Brain Stimulation Therapies for Treatment Resistant Depression

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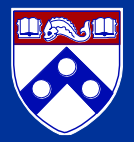

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Pre-Lecture Exam Question 1

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

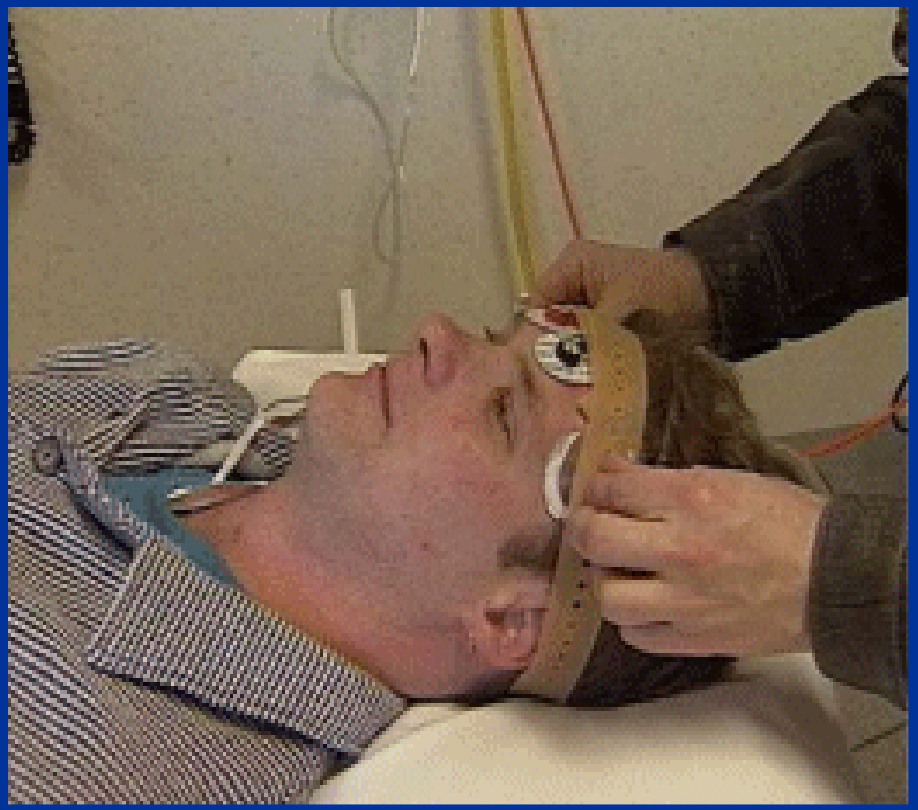
- Therapeutic alteration of nerve activity
- Central, peripheral or autonomic nervous systems
- Electrically or pharmacologically
- Implanted devices
- Pain, movement disorders, spasticity, epilepsy, sensory deprivation, urinary incontinence, gastric dysfunction, pancreatitis/visceral disorders

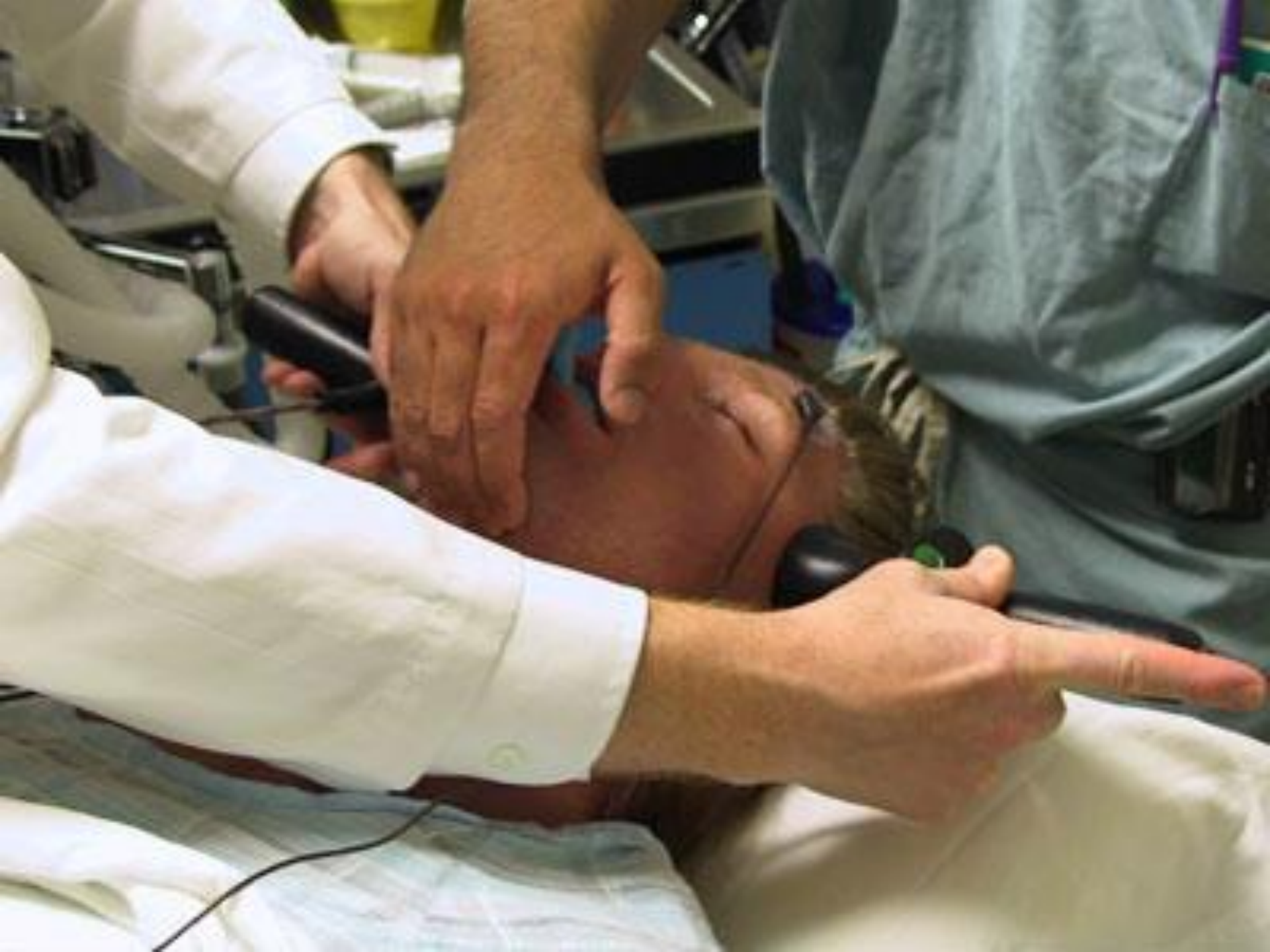
Neurostimulation

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

Electroconvulsive Therapy (ECT)

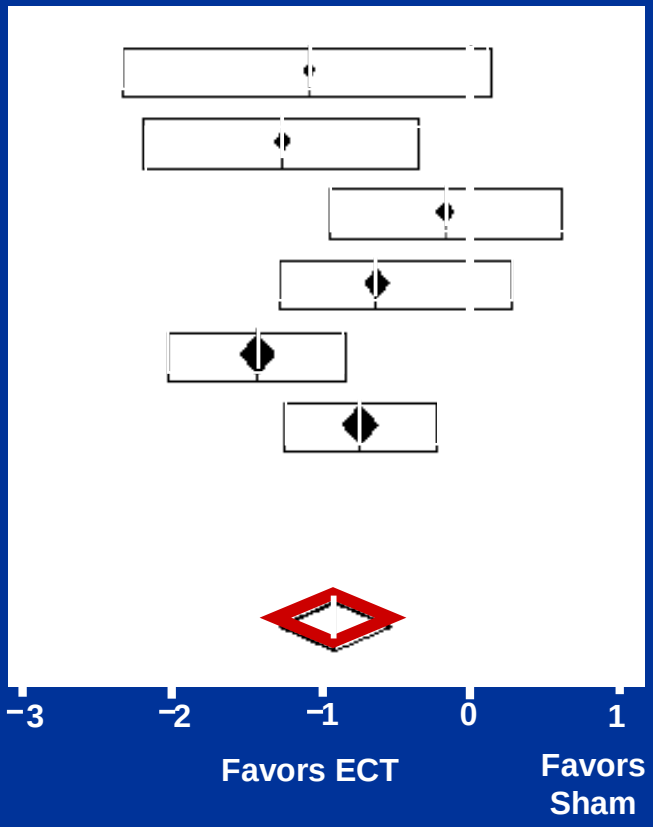
- 1st administered in 1938 (in Rome)
- FDA - approved since 1979 (grand-fathered)
- Brief electrical pulse passed through scalp (0.5 to 6 seconds duration)
- Patient under anesthesia
- Produces seizure on EEG
- Muscle paralysis prevents convulsive movement
- Bilateral or unilateral
- 6 - 12 treatments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





Efficacy of ECT versus Sham control

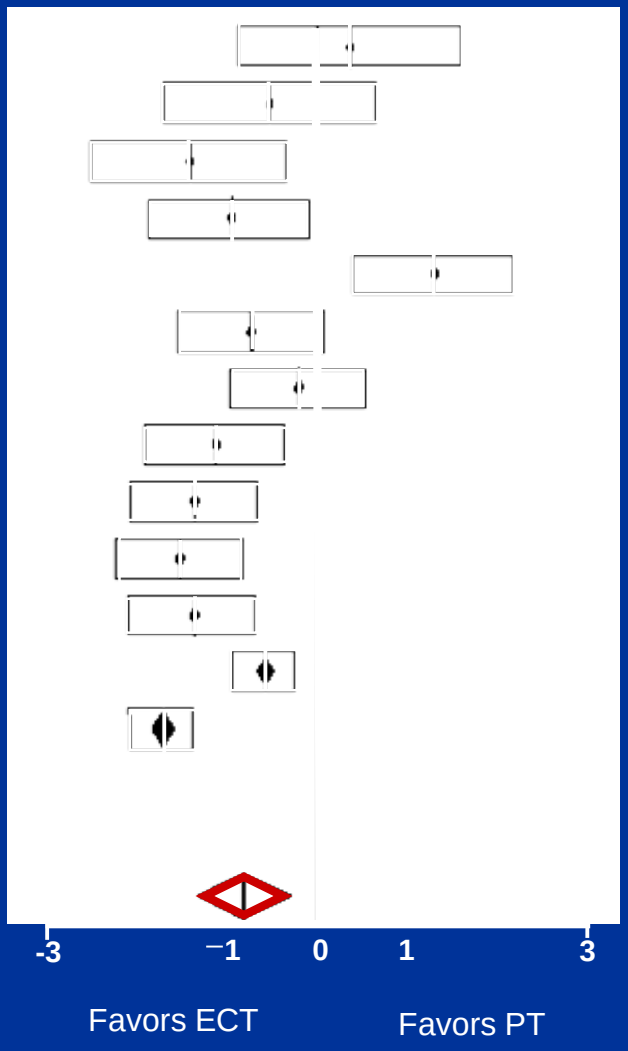
Trial	# of Participants	Standard Effect Size (95%CI)
Wilson 1963	12	-1.078 (-2.289 to 0.133)
West 1981	25	-1.255 (-2.170 to -0.341)
Lambourn 1978	40	-0.170 (-0.940 to 0.600)
Freeman 1978	40	-0.629 (-1.264 to 0.006)
Gregory 1985	69	-1.418 (-2.012 to -0.824)
Johnstone 1980	70	-0.739 (-1.253 to -0.224)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

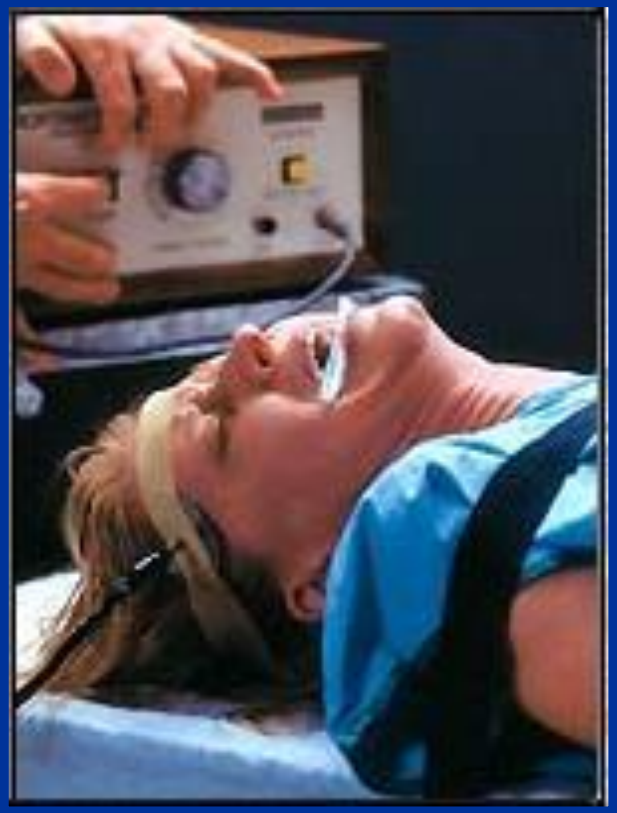
Access: Hospital, Often Inpatient

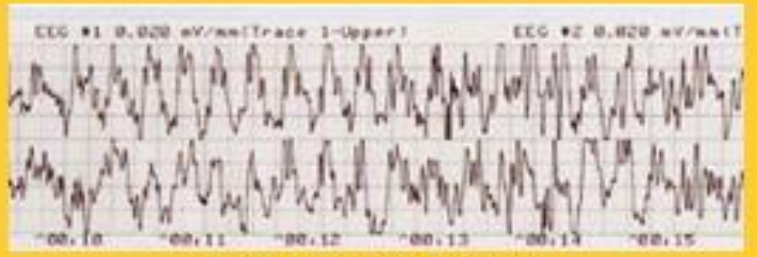
Stigma

Anesthesia Risks

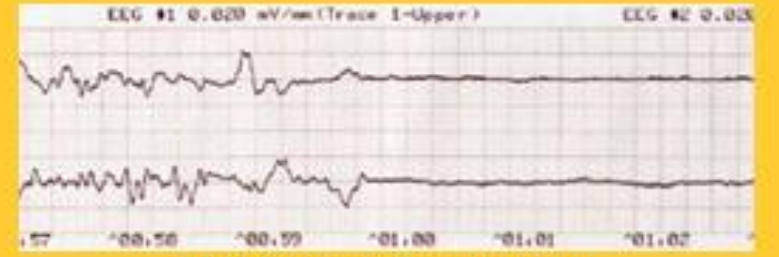
Cost

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

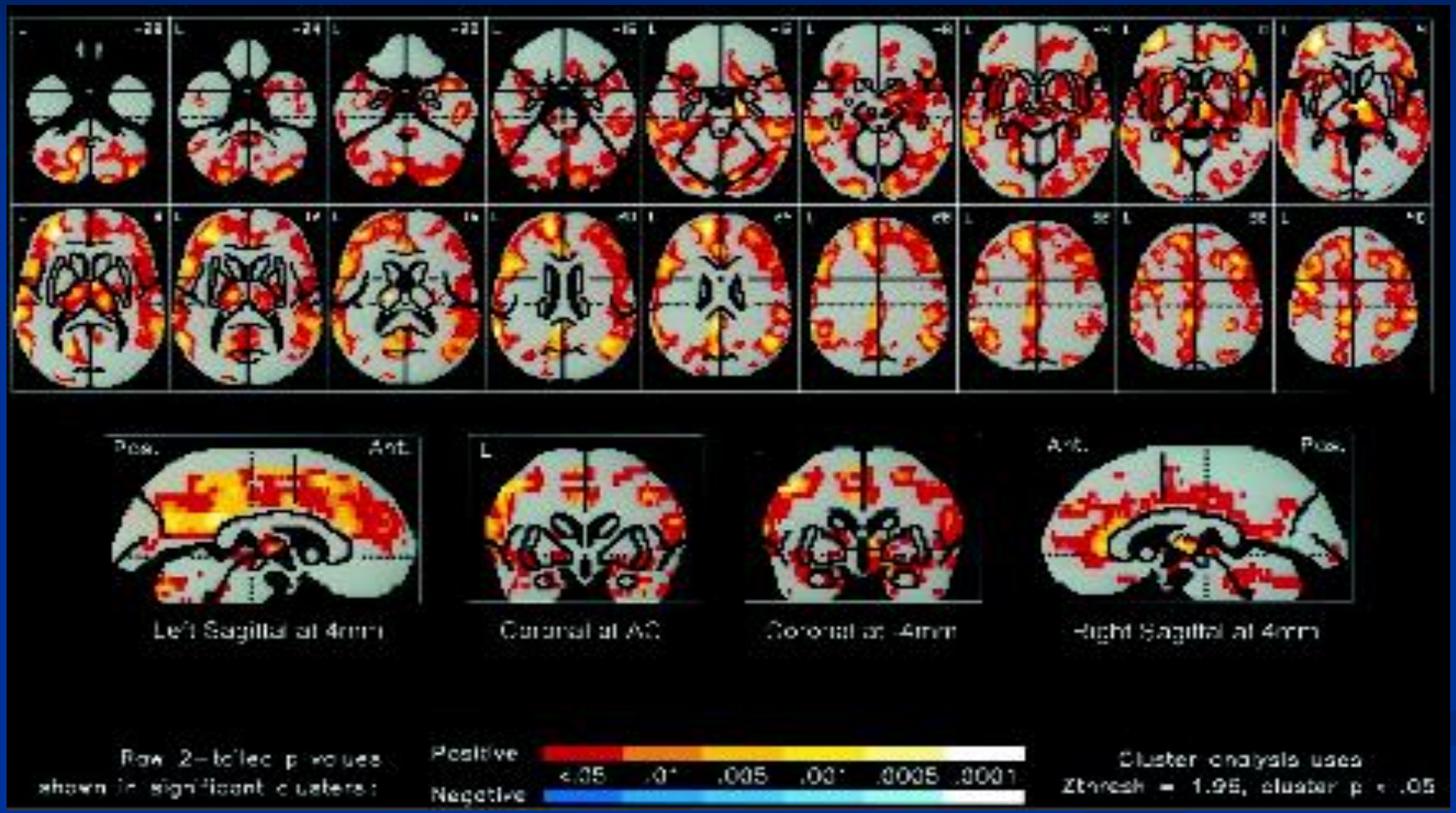
Coil placed on head in awake patient

Induces electrical current in cortex which depolarizes neurons

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

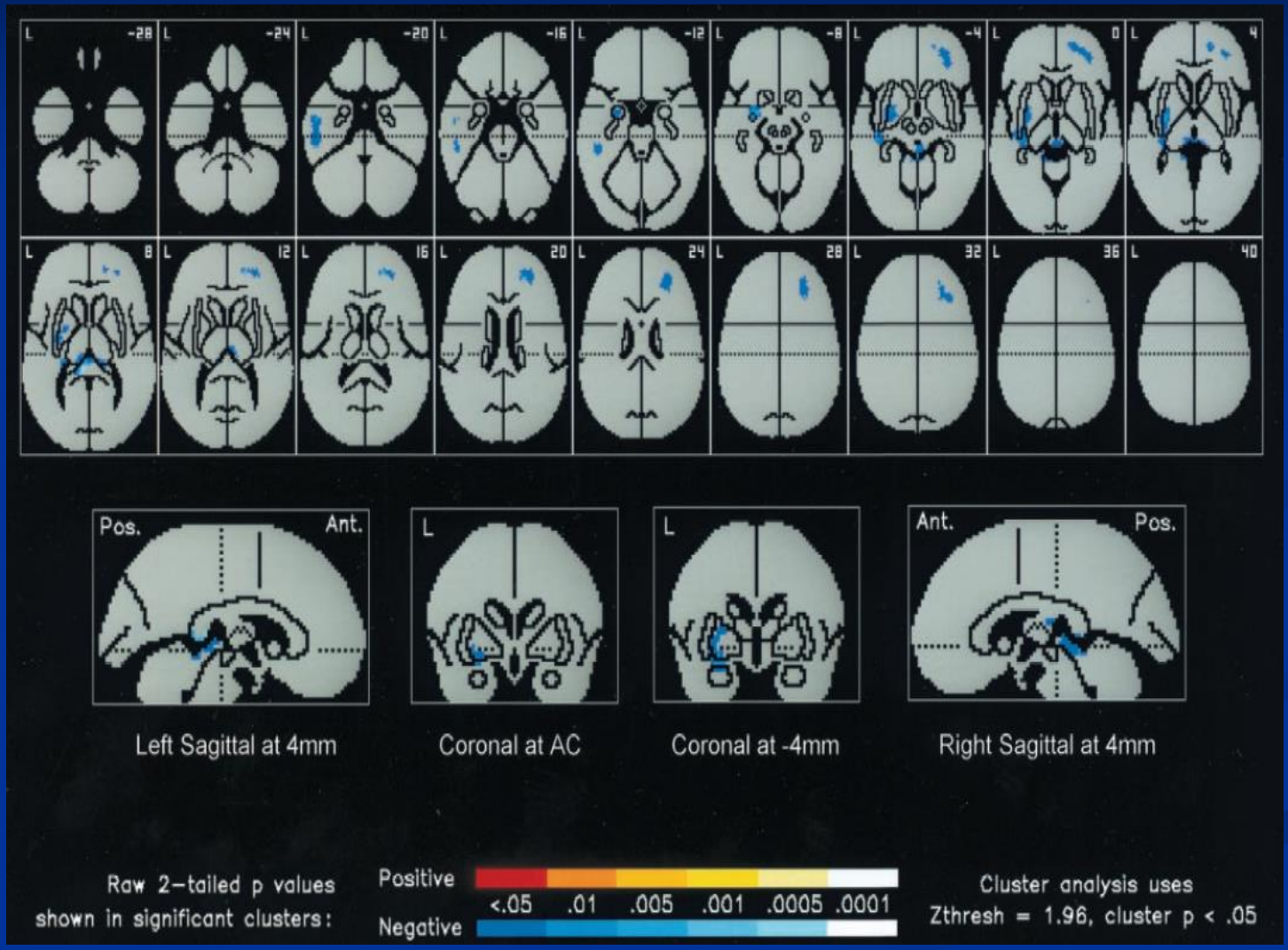
No anesthesia, no cognitive adverse effects

Fast (20 Hz) TMS - excitatory



Speer et al Biol Psych 2000

Slow (1Hz) TMS - inhibitory



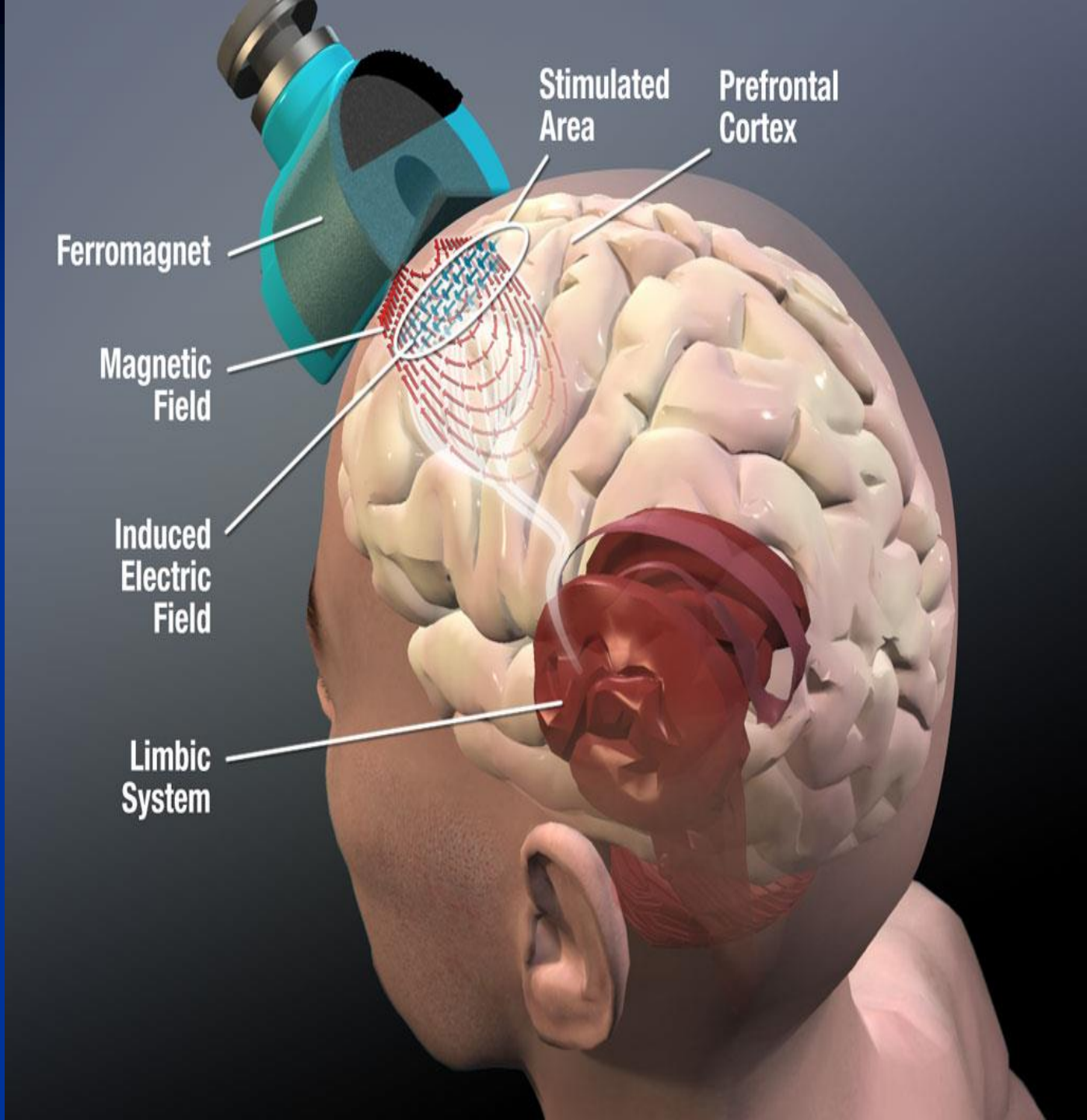
Speer et al Biol Psych 2000

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)

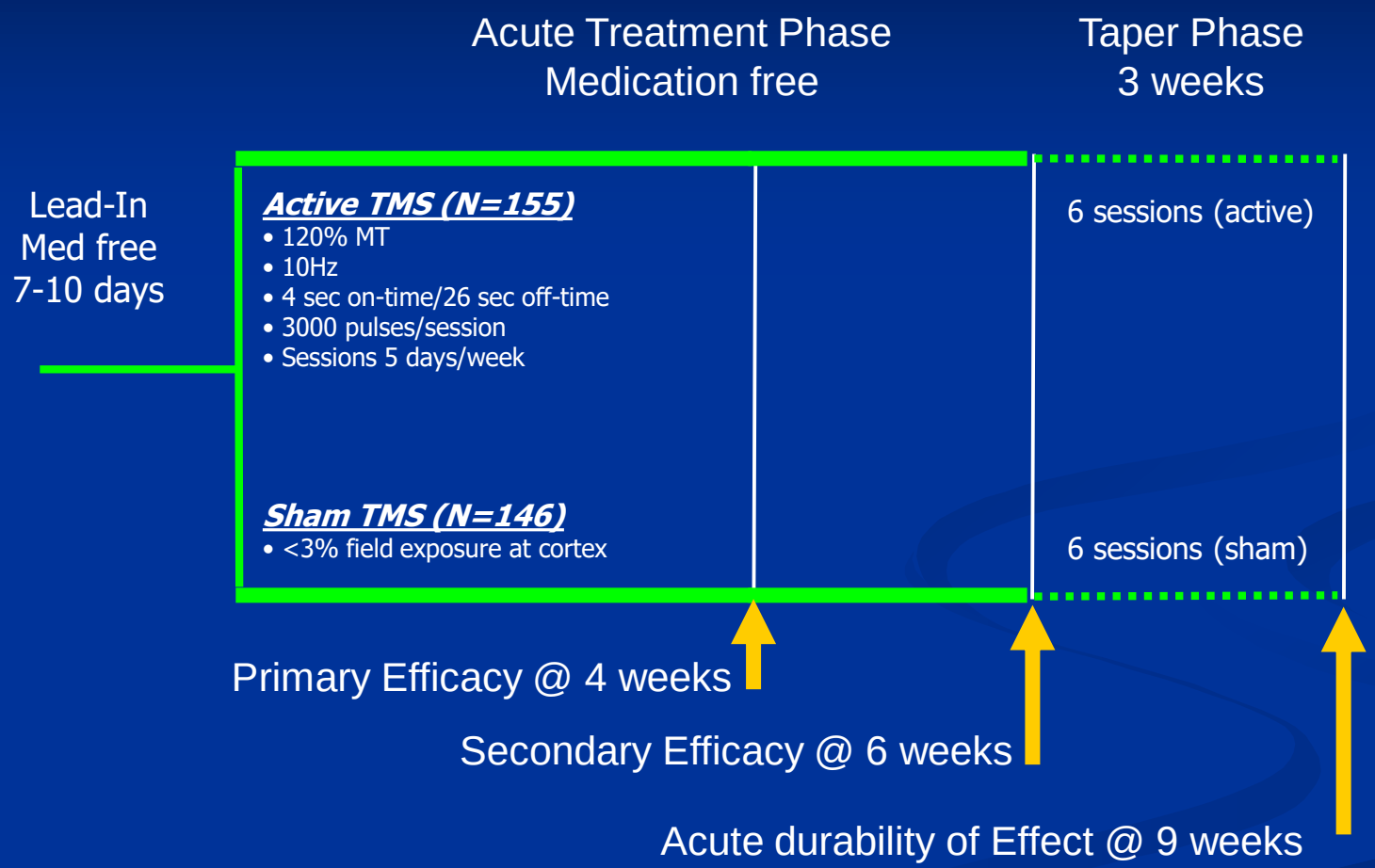


TMS application in Psychiatry

- 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]

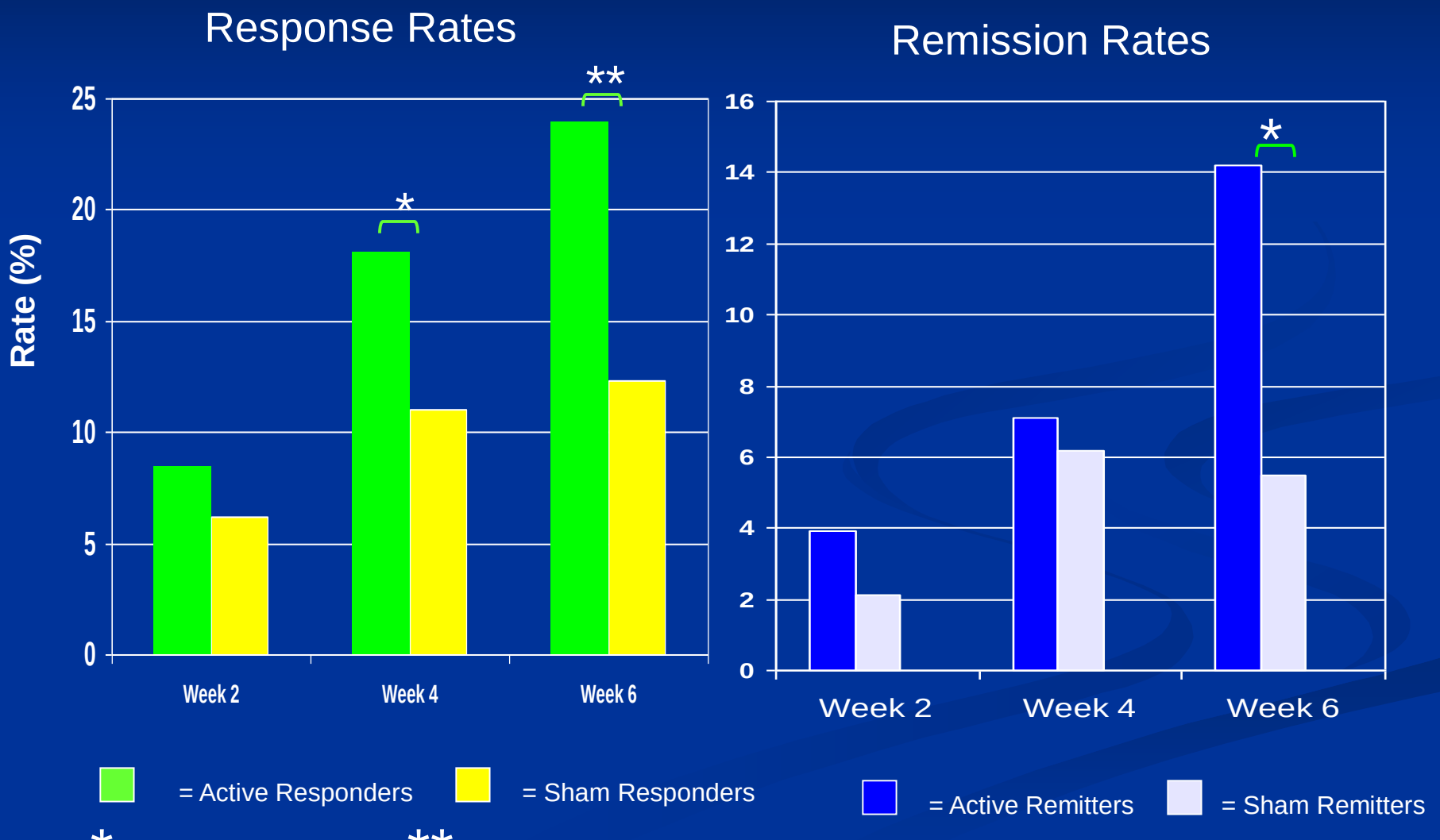
1. Gross et al. Acta Psy Scan 2007. 2. O'Reardon et al. Bio Psy 2007

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

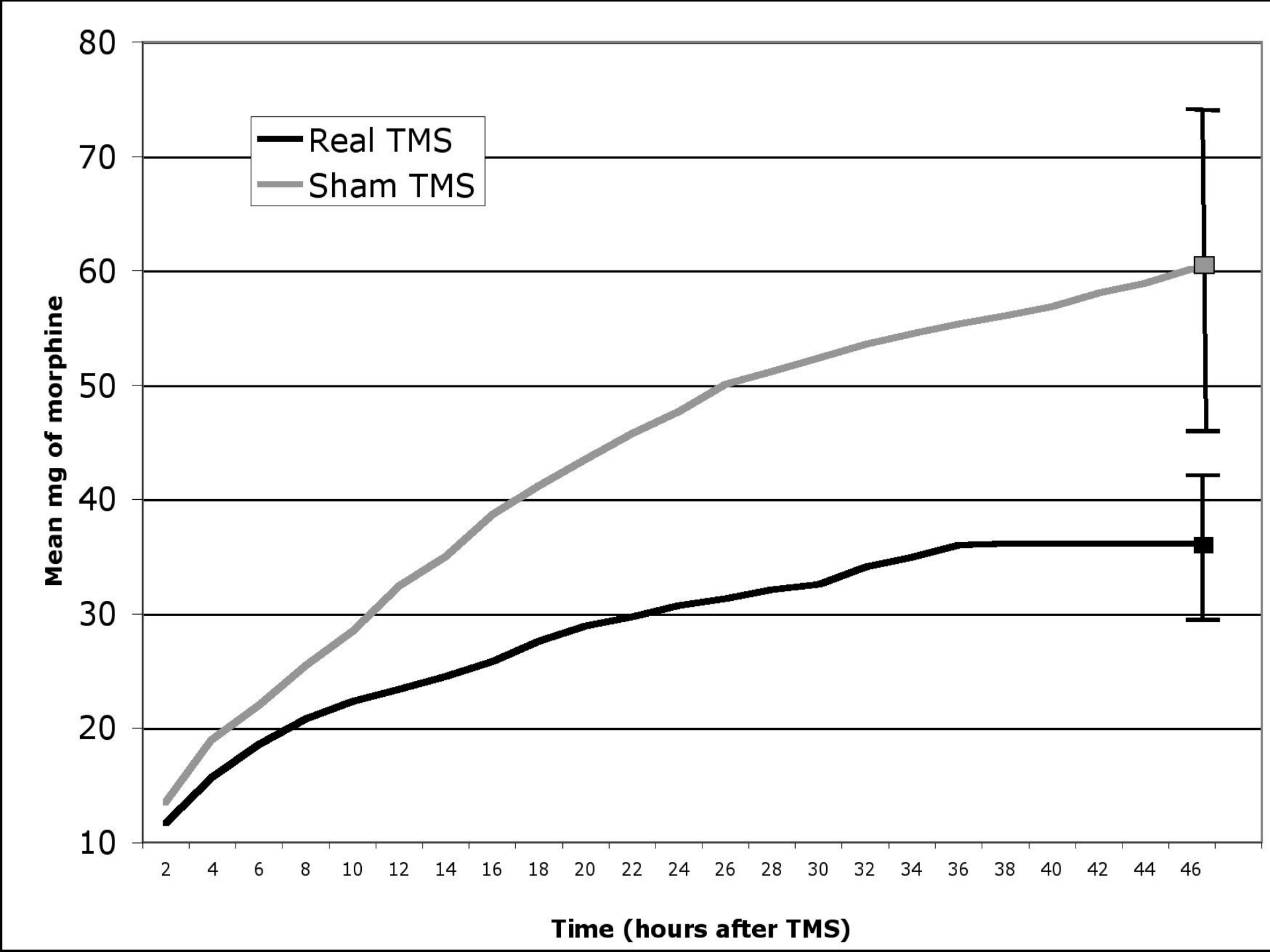
- Application of continuous 1 Hz TMS over temperoparietal cortex to inhibit generation of AH
- Recent metaanalysis of 10 controlled studies (n=212) was positive, with a substantial ES of 0.76 (95% CI range 0.36-1.17)
- Sample sizes generally small (range 10-50 subjects)
- Well tolerated, implies language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

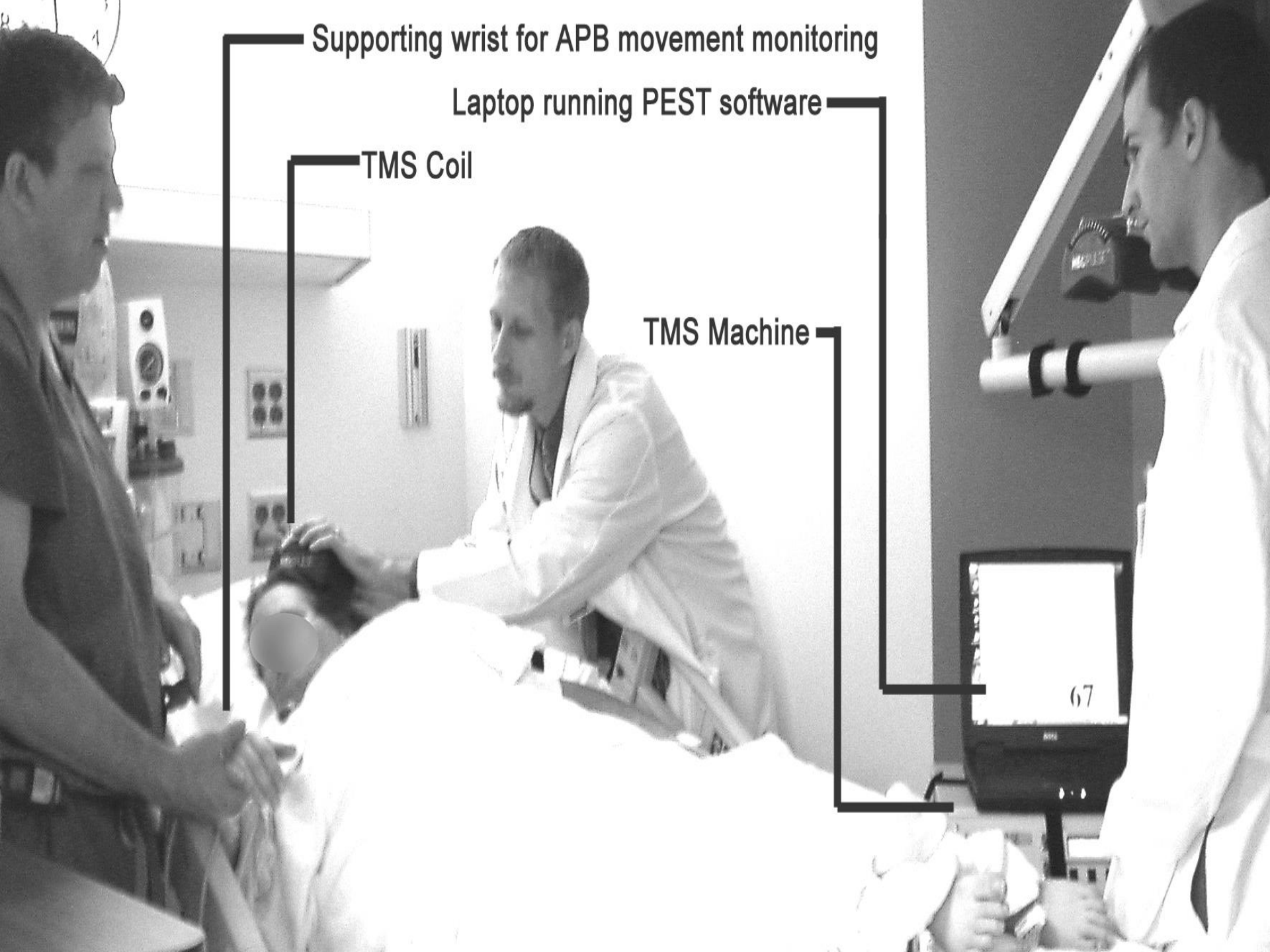
Aleman et al. J Clin Psy 2007;68:416-21

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%)