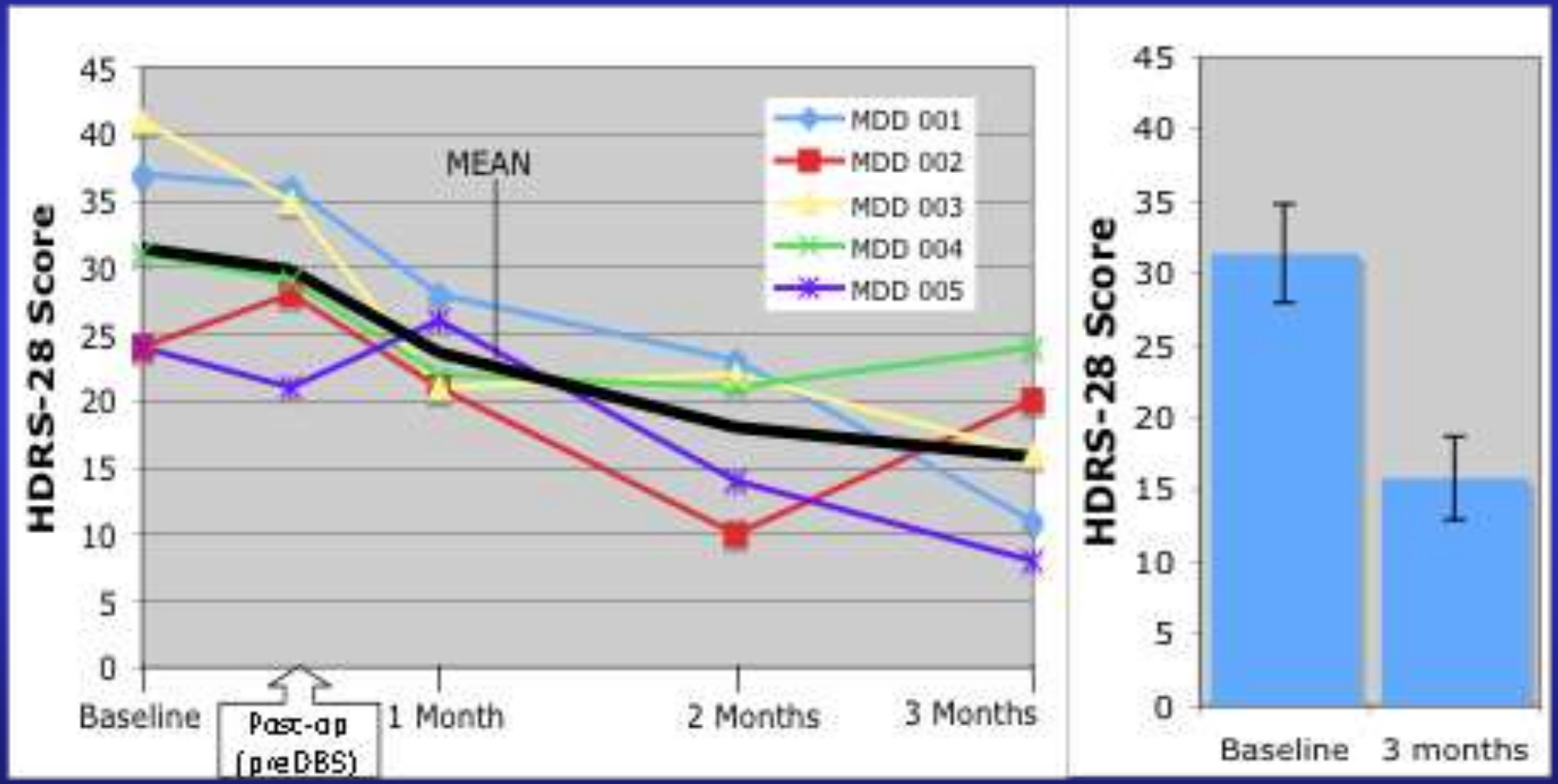
- **Surgical**
  - **Small hemorrhage without symptoms or sequelae**
  - **Superficial infection**
  - **Single intraoperative seizure**
- **Stimulation**
  - **Hypomania (4/10)**
  - **Sensorimotor effects (facial)**
  - **Insomnia**
  - **Autonomic**
  - **Memory flashbacks**
  - **Panic**
- **OFF effects**
  - **Symptom return**

Brown DBS for TRD: Pilot Study n=5

	AGE	SEX	HANDED-NESS	DIAGNOSIS DSM-IV	DURATION OF MDD	MEDS/ECT RESPONSE
001	**54**	**Male**	**Right**	**Severe/chronic unipolar MDD, w/ melancholia**	**36 years**	**None**
002	**60**	**Male**	**Right**	**Severe bipolar I disorder, MDD w/ melancholia**	**35 years**	**No sustained benefit**
003	**51**	**Female**	**Left**	**Unipolar MDD w/ melancholia**	**19 years**	**None**
004	**51**	**Female**	**Right**	**Unipolar MDD w/ melancholia**	**9 years**	**Intermittent benefit**
005	**43**	**Female**	**Right**	**Severe unipolar MDD, single episode, w/ melancholic features**	**6 years**	**Minimal, short-lived improvement**

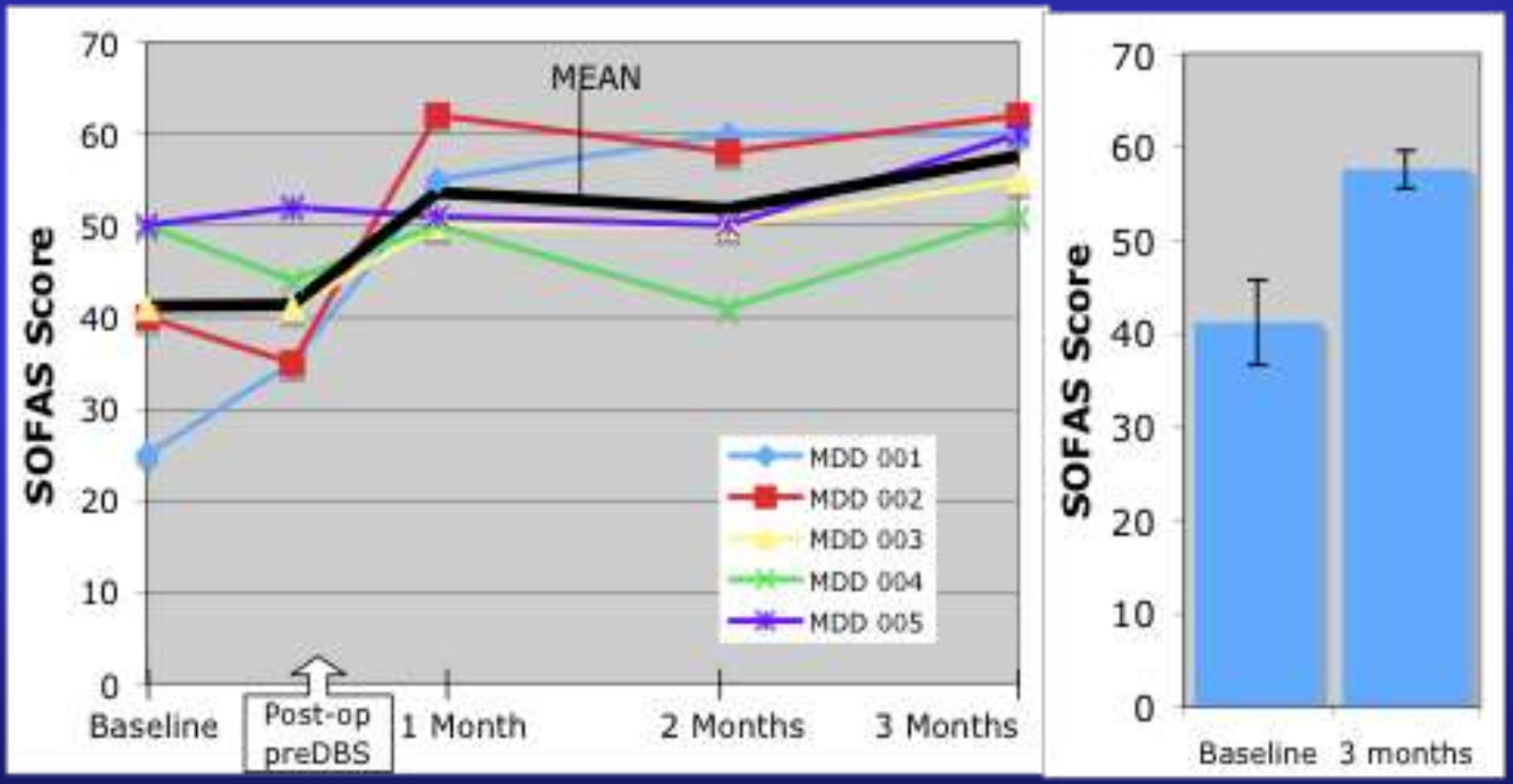
Greenberg BD et al, Neuropsychopharmacology 29:s32, 2004

Depression Improvement During DBS in Intractable Depression



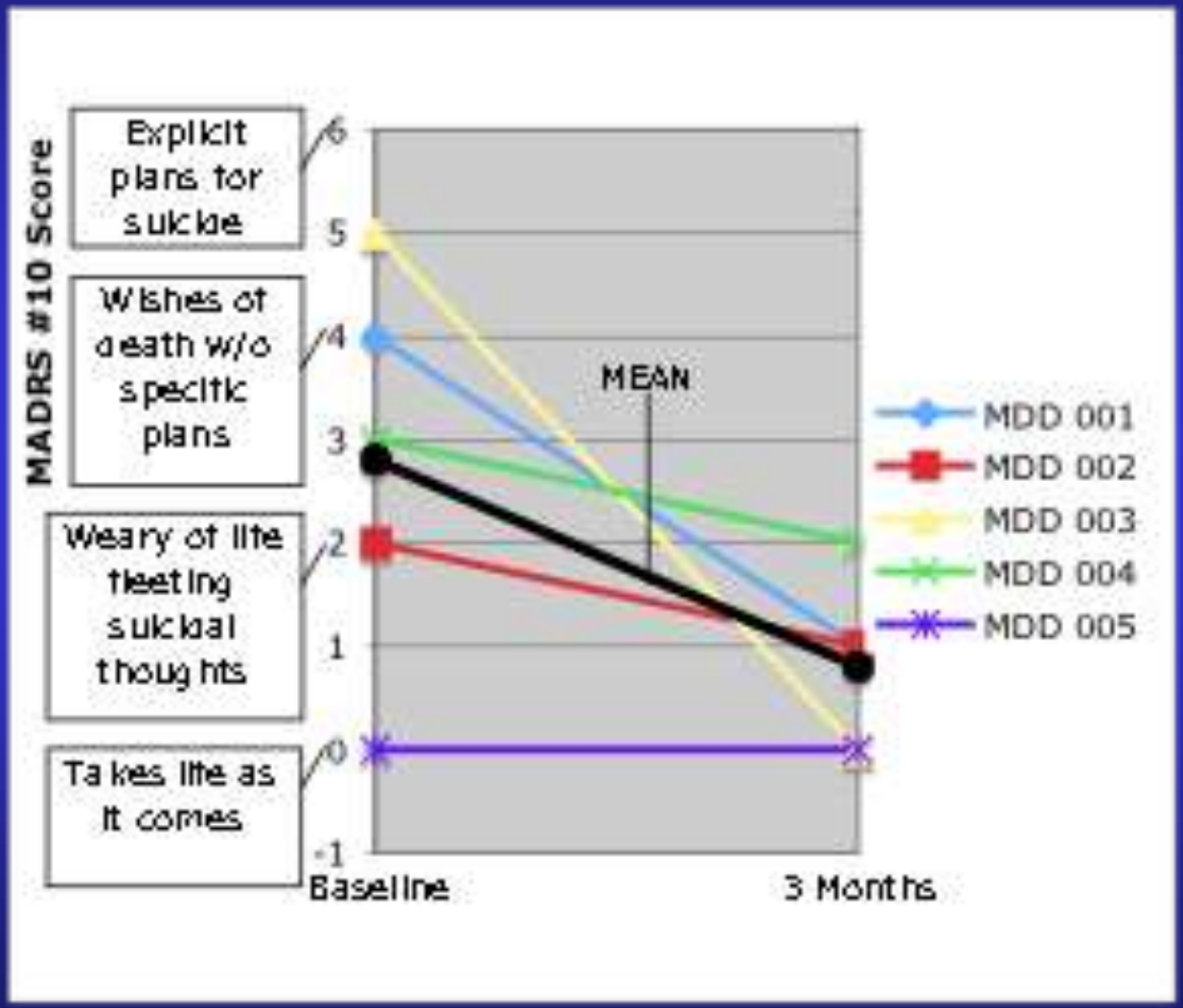
Greenberg BD et al, Neuropsychopharmacology 29:s32, 2004

Functional Improvement During DBS in Intractable Depression



Greenberg BD et al, Neuropsychopharmacology 29:s32, 2004

Reduced Suicidality During DBS



Greenberg BD et al, Neuropsychopharmacology 29:s32, 2004

DBS: Subgenual Cingulate (Cg25) Region

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

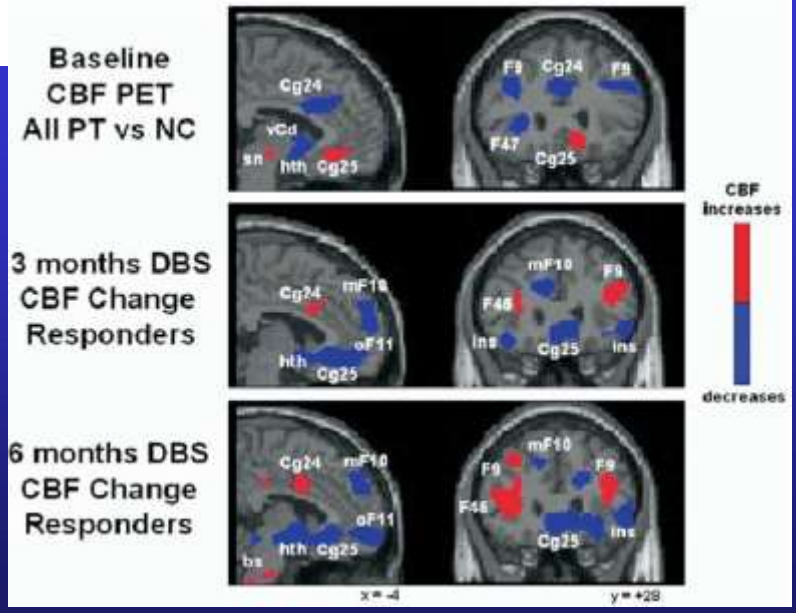
Time	Hamilton Score[a]					
	Pt 1[b]	Pt 2[c]	Pt 3[b]	Pt 4[c]	Pt 5[b]	Pt 6[b]
Preop baseline	29	22	29	24	26	25
1 week postop (acute stimulation)	5	10	12	18	17	12
2 weeks postop (DBS off)	9	13	23	18	22	n/a
1 month	10	14	17	20	22	12
2 months	13	11	12	18	10	12
3 months	2	15	14	25	7	14
4 months	4	9	12	24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

Response in 4 of 6 patients
Response associated with reduction in local and downstream limbic CBF on PET

Mayberg HS et al. *Neuron*. 2005.

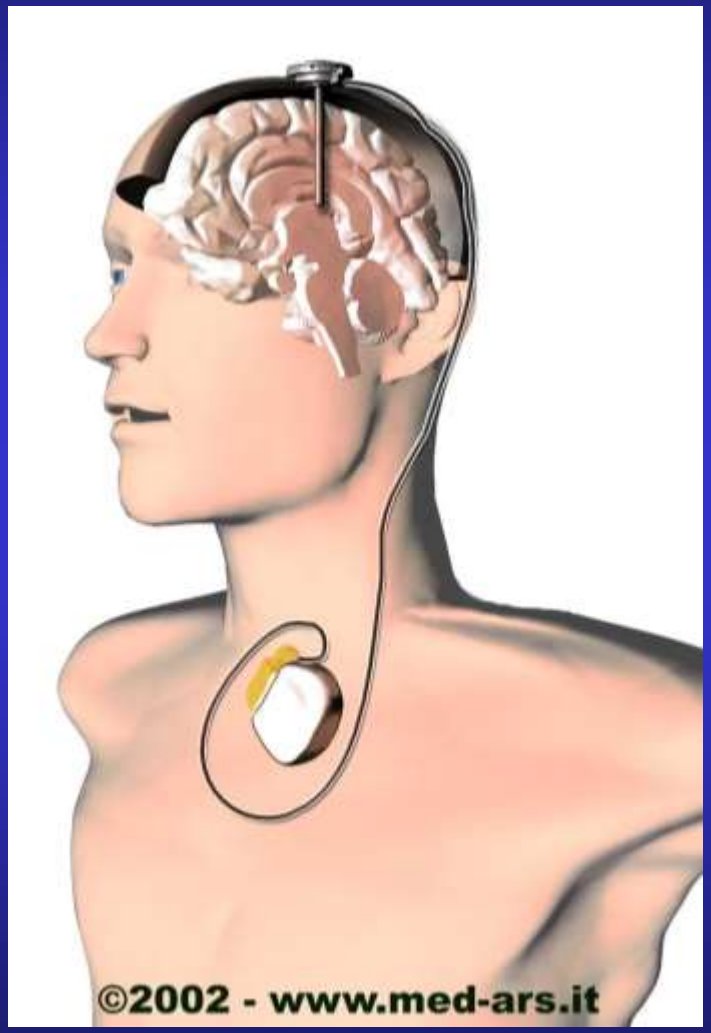
This information concerns a use that has not been approved by the U.S Food and Drug Administration



Deep Brain Stimulation (DBS)

Limitations

- Limited, short-term, open-label data in psychiatry
- Considerable Surgical Risk
- Cosmesis
- Targets and stimulation parameters not established
- MRI contraindication
- Risk of hypomania
- Battery Life



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Brain Stimulation Therapies for Treatment Resistant Depression

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