Brain Stimulation Therapies for Treatment Resistant Depression

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Major Stockholder:	None
Other Financial/ Material Interest:	None

Pre-Lecture Exam Question 1

Magnetic Seizure Therapy (MST) differs from ECT in that:

a. the goal is not to induce a therapeutic seizure
b. the use of focused stimulation to produce a seizure
c. general anesthesia is not required
d. daily sessions of MST are needed to produce a therapeutic effect
e. it has a more benign profile in terms of cognitive adverse effects

Question 2

The most common side effect reports with VNS is:

a. weight gain
b. sexual dysfunction
c. cognitive impairment
d. hoarseness
e. chest pain

Question 3

Deep brain stimulation is currently FDA approved for the treatment of:

a. auditory hallucinations in schizophrenia
b. chronic neuropathic pain
c. obsessive compulsive disorder
d. parkinson's Disease
e. intractable migraine

Question 4

Transcranial Magnetic Stimulation (TMS) differs from Magnetic Resonance Imaging (MRI) technology in that:

a. the magnetic fields produced are much weaker in intensity
b. the rate of change of the magnetic field is higher with an MRI versus TMS
c. MRI technology activates neurons whereas TMS does not
d. scalp discomfort is common with TMS but not with an MRI

Question 5

Which of the following statements about ECT is not true?

a. ECT appears to be particularly efficacious in psychotic depression
b. ECT is not effective in the treatment of mania
c. ECT is effective in the treatment of bipolar depression
d. ECT is associate with retrograde memory impairments
e. ECT is effective in the treatment of pharmacotherapy-resistant major depression

Educational Goals

- Describe the range of brain stimulation technologies (TMS, VNS, DBS, & DCS) being currently investigated in psychiatry for possible therapeutic application
- Examine current evidence for application of these devices in a number of clinical disorders
- Understand the comparative safety profile and adverse events associated with these device technologies for brain stimulation

Overview

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

Definitions

Neurotherapeutics

- Treatments for nervous system disorders
- Pharmacological and other modalities

Neuromodulation

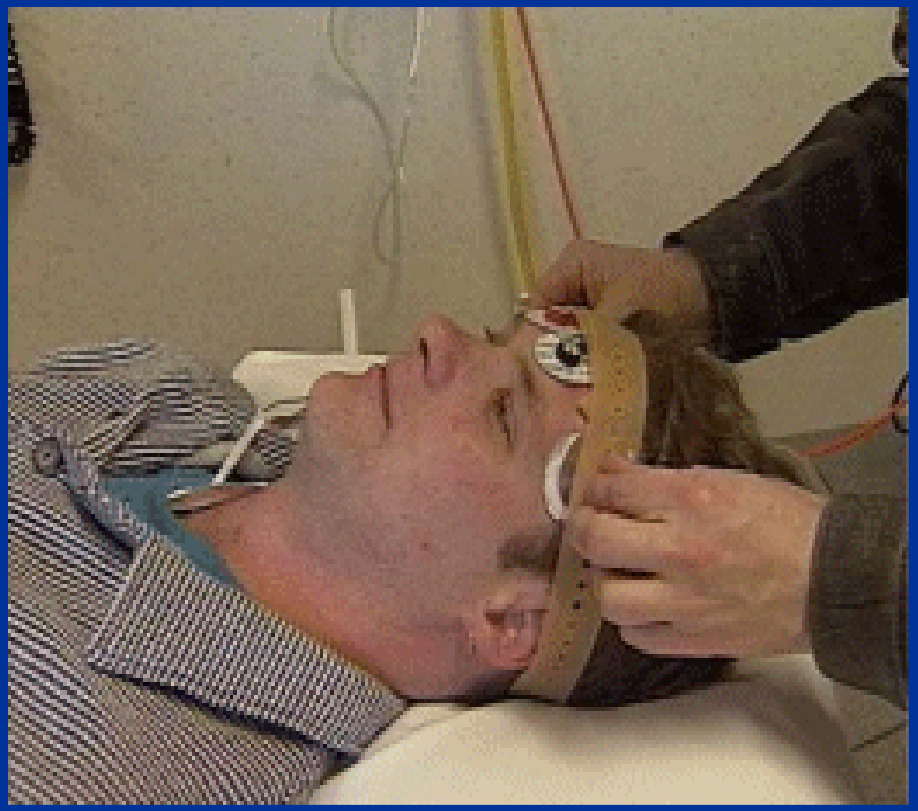
- Therapeutic alteration of nerve activity
- Central, peripheral or autonomic nervous systems
- Electrically or pharmacologically
- Implanted devices
- Pain, movement disorders, spasticity, epilepsy, sensory deprivation, urinary incontinence, gastric dysfunction, pancreatitis/visceral disorders

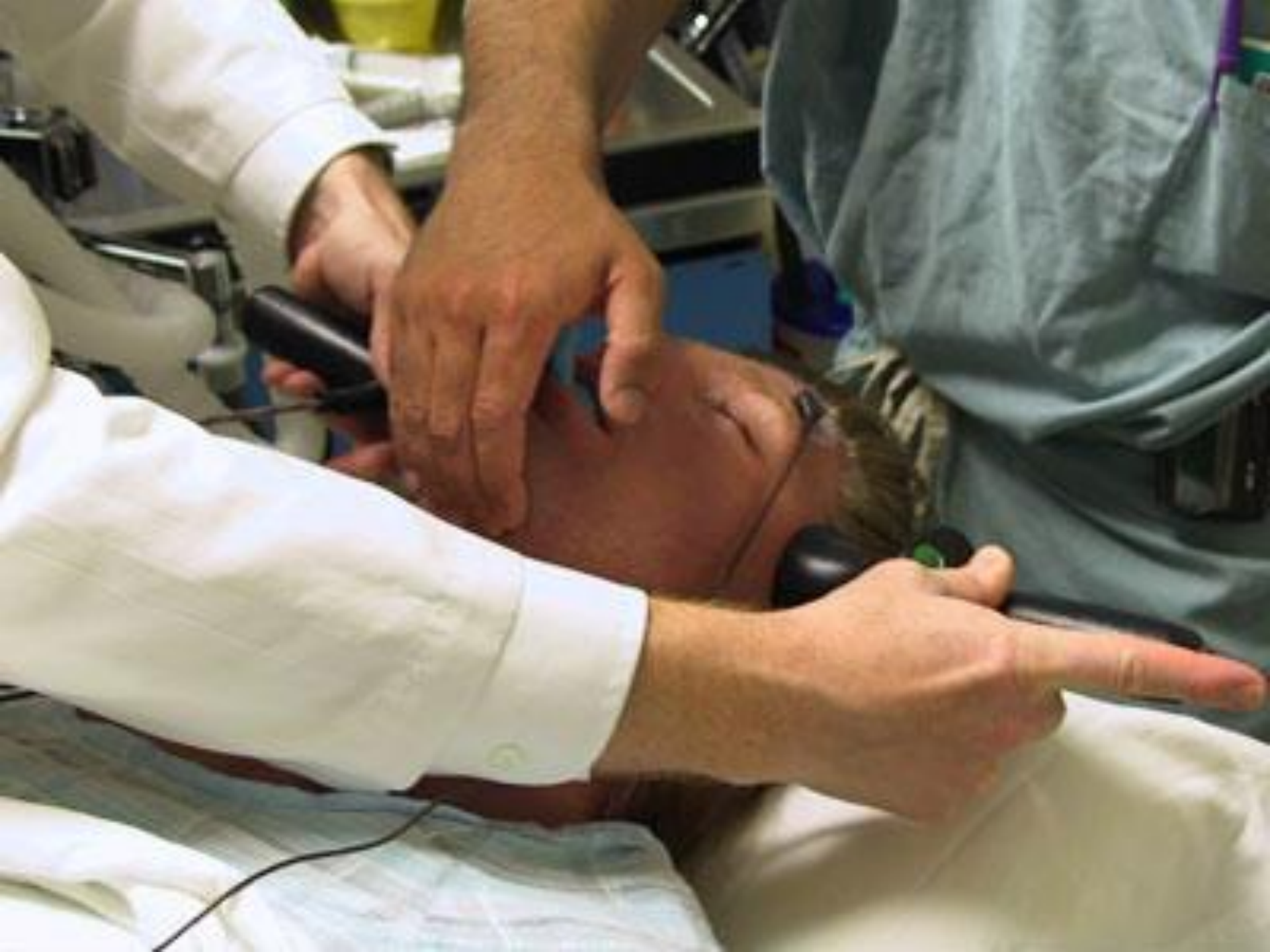
Neurostimulation

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

Electroconvulsive Therapy (ECT)

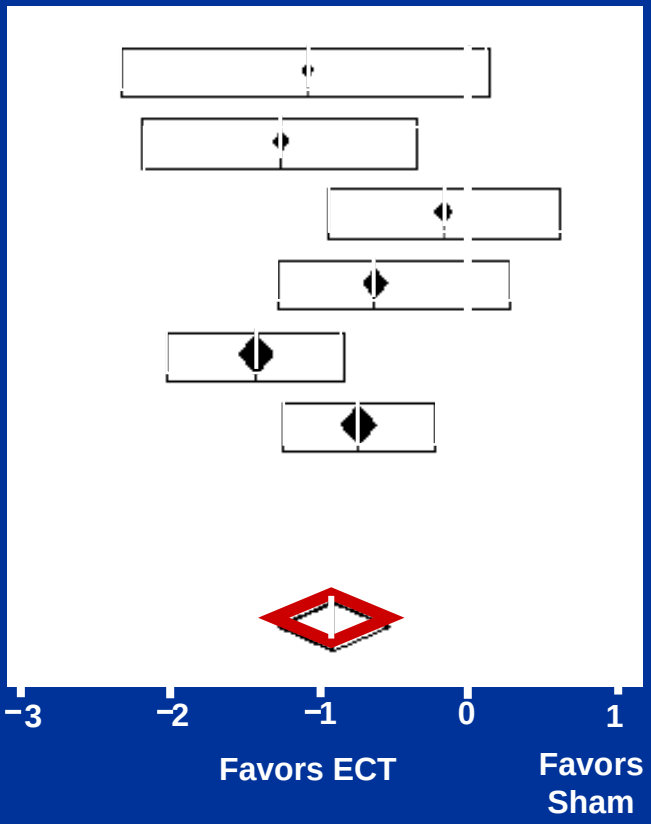
- 1st administered in 1938 (in Rome)
- FDA - approved since 1979 (grand-fathered)
- Brief electrical pulse passed through scalp (0.5 to 6 seconds duration)
- Patient under anesthesia
- Produces seizure on EEG
- Muscle paralysis prevents convulsive movement
- Bilateral or unilateral
- 6 - 12 treatments
- 2 - 3 treatments per week





Efficacy of ECT versus Sham control

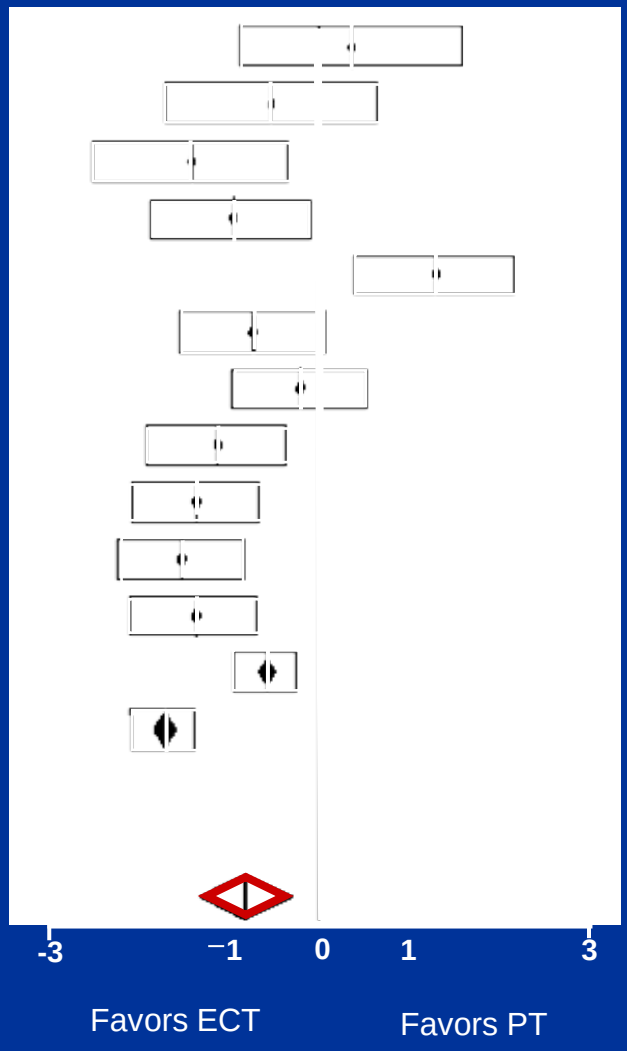
Trial	# of Participants	Standard Effect Size (95%CI)
Wilson 1963	12	-1.078 (-2.289 to 0.133)
West 1981	25	-1.255 (-2.170 to -0.341)
Lambourn 1978	40	-0.170 (-0.940 to 0.600)
Freeman 1978	40	-0.629 (-1.264 to 0.006)
Gregory 1985	69	-1.418 (-2.012 to -0.824)
Johnstone 1980	70	-0.739 (-1.253 to -0.224)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

Efficacy ECT versus Antidepressants

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)
MRC 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

ECT Limitations

Limitations

Headache, muscle aches

Cognitive Side Effects: Memory

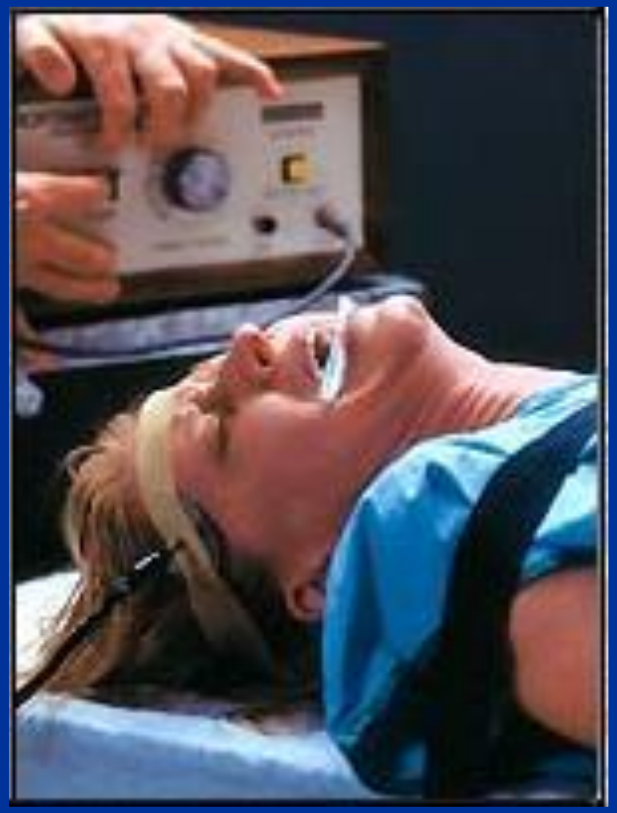
Access: Hospital, Often Inpatient

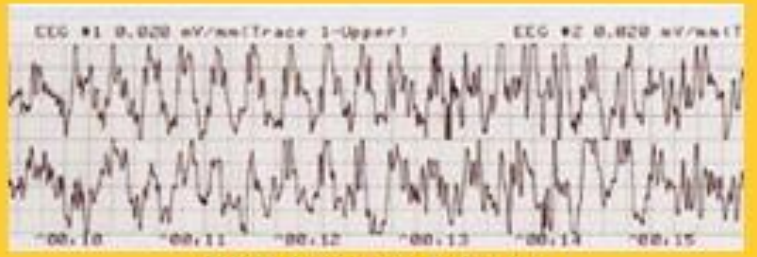
Stigma

Anesthesia Risks

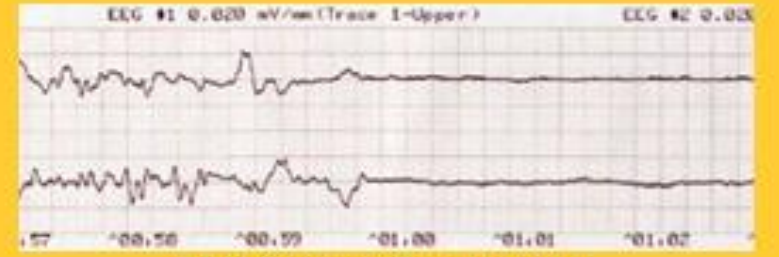
Cost

Maintenance: ECT v. meds





EEG Seizure Activity



EEG Seizure Termination

Role of ECT in 21st century

- ECT remains a gold standard treatment for severe depression and has yet to be superseded by medication or by any other brain stimulation treatment
- In recent multicenter trials remission rates with ECT are about 75%
- This is 3-4 fold superior to antidepressants

Clinical indications for ECT

- Unipolar and Bipolar Depression
- Catatonia (due to schizophrenia, mood disorders, or medical disorders)
- Mania non-responsive to medication
- Occasionally - schizoaffective disorder, NMS, PD, severe depression in pregnancy

Transcranial Magnetic Stimulation (TMS)

Non-invasive technology

USA: Investigational

Approved: Canada, Israel, Europe

Strong, pulsed (e.g., 2/28 sec) magnetic fields pass through skull unimpeded

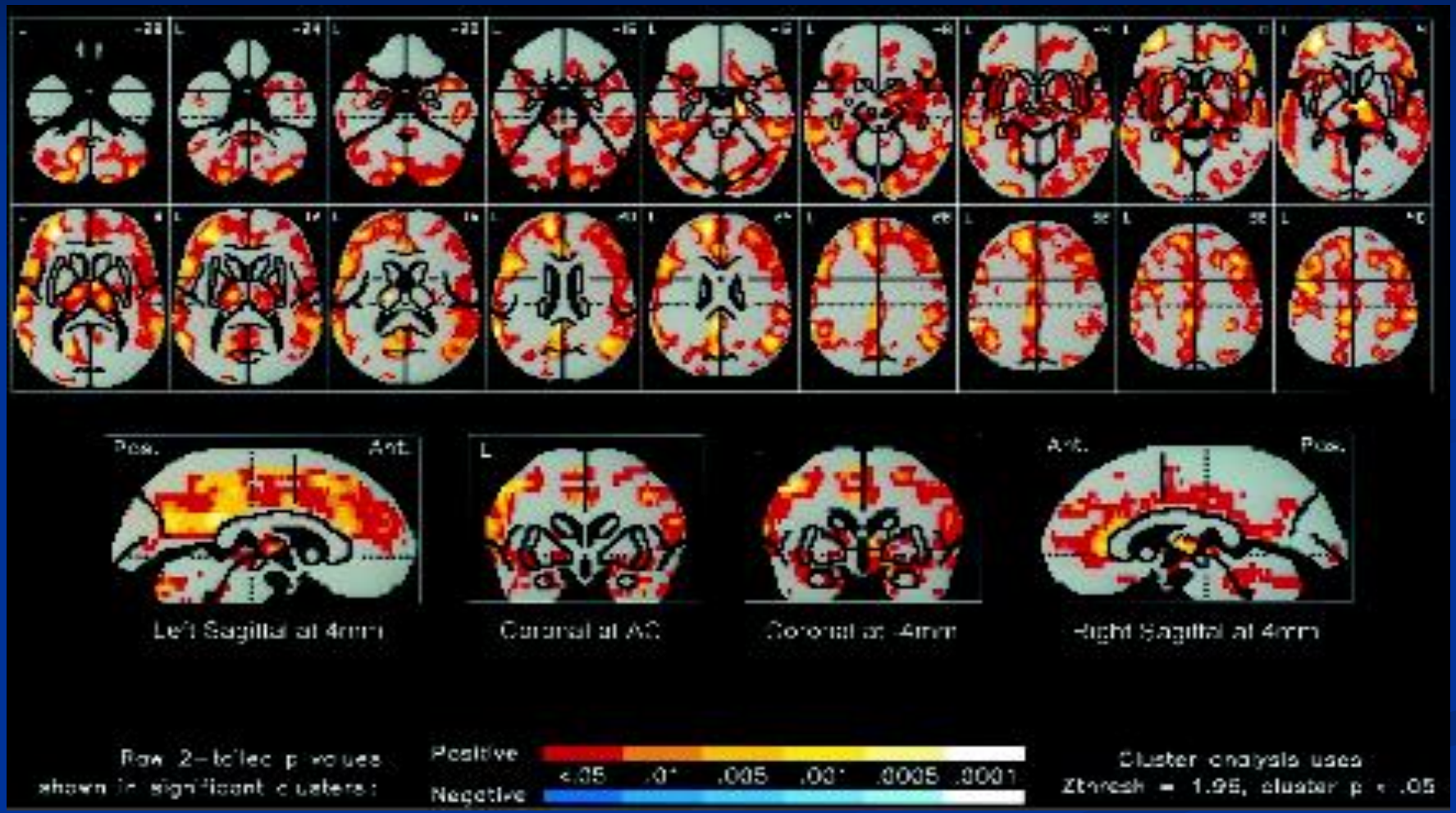
Coil placed on head in awake patient

Induces electrical current in cortex which depolarizes neurons

Greater control over site and intensity of stimulation (e.g, left DLPFC)

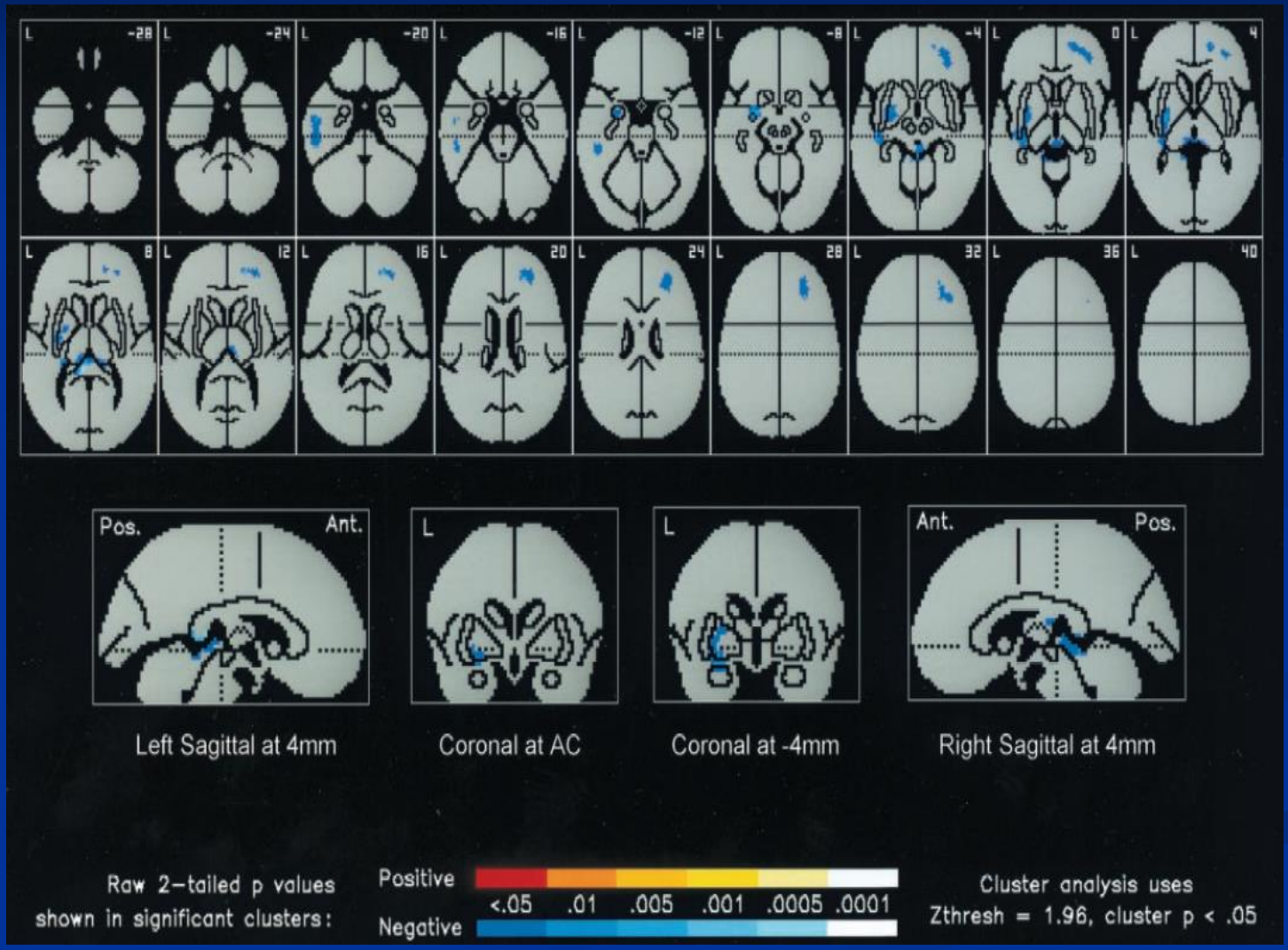
No anesthesia, no cognitive adverse effects

Fast (20 Hz) TMS - excitatory



Speer et al Biol Psych 2000

Slow (1Hz) TMS - inhibitory



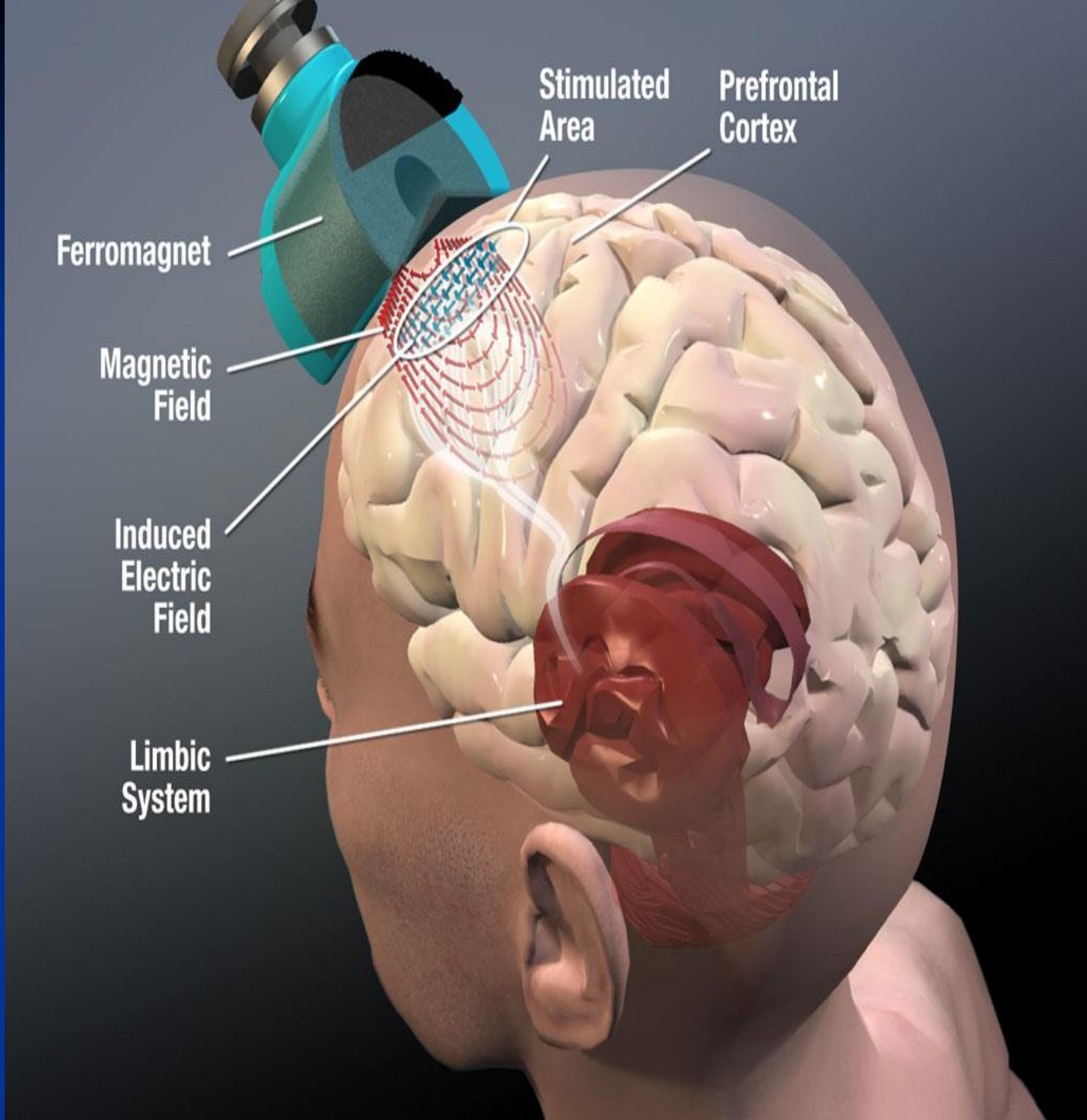
Speer et al Biol Psych 2000

How do MRI and TMS Differ?

	MRI	TMS
Magnetic Field Strength	1.5 Tesla	2 Tesla
Rate of Change of Magnetic Field	20 T/s	20,000 T/s
Induces Current in Brain	No	Yes

Overview of TMS

1) Electrical energy in insulated coil on the scalp induces
2) Pulsed magnetic field of about 1.5 Tesla in strength
3) Passes unimpeded through the cranium for 2-3 cm
4) In turn induces a focal electrical current in the brain
5) Get desired local and distal effects on the target neural circuitry
6) Delivered as single pulses or repeated trains (rTMS)

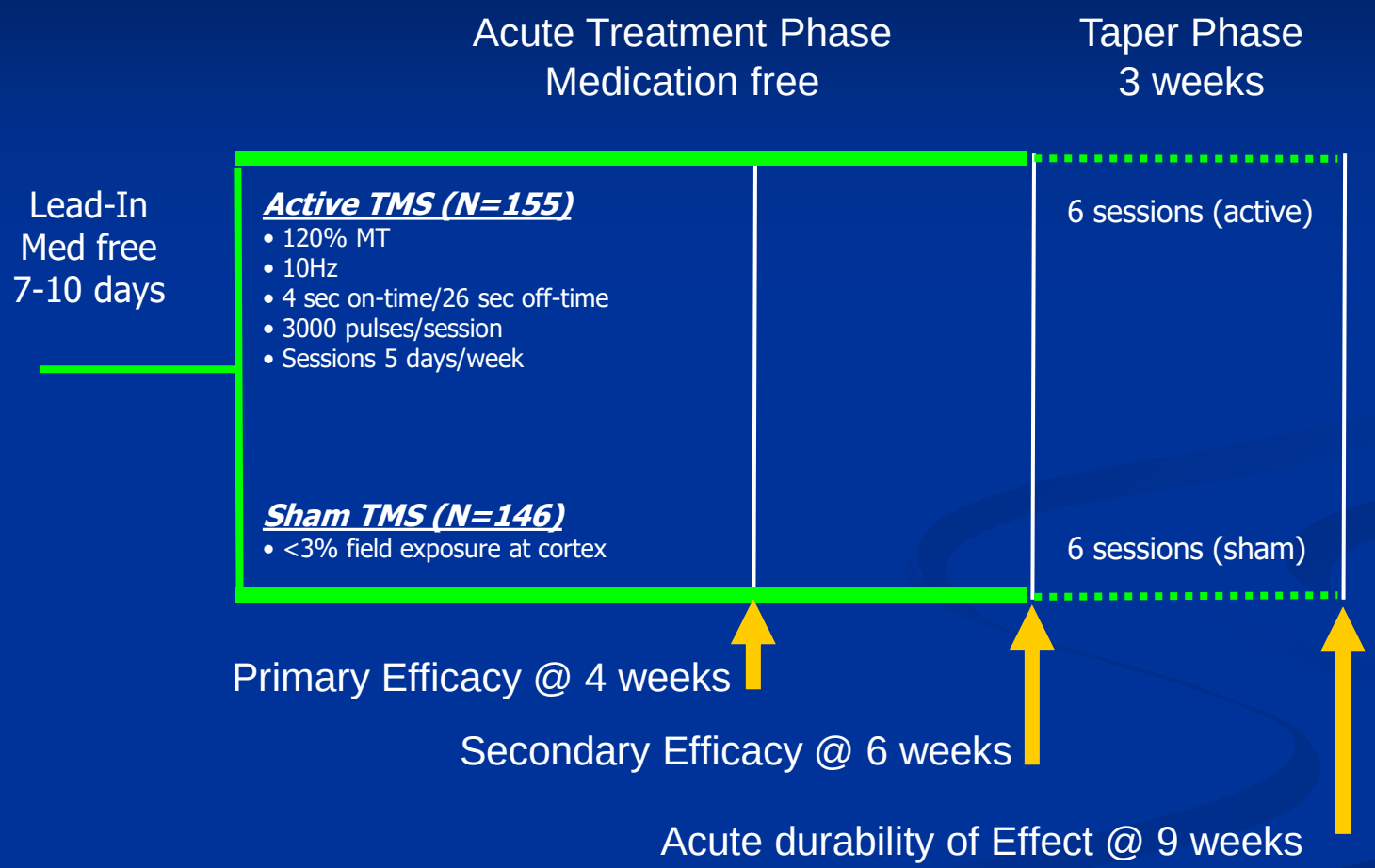


TMS application in Psychiatry

- Best studied in depression, with about 30 RCT of active versus sham TMS (n=1500)
- Evidence for efficacy reasonable at this juncture with an effect size of about 0.75 in most recent metanalysis[1]
- Safety is excellent, with minimal side effects, & low dropout rates (~ 5%)[2]

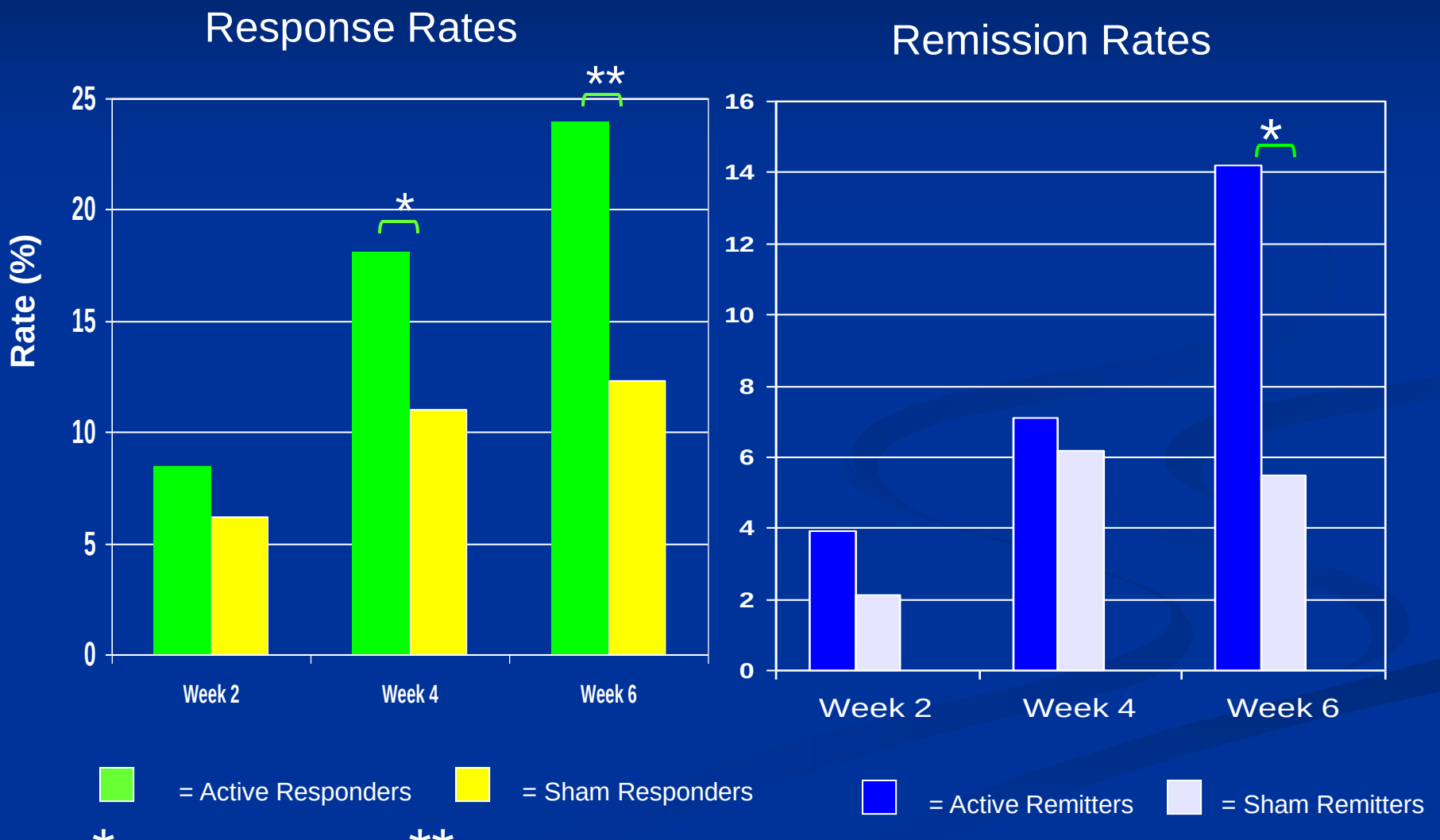
1. Gross et al. Acta Psy Scan 2007. 2. O'Reardon et al. Bio Psy 2007

Multicenter study of TMS in MDD



O'Reardon et al., Biological Psychiatry, 2007

Categorical Outcomes at 4 & 6 weeks



* P < .05 vs. sham, ** P < .01 vs. sham, LOCF analysis

TMS for other disorders

- TMS has an inbuilt flexibility in treatment targeting
- Electromagnet can be moved over scalp and targeted to desired area of the cortex
- Frequency selection allows activation or inhibition of circuits accessible at the level of cortex, guided by imaging findings

Other possible applications of TMS

- Auditory hallucinations in schizophrenia – 1 Hz TMS over superior temporal gyrus
- PTSD – 10 Hz over R prefrontal cortex
- ADHD – to target the R medial frontal gyrus
- Other areas being studied include stroke rehab, migraine, Tourette's Syndrome

Schizophrenia and TMS

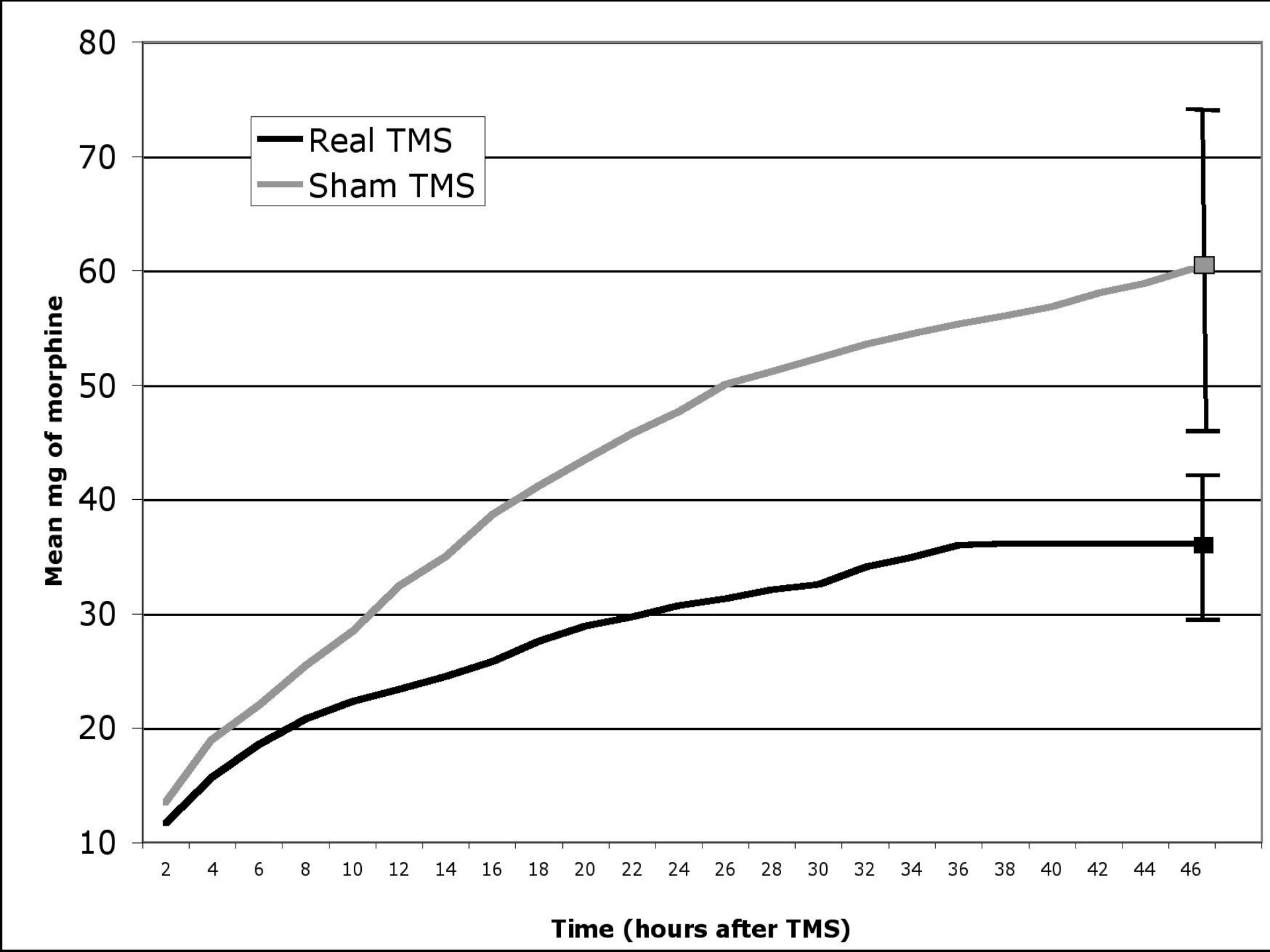
- Application of continuous 1 Hz TMS over temperoparietal cortex to inhibit generation of AH
- Recent metaanalysis of 10 controlled studies (n=212) was positive, with a substantial ES of 0.76 (95% CI range 0.36-1.17)
- Sample sizes generally small (range 10-50 subjects)
- Well tolerated, implies language perceptual disturbance key to etiology of AH

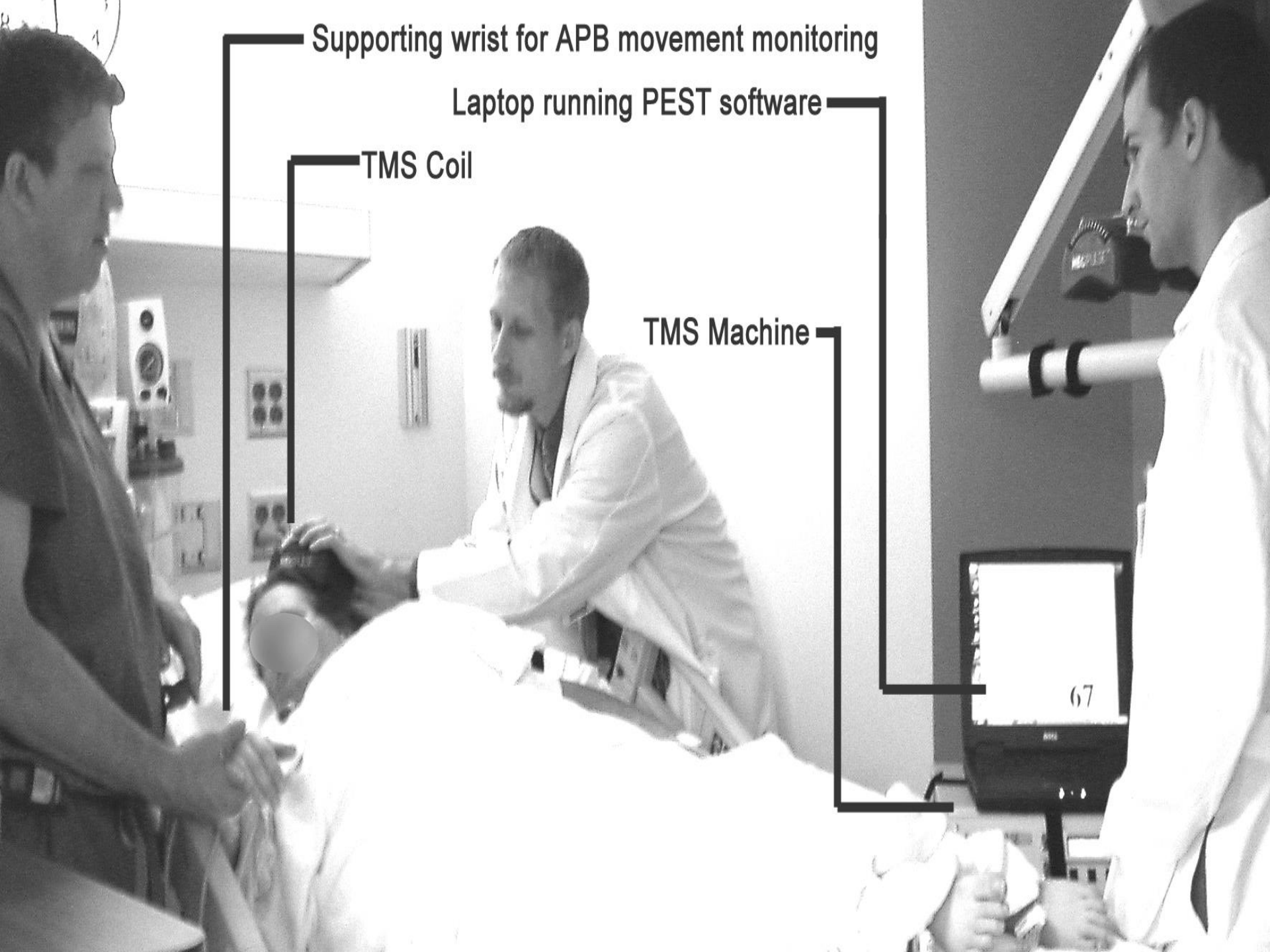
Aleman et al. J Clin Psy 2007;68:416-21

Post-operative pain & TMS

- Recent sham-controlled study of 1 session of 20 minutes of 10 Hz TMS over L PFC (4000 pulses total) in bariatric surgery patients (n=20)
- Main outcome was PCA of morphine/opioids in first 48 hours post surgery
- With active TMS there was 40% less usage of PCA (=24 mg less of morphine over 48 hours)

Bockardt et al. ACNP 2006


Real TMS
Sham TMS
Mean mg of morphine
80
70
60
50
40
30
20
10
2
4
6
8
10
12
14
16
18
20
22
24
26
28
30
32
34
36
38
40
42
44
46
Time (hours after TMS)


Supporting wrist for APB movement monitoring
Laptop running PEST software
TMS Coil
TMS Machine

TMS in Migraine

- TMS used to understand the pathophysiology of migraine – migraineurs have been shown to a lower phosphene threshold (excitation) over V1 (primary visual cortex) compared to controls

- Recent positive results with inhibitory TMS in controlled study of migraine with occipital target

- A 2:1 advantage found over the control condition in migraine with aura (~75% vs. 40%)

A TMS Investigational Device for Migraine relief

Lightweight device, intended for home use, delivers fixed pulse, has over use limits in place

TMS future as clinical treatment

- Currently FDA reviewing application for approval for TMS as a treatment for major depression
- TMS clinically available in Canada, Australia, Israel & Europe
- Available off-label in some centers in the US
- TMS is a safe intervention & may be promising option for a number of psychiatric & neurological disorders

Magnetic Seizure Therapy (MST)

Investigational

Magnet-induced stimulus (like rTMS)

High Intensity

Target "antidepressant regions"

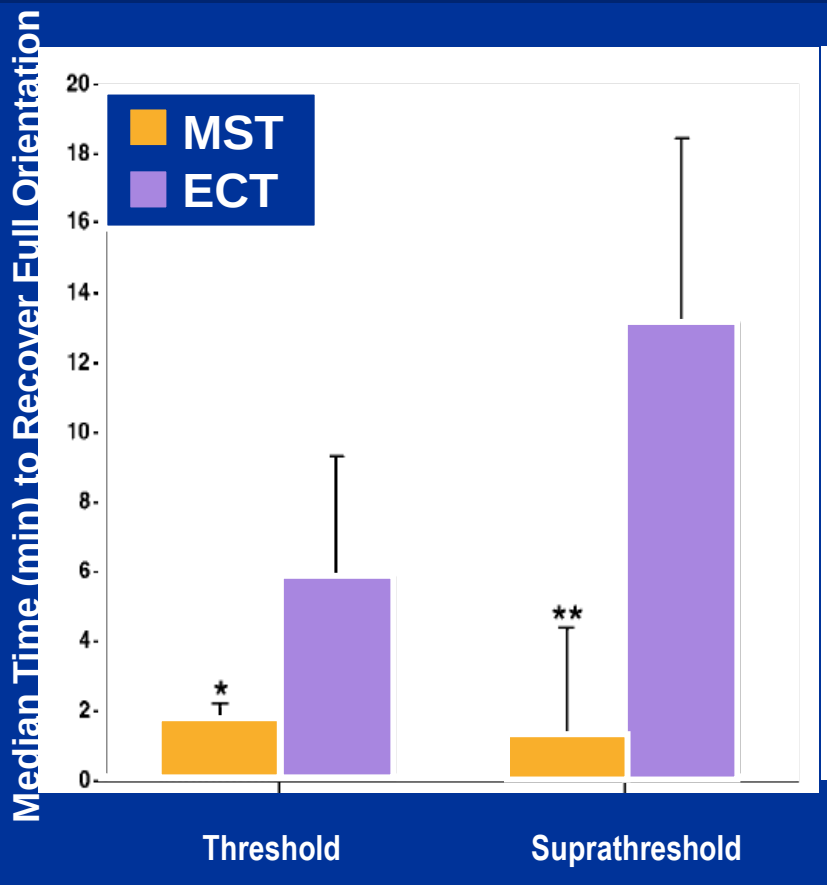
Fewer side effects

3 sessions/week

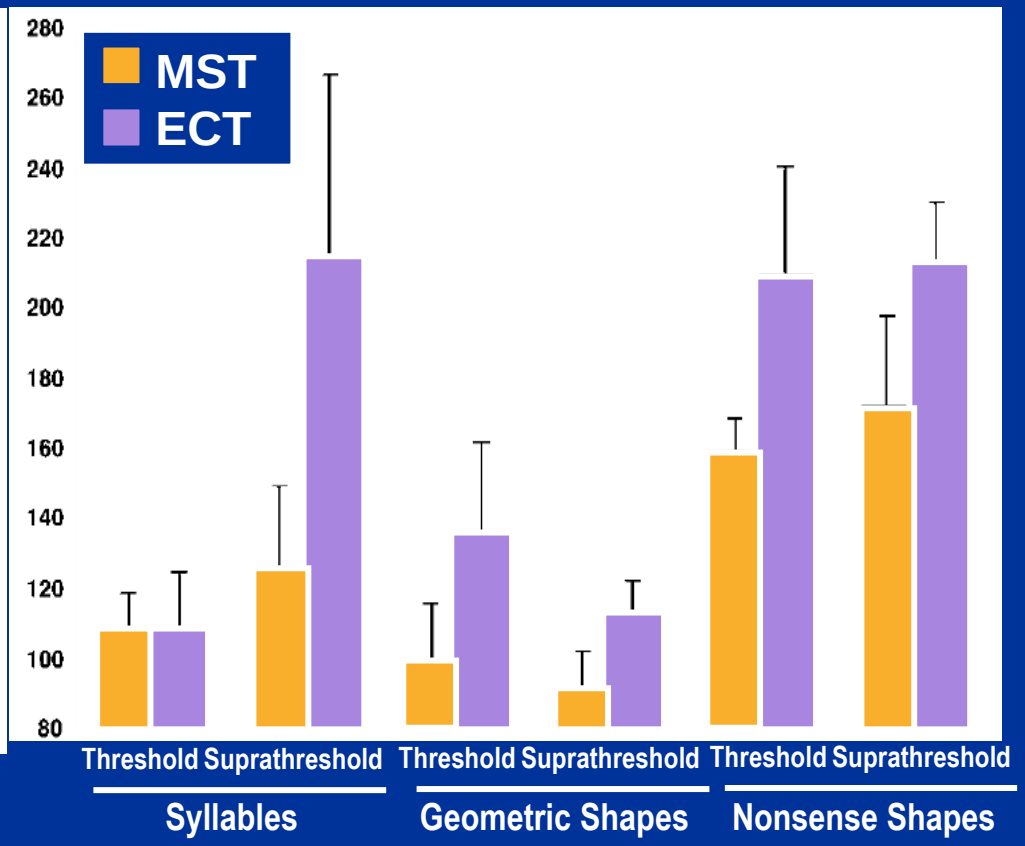
Same as ECT

- Anesthesia
- Tonic clonic seizure
- Monitor EEG, vitals

MST: Shorter Period of Post-Ictal Disorientation and Inattention



*Threshold MST v.ECT, p<.004



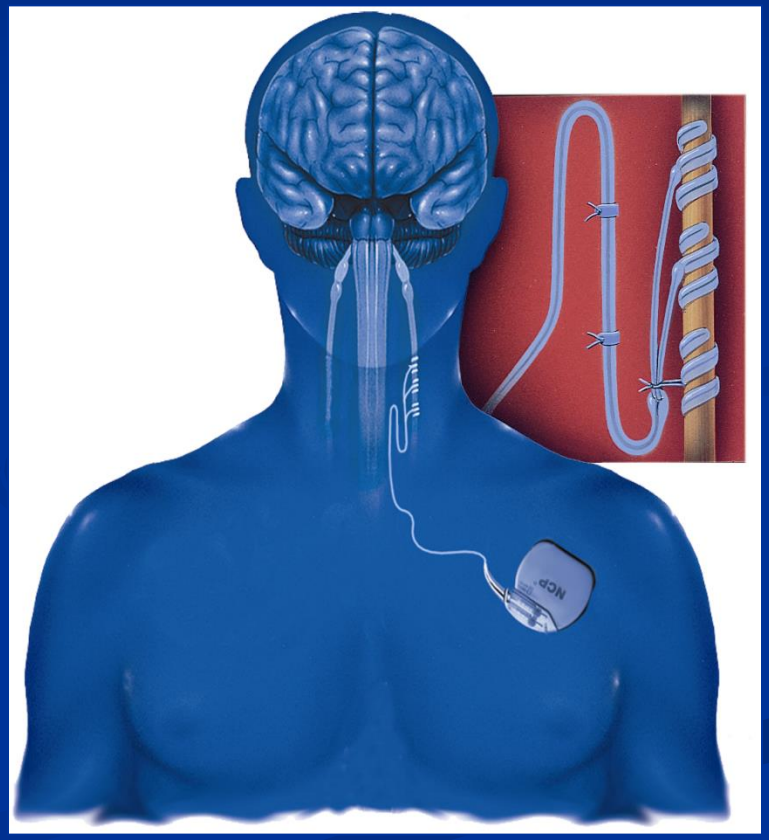
Faster following MST, p<.01

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
- 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, cycled stimulation

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

In-office programming (dosing) by the treating physician

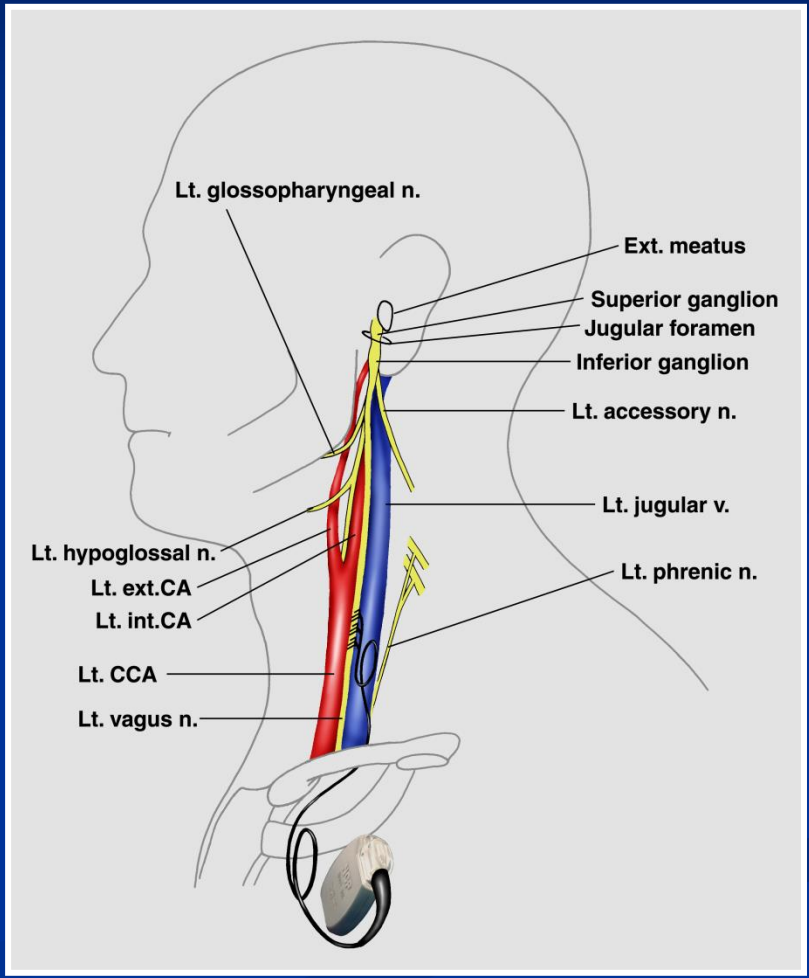
Fact that it is an implant helps adherence/compliance

Cervical Vagus Nerve Anatomy

~80% afferent fibers, mostly unmyelinated

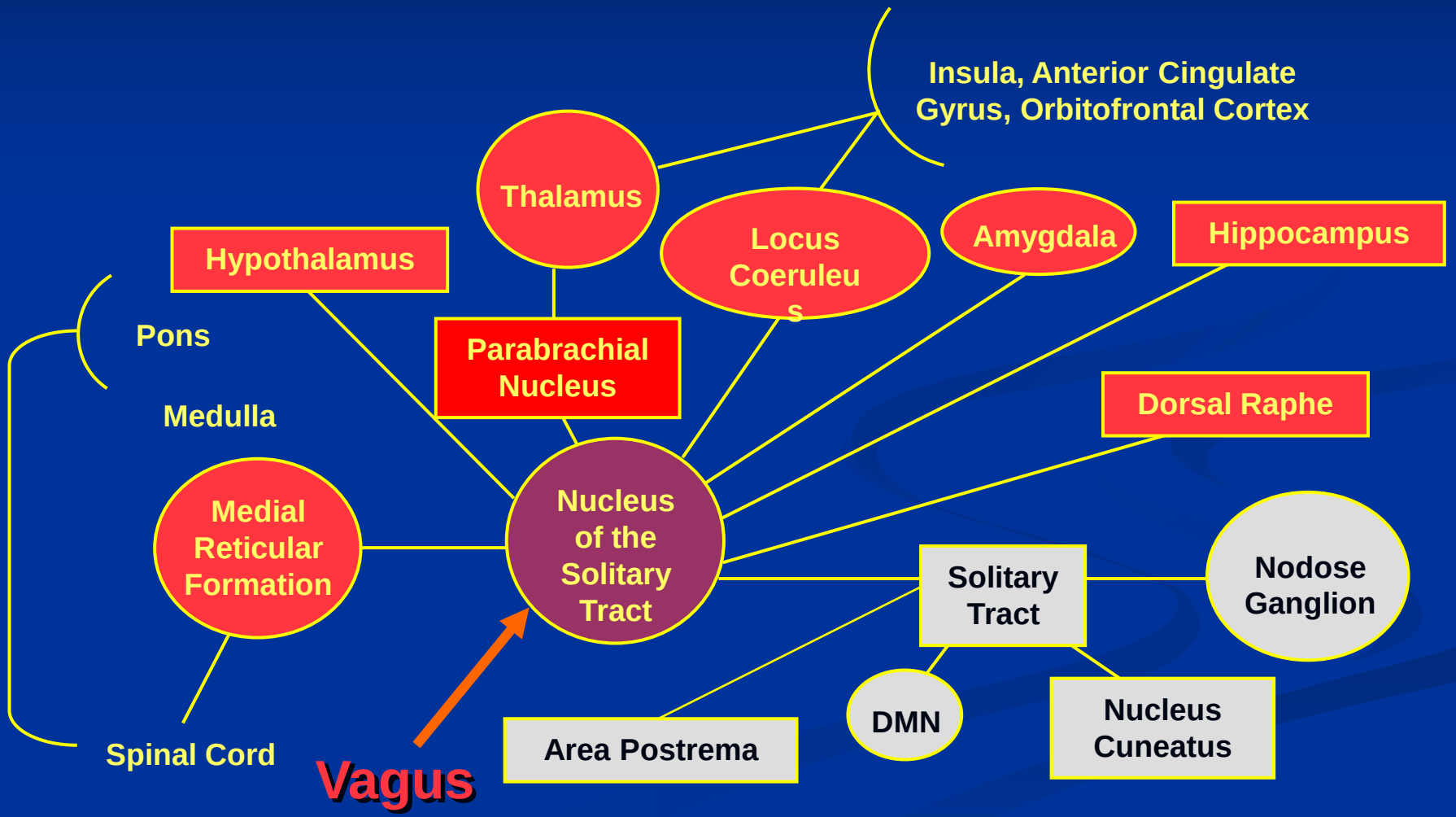
~20% efferent fibers, mostly unmyelinated parasympathetic fibers to thoraco-abdominal viscera

Some myelinated fibers to striated muscles of the pharynx and larynx

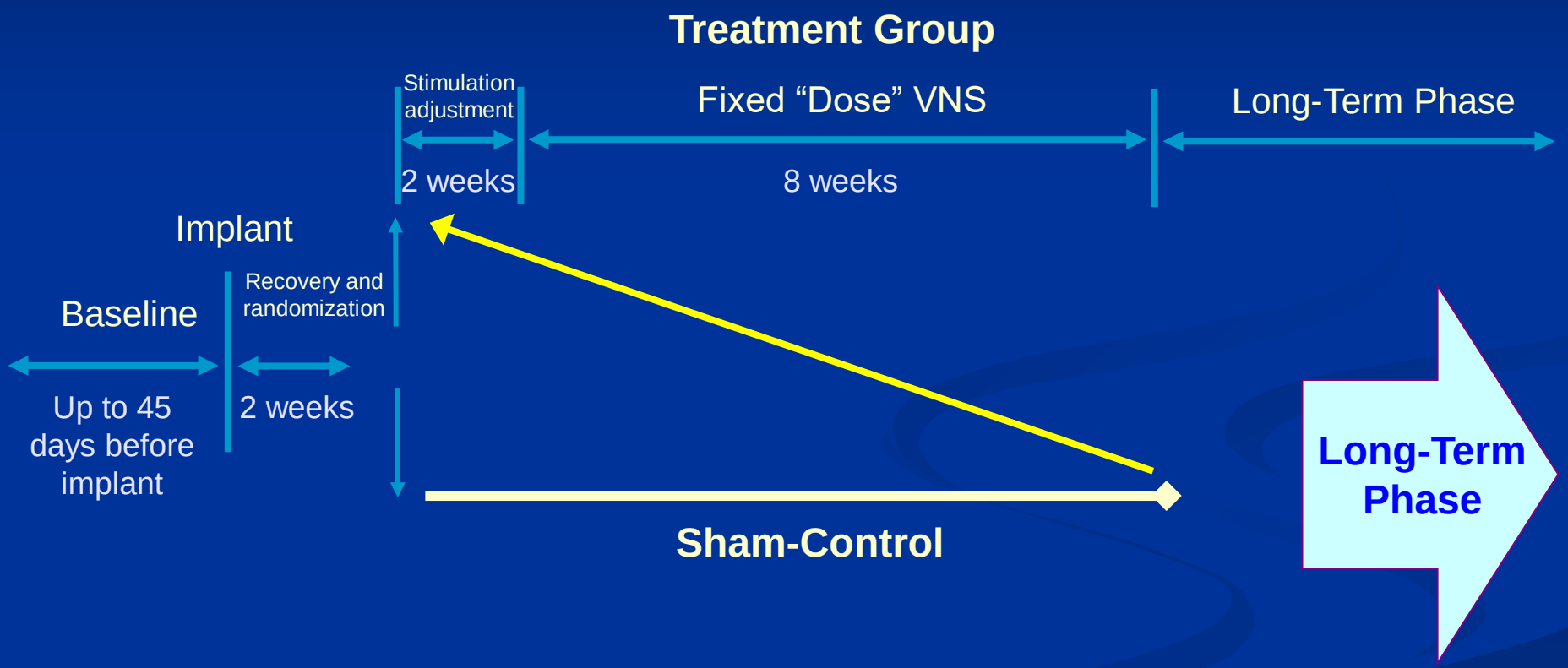


Henry TR. *Neurology.* 2002;59(suppl 4):S3-S14.

VNS: Afferent Pathway to the Brain

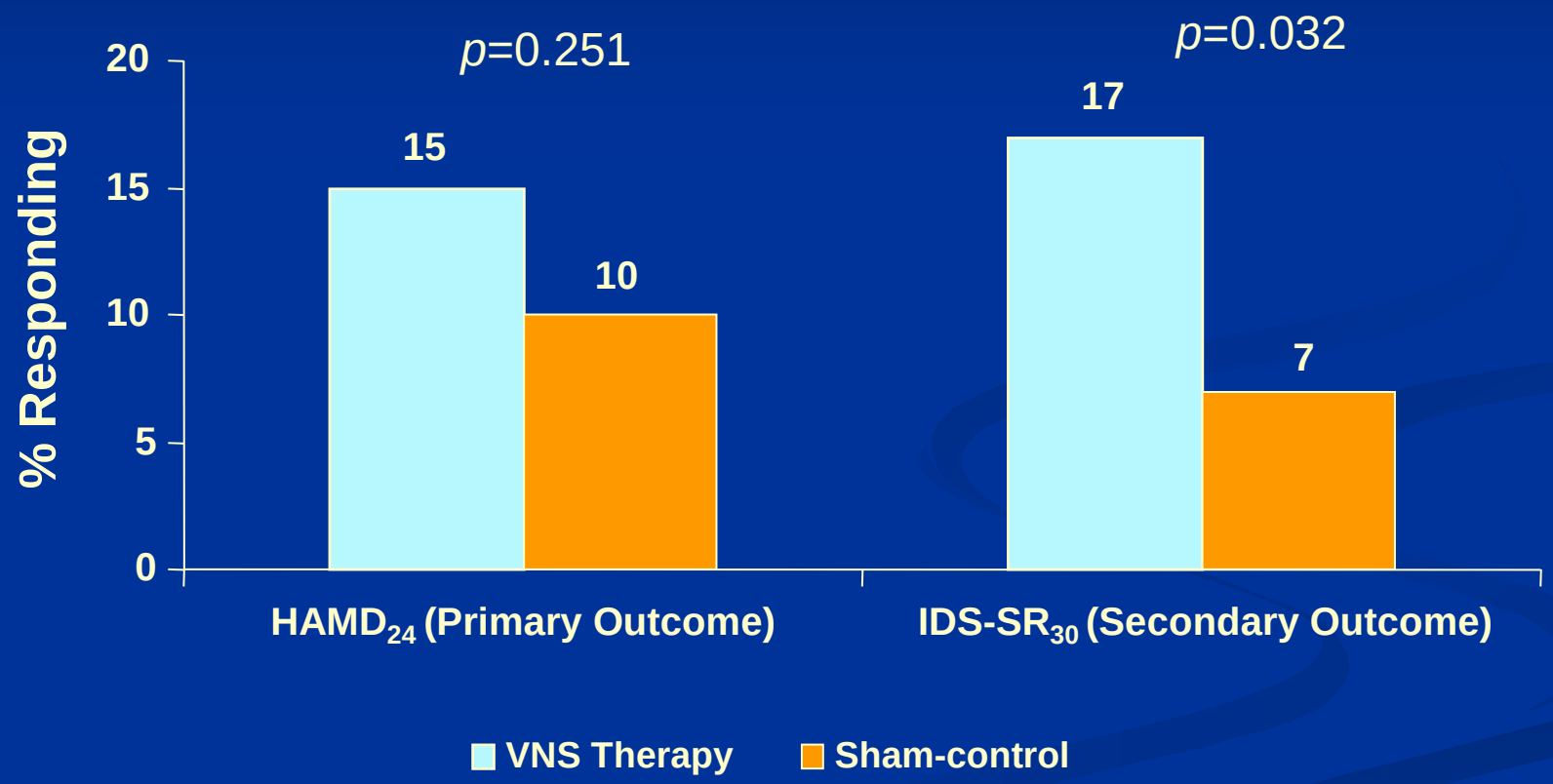


VNS Pivotal Study Design



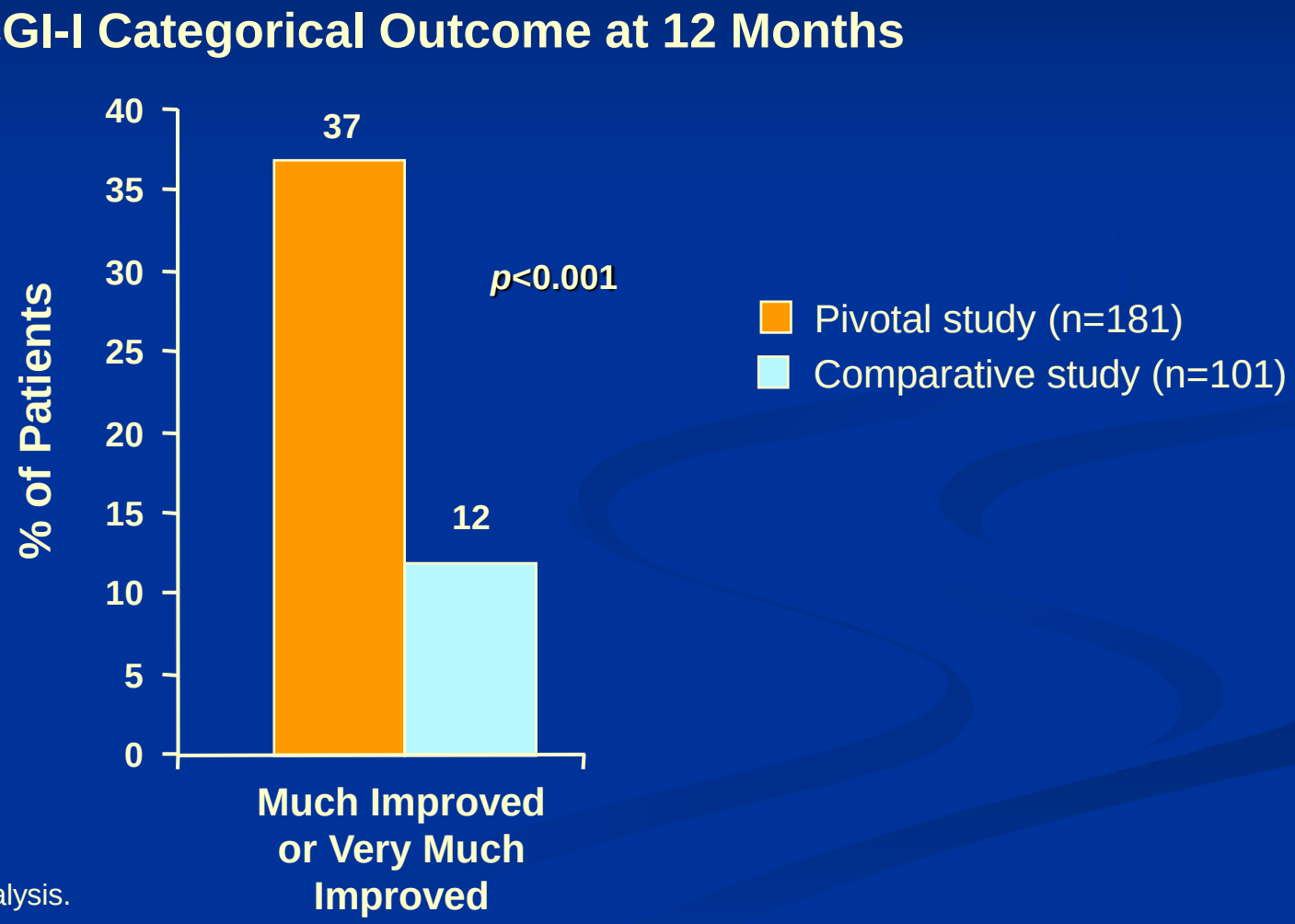
Rush AJ, et al. *Biol Psychiatry*. 2005;58:347-354.

Acute outcome at 12-weeks



Rush AJ, et al. *Biol Psychiatry*. 2005;58:347-354.

VNS versus Treatment as Usual

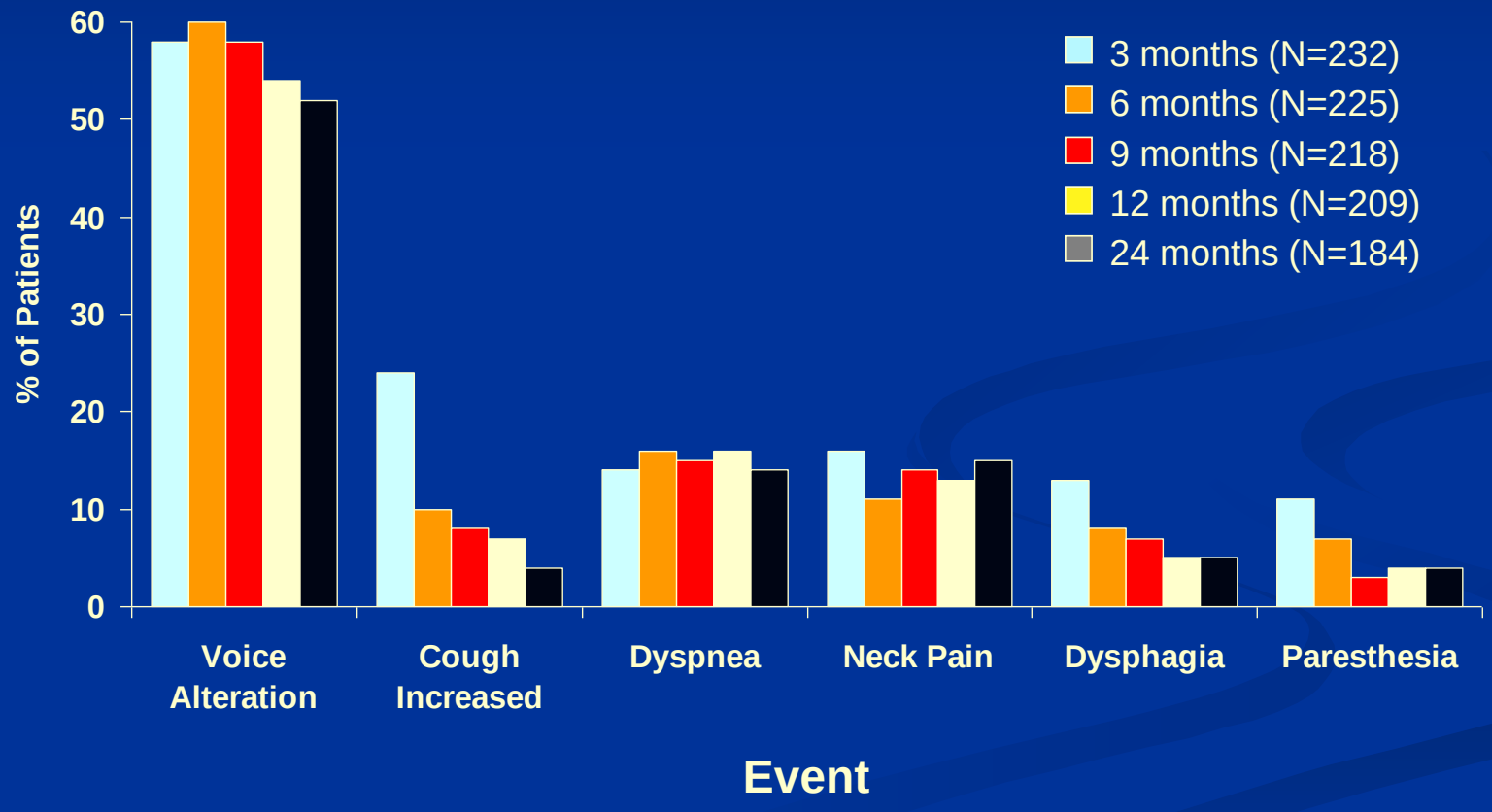


Evaluable observed analysis.

George MS, et al. *Biol Psychiatry*. 2005;58:364-373.

Safety profile of VNS

Most Frequently Reported Stimulation-Related AEs at 3 Months (≥10%)



1. Rush AJ, et al. *Biol Psychiatry*. 2005;58:355-363. 2. Cyberonics, Inc. *Depression Physician's Manual.* Houston, Tex; 2005.

VNS Advantages

- ✓ Well tolerated with high adherence rates
- ✓ Implant so guaranteed treatment delivery
- ✓ No cognitive impairment, or related stigma
- ✓ No weight gain, no known metabolic issues, no sexual dysfunction side effects

Disadvantages/Controversies

- Surgery is an obstacle for some patients, and overall costs upfront are high relative to pharmacotherapy and psychotherapy
- Controversy associated with FDA approval, given failed pivotal trial, has limited access in practice for patients – Medicare has decided against covering VNS for TRD
- May be a disincentive for future development of neuromodulation devices in psychiatry

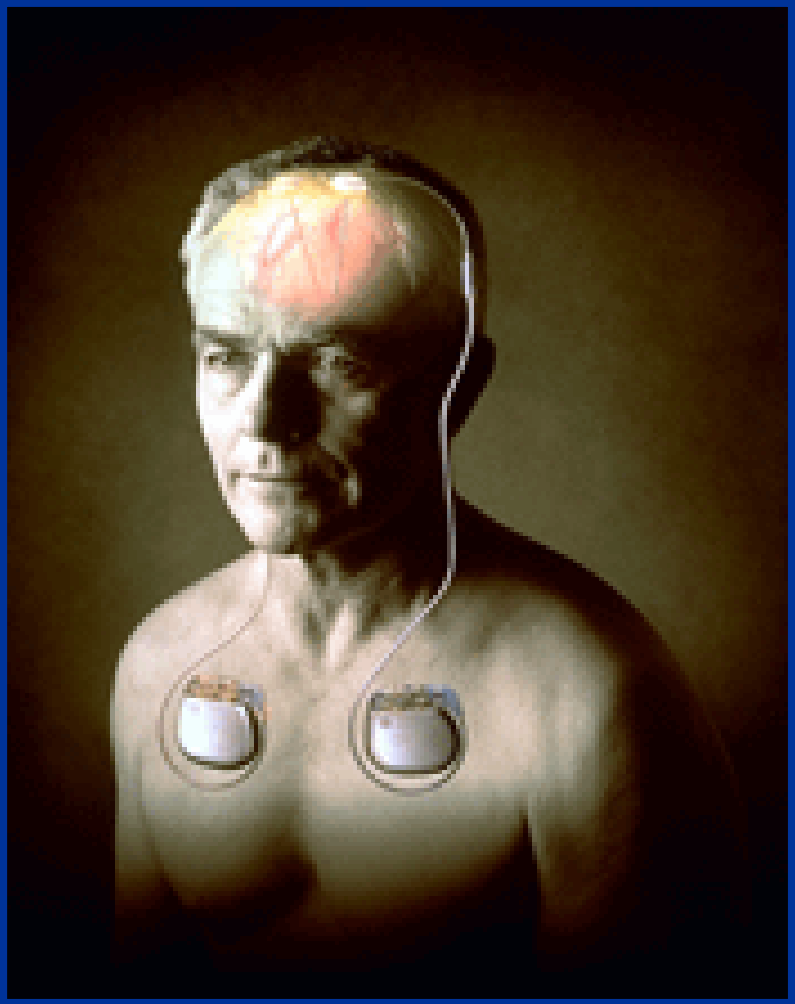
CMS denial of VNS coverage

- "CMS does not believe there is a treatment effect directly attributable to VNS therapy based on the current evidence"[1]
- "The pivotal randomized, controlled trial of VNS, subsequent to a pilot study, failed"[1]
- Medicare, however, has covered VNS for epilepsy since 1999, where evidence for efficacy is similar to TRD

1. www.cms.hhs.gov/MCD/viewdraftdecisionmemo.asp?id=195, accessed 2/13/07

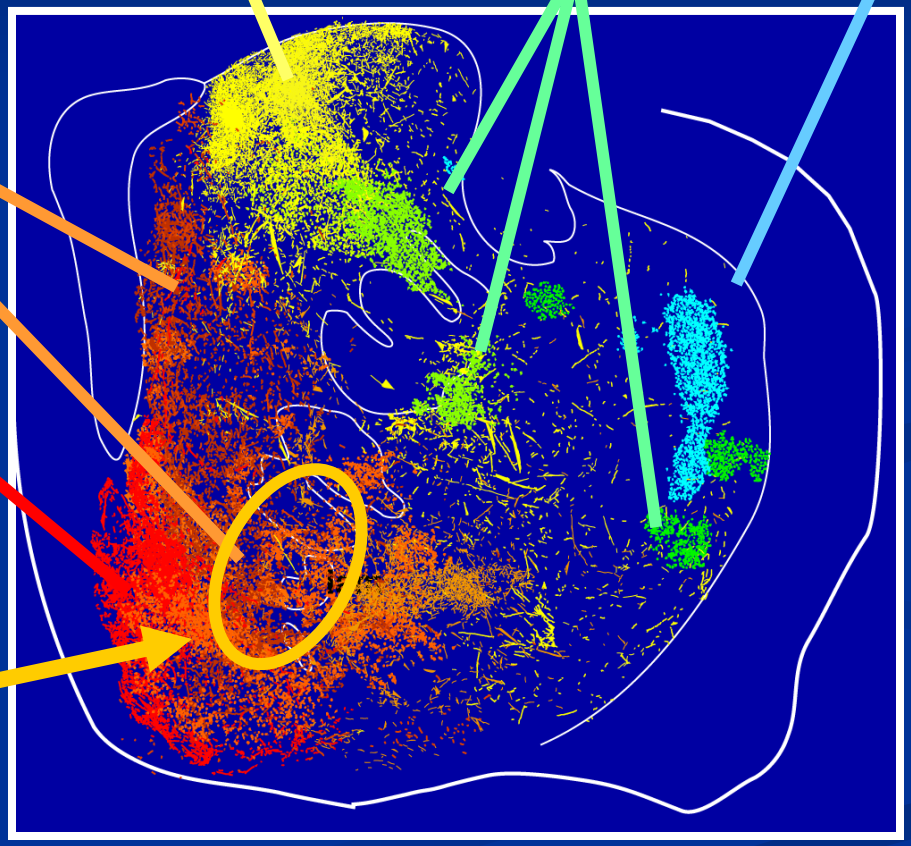
Deep Brain Stimulation (DBS)

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



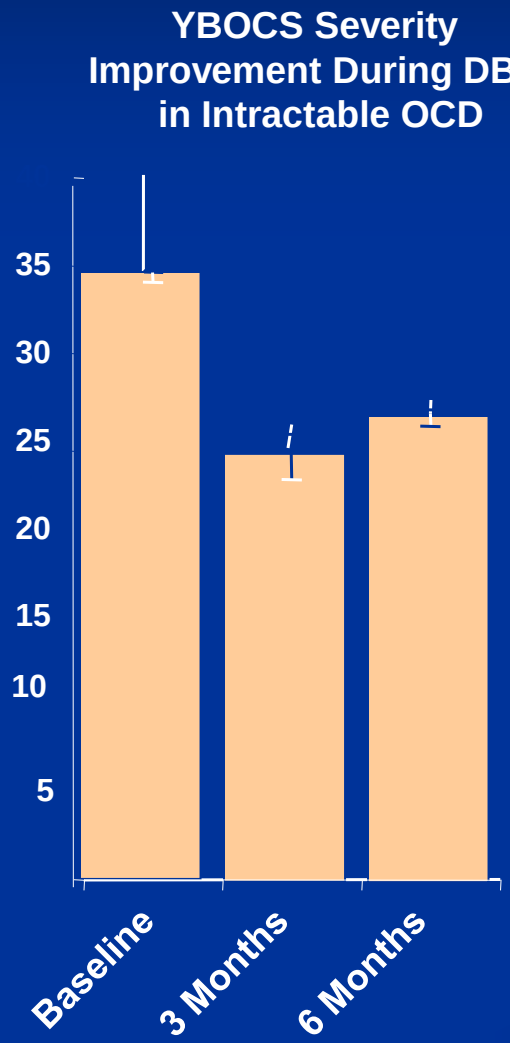
This information concerns a use that has not been approved by the U.S Food and Drug Administration

DBS Targets - Anterior Limb of the Internal Capsule/Ventral Striatum



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

Brown experience with DBS for OCD (n=10)

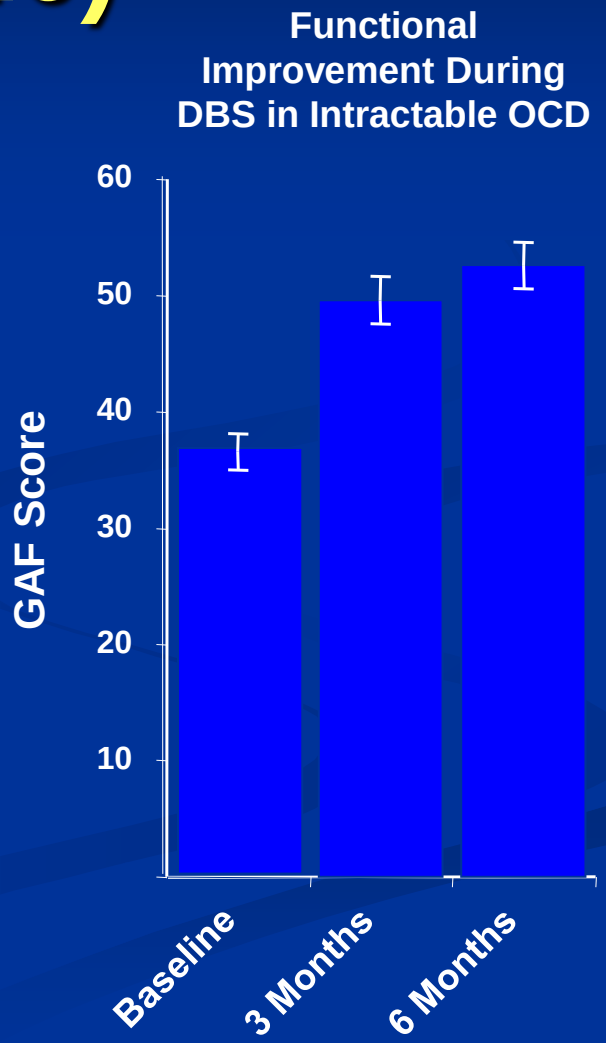


35% ⇓ YBOCS

3/10 (6 months)

25% ⇓ YBOCS

5/10 (6 months)



DBS for OCD: Adverse Effects

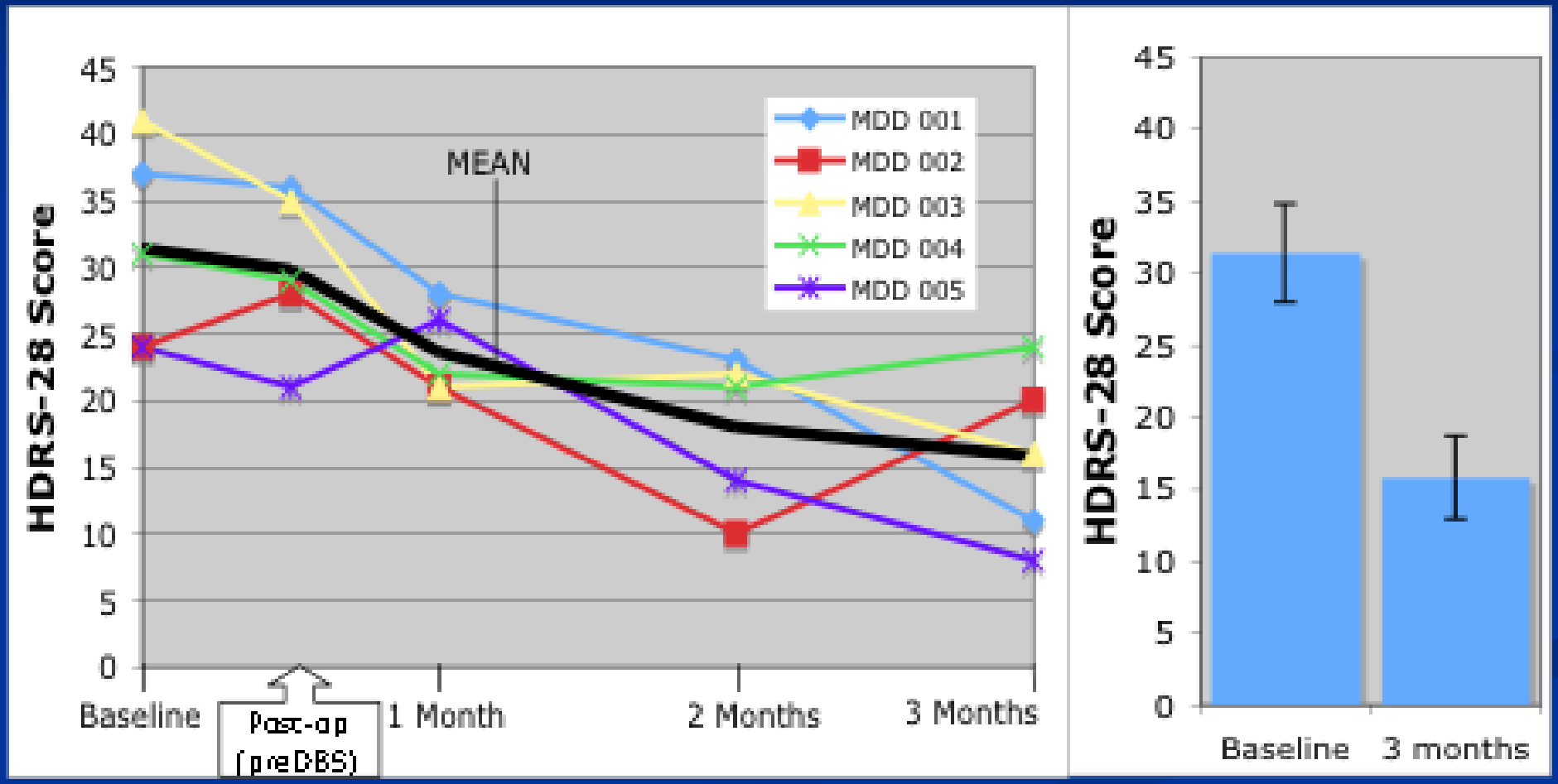
- Surgical
  - Small hemorrhage without symptoms or sequelae
  - Superficial infection
  - Single intraoperative seizure
- Stimulation
  - Hypomania (4/10)
  - Sensorimotor effects (facial)
  - Insomnia
  - Autonomic
  - Memory flashbacks
  - Panic
- OFF effects
  - Symptom return
- No AEs were persistent

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

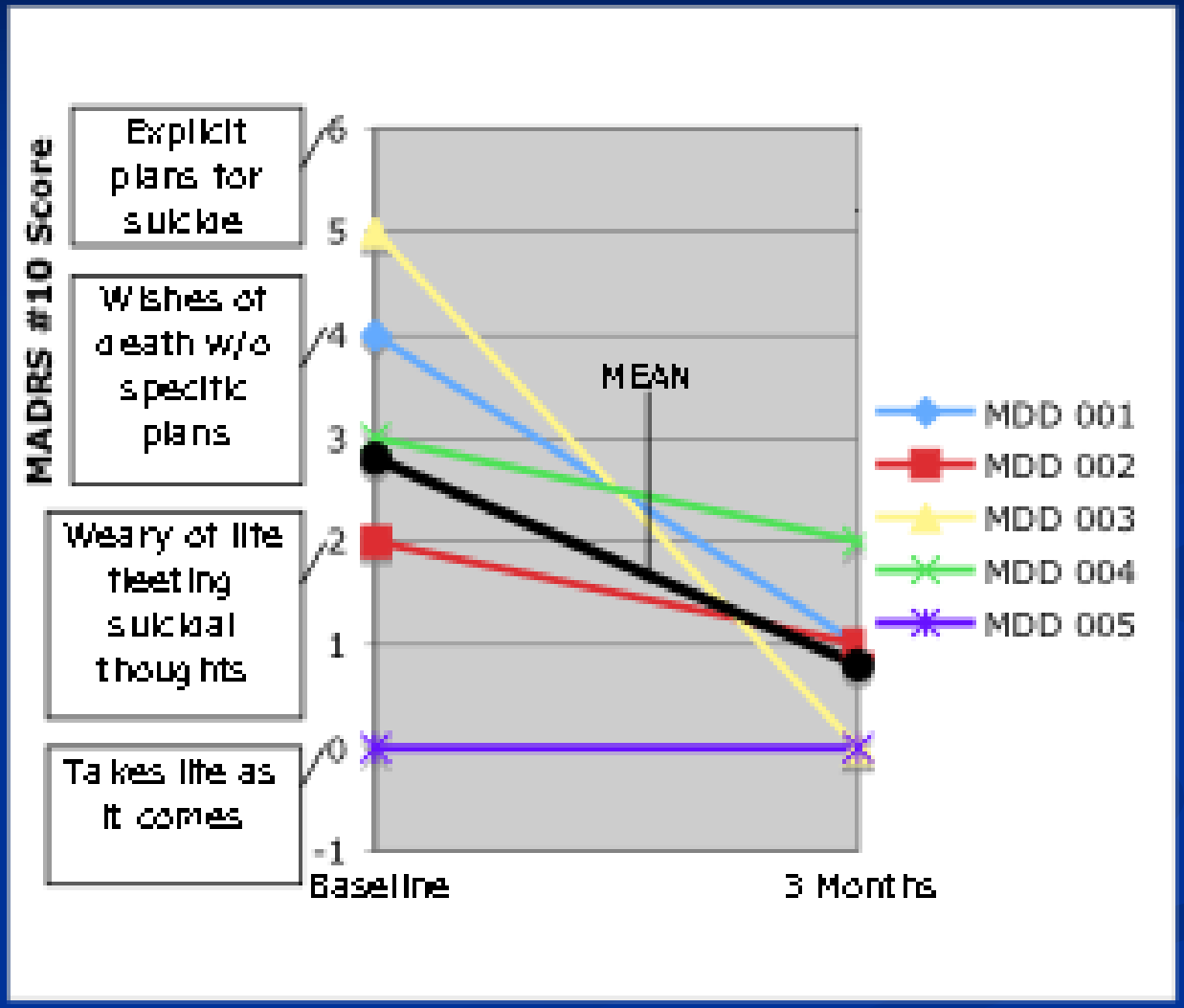
Greenberg BD et al, Neuropsychopharmacology 29:s32, 2004

Depression Improvement During DBS in Intractable Depression



Greenberg BD et al, Neuropsychopharmacology 29:s32, 2004

Reduced Suicidality During DBS



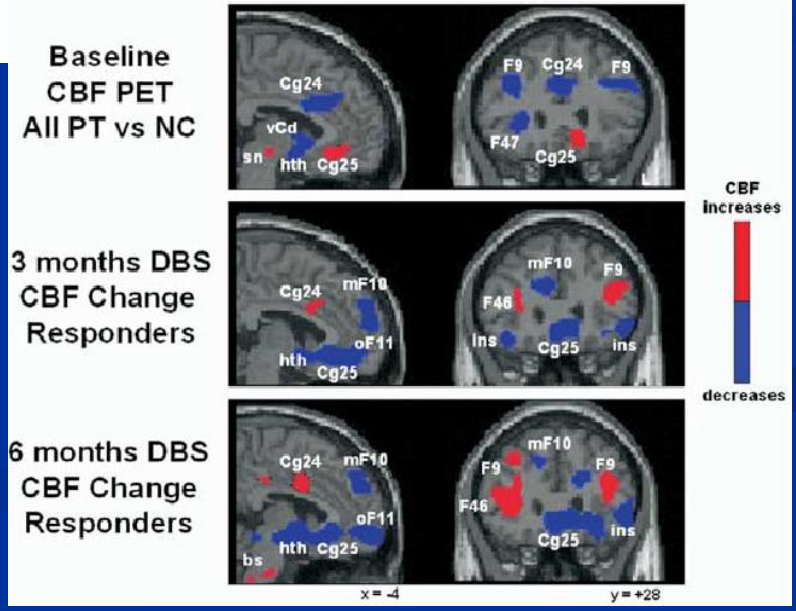
Greenberg BD et al, Neuropsychopharmacology 29:s32, 2004

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.

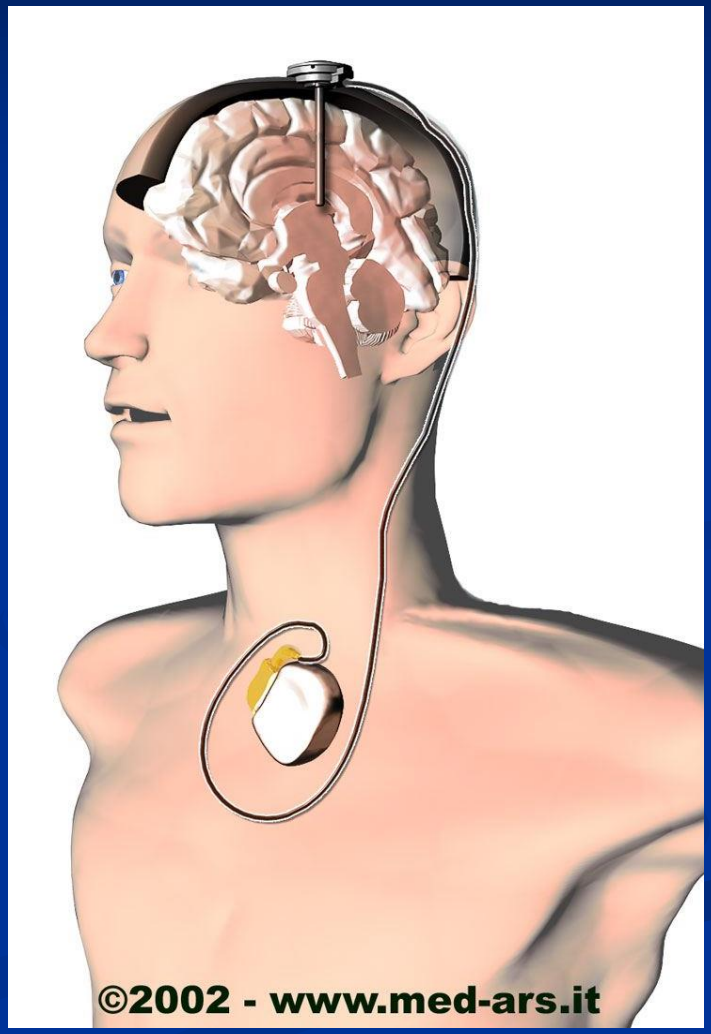


Mayberg HS et al. *Neuron*. 2005.

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



Neuromodulation overview

- ECT non-invasive, hospital procedure, requires anesthesia, safe, very efficacious, but stigmatized, no clear neurology application
- TMS is non-invasive, office based, most flexible, possible multiple applications, very acceptable to patients, but is it robust enough?
- VNS bottom-up modulation, limited surgery, but efficacy less than hoped for, & access problems
- DBS most invasive, only preliminary data to date (n~50), but looks robust

21st century neuromodulation therapies in psychiatry

- ✓ Psychiatry treatment may be at similar threshold as cardiology 25 years ago, in terms of potential for devices to improve our therapeutics
- ✓ Effective medications & psychosocial interventions help many but by no means all of our patients
- ✓ Devices have potential to help our severely ill patients and clearly warrant intensive research going forwards

Post-Lecture Exam Question 1

Magnetic Seizure Therapy (MST) differs from ECT in that:

a. the goal is not to induce a therapeutic seizure
b. the use of focused stimulation to produce a seizure
c. general anesthesia is not required
d. daily sessions of MST are needed to produce a therapeutic effect
e. it has a more benign profile in terms of cognitive adverse effects

Question 2

The most common side effect reports with VNS is:

a. weight gain
b. sexual dysfunction
c. cognitive impairment
d. hoarseness
e. chest pain

Question 3

Deep brain stimulation is currently FDA approved for the treatment of:

a. auditory hallucinations in schizophrenia
b. chronic neuropathic pain
c. obsessive compulsive disorder
d. parkinson's Disease
e. intractable migraine

Question 4

Transcranial Magnetic Stimulation (TMS) differs from Magnetic Resonance Imaging (MRI) technology in that:

a. the magnetic fields produced are much weaker in intensity
b. the rate of change of the magnetic field is higher with an MRI versus TMS
c. MRI technology activates neurons whereas TMS does not
d. scalp discomfort is common with TMS but not with an MRI

Question 5

Which of the following statements about ECT is not true?

a. ECT appears to be particularly efficacious in psychotic depression
b. ECT is not effective in the treatment of mania
c. ECT is effective in the treatment of bipolar depression
d. ECT is associate with retrograde memory impairments
e. ECT is effective in the treatment of pharmacotherapy-resistant major depression

Answers to Pre and Post-Lecture Exams

1. E
2. D
3. D
4. D
5. B