NEW DEVELOPMENTS IN NEUROMODULATION

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Disclosures 2018

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Biolite
Lundbeck
Astra Zeneca

Introduction

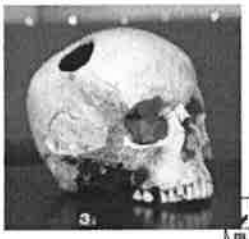
- Psychiatric disorders inadequately defined.
- Treatments (medications/therapy) limited.
- Several approved devices
- Direct access to the brain informs psychiatry.
- Surgical interventions exist for severe psychiatric disorders.

Introduction

- Neuromodulation (interventional psychiatry) is an emerging subspecialty utilizing non-pharmacological, somatic therapies.
- It shares aspects of functional neurosurgery in that both target physiology where there may be normal anatomy.
- Great potential exists for interventional and functional treatments for neuropsychiatric disorders.

History

Trepanation (9500 BC):

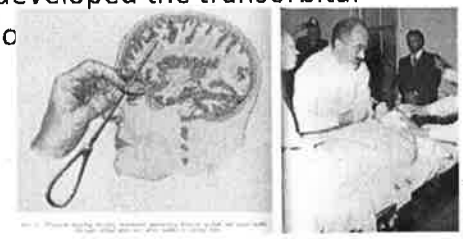
The Stone Cutting, Hieronymus Bosch

Psychosurgery

António Egas Moniz (1874-1955) considered the founder of modern psy


Psychosurgery

Walter Freeman (1895-1972) developed the transorbital lo



Psychosurgery

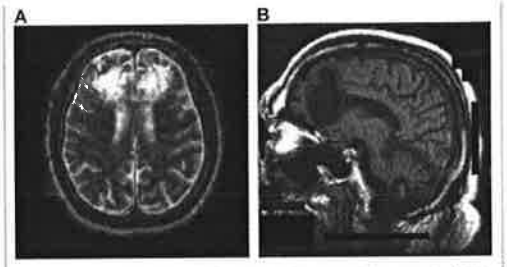
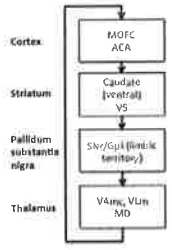


Figure 1. Lobotomy. (A) Axial T2-weighted and (B) sagittal T2-weighted images of lobotomy lesion.

Psychosurgery

- Neurosurgical techniques:
  - Cingulotomy
  - Capsulotomy
  - Subcaudate tractotomy
  - Limbic leukotomy
- 30-50% response rate in severe cases of depression and OCD.

Cortex-Basal Ganglia-Thalamocortical Circuit (limbic):



Psychosurgery

Anterior c

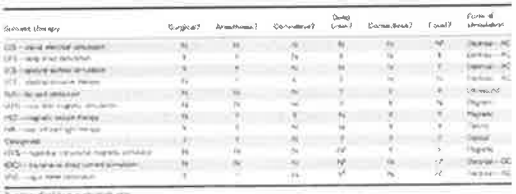
Figure 4. Cingulotomy pathology. Gross pathology of brain with cingulotomy lesion. The lesion is more complete on the right than the left side. Reproduced with permission from Lichter D, Livingston K. Surgical approaches in psychiatry. Proceedings of the 2nd International Congress of Psychosurgery. Baltimore University Park Press, 1973.

Functional Neurosurgery

- Psychosurgery decreased after discovery of electroconvulsive therapy (ECT) and chlorpromazine in mid-20th century.
- Stereotaxis and deep brain stimulation (DBS) led to renewed interest.
- Functional Neurosurgery reported to potentially benefit:
  - Obsessive compulsive disorder
  - Tourette's disorder
  - Depression (unipolar and bipolar)
  - Schizophrenia
  - Alzheimer's dementia
  - Aggression
  - Addiction
  - Eating disorders
  - Pain

Neuromodulation

Invasive vs. non-invasive:



Rosa et al., Neuropsychopharm, 2018

FDA Approved

1976: Electroconvulsive therapy (ECT)
2005: Vagus nerve stimulation (VNS)
2008: Transcranial magnetic stimulation (rTMS)
2009: Deep brain stimulation (DBS)
2013: Deep TMS (dTMS)

Future: Synchronized TMS (sTMS), theta-burst TMS, magnetic seizure therapy (MST), responsive neurostimulation (RNS), radiosurgery, focused ultrasound, thermal ablation, etc.

Electroconvulsive Therapy

Electroconvulsive Therapy

FDA indications:

1. Major depressive disorder (esp. geriatric depression)
2. Bipolar disorder (manic, mixed, and depressed episodes)
3. Schizophrenia and schizoaffective disorder
4. Catatonia

May be useful for:

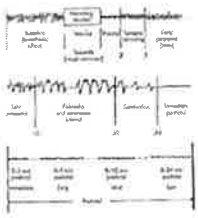
1. Neuroleptic malignant syndrome
2. Status epilepticus
3. Parkinson's disease
4. Severe autistic disorder

Electroconvulsive Therapy

Electroconvulsive Therapy

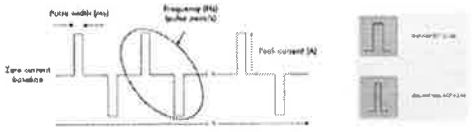
Electrode placement:

Right unilateral
Bifrontal
Bitemporal



Electroconvulsive Therapy

AC current waveform:

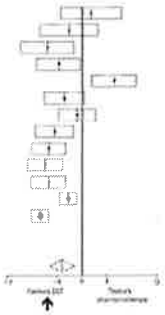


Electroconvulsive Therapy

Mechanism of action:

- Unknown how ECT exerts a therapeutic effect.
- Acutely changes monoaminergic, glutaminergic, and GABAergic neurotransmitter function in addition to altering parasympathetic and sympathetic nervous system tone.
- May alter neuronal connectivity and restore corticothalamic rhythms.
- Antidepressant effect may be mediated by increased BDNF.

ECT vs. Antidepressants



UK ECT Review Group, Lancet, 2003

Neurostimulation Therapies

Non-Surgical

Therapy	Level of Treatment Resistance	Response*	Remission*		Considerations
		Acute	Acute	Long-term	
ECT[2,3]	Failure of 1+ treatments and/or resistance to adequate trials of 2+ ADs and/or CBT	50– 60% (1+ AD failure)	64.2%	46.1%	• ~37.1% disease relapse • Safe procedure, low mortality rate • Frequently reported side-effects • Mild to severe cognitive side-effects • Superior efficacy relative to sham and to pharmacotherapies during acute phase (when delivered 3x/wk) • Combination efficacy does not increase therapeutic effects
		80+% (resistant to 2+ adequate AD therapies/CBT)			

*Response and remission rates are listed for active stimulation group vs. sham control

1 – George MS, et al. Daily Left Prefrontal Transcranial Magnetic Stimulation Therapy for Major Depressive Disorder. Arch Gen Psychiatry. 2010;67(5):507-516.

2 – Kennedy SH, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. Journal of Affective Disorders. 2009;117 Suppl 1:S44-S53.

3 – Kellner CH, et al. Continuation Electroconvulsive Therapy vs. Pharmacotherapy for Relapse Prevention in Major Depression. Arch Gen Psychiatry. 2006;63:1337-1344.

Electroconvulsive Therapy (ECT)

ECT- Delivery of electrical current to brain to induce seizure

Indication	• Major depressive episode treatment resistant to adequate trials of 3+ pharmacotherapies, including combination Rx and/or cognitive therapy		
Method	ELECTRODE PLACEMENT	PULSE FREQUENCY	
	• Bilateral – bifrontal • Bilateral – bitemporal • Unilateral Induction – right-side (RUL)	• Brief pulse • Ultra brief pulse	
Parameters	• Current (500 – 800 mA) • Frequency (20 – 130 Hz) • Pulse width (0.25 – 2 ms) • Duration (0.5 – 8+ seconds)		
Seizure Threshold	• Minimum charge to induce seizure above motor threshold (MT)	BILATERAL: 1.5 – 2.5 x MT	RUL: 6 x MT
Session Frequency	• Acute episode 2 – 3 x per week • Maintenance 1x every 1 – 3 weeks		
Efficacy	RESPONSE	REMISSION	RELAPSE
	• Response rates in 80% -90% range When medication resistance is due to inadequate dose or duration of antidepressant trial • Response rates in 50 – 60% range When dealing with 1+ treatment failures	• 64.2% (Acute) • 46.1% (Long-term)	• 37.1%

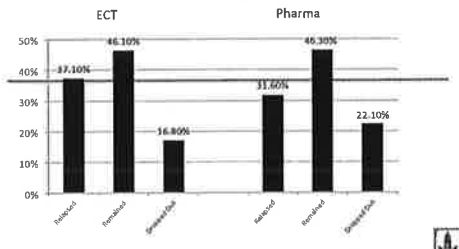
Safety Profile	• Safe procedure, low mortality rates
	• Cognitive side-effects (mild to severe)
	  • Autobiographical memory deficits, acute confusional states, anterograde and retrograde amnesia, verbal and word fluency impairments
	• Short-term side-effects (frequently reported)
	  • Nausea, headache, muscle pain, persistent myalgia, oral lacerations, dental injuries		

2 3 Kennedy et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. Journal of Affective Disorders. 2009;117 Suppl 1:S44-S53.

CORE Study

Consortium for Research in Electroconvulsive Therapy (CORE)

Percent of patients remitted after acute ECT and 6 Months of maintenance ECT or Pharma therapy



2 4 Kellner CH, et al. Continuation Electroconvulsive Therapy vs. Pharmacotherapy for Relapse Prevention in Major Depression. Arch Gen Psychiatry. 2006;63:1337-1344.

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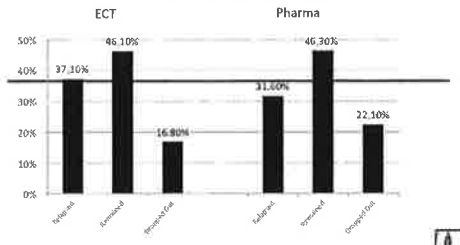

Kellner CH, et al. Continuation Electroconvulsive Therapy vs Pharmacotherapy for Relapse Prevention in Major Depression: A 6-Month Study. Arch Gen Psychiatry. 2016;73(12):1208-1216

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Transcranial Magnetic Stimulation

Faraday's law of electromagnetic

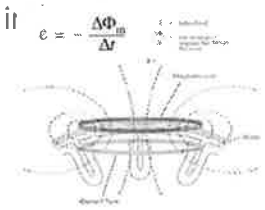

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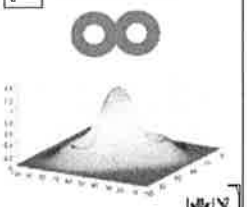
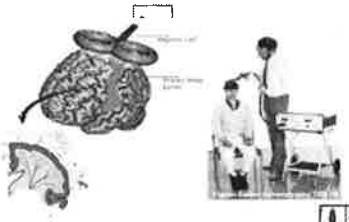
Figure-of-Eight Coil



Transcranial Magnetic Stimulation

Anthony Barker (1950-) developed TMS in 1985 to study the motor cortex.



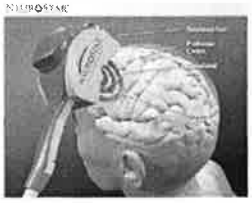
Transcranial Magnetic Stimulation

Figure 8 coil:

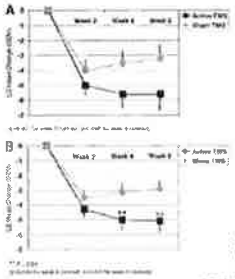
H coil:

rTMS for Depression

NeuroStar rTMS sys



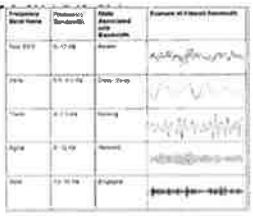
FDA approved for treatment of major depression after *one failed trial of an antidepressant.*

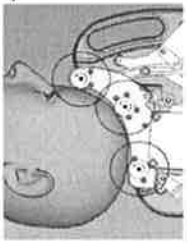


O'Reardon et al., Biological Psych, 2007

Synchronized TMS

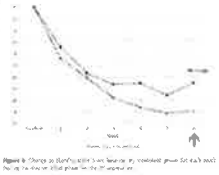
TMS applied at a unique EEG fr





Leuchter et al., Brain Stimulation, 2015

sTMS for Depression



Leuchter et al., Brain Stimulation, 201

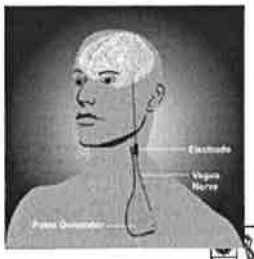
Brainsway Deep TMS Coil

Deep TMS

- Uses H1
- Penetrates 5-6 cm vs 1-2 cm for standard TMS
- Approved by FDA in 2013 for MDD who failed any number of medication trials.
- Multicenter sham controlled trial (22 centers, N=230

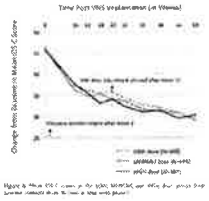
Vagus Nerve Stimulation

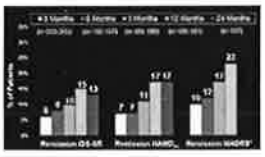
- Applied to the left vagus nerve to treat epilepsy (1997).
- Antidepressant effect observed in epilepsy patients (including those without an anticonvulsant effect).
- Antidepressant actions mediated via stimulation of left afferent nerve fibers leading to activation of monoaminergic cell bodies.
- Associated with few side effects (hoarse voice, cough. etc).



Vagus Nerve Stimulation

VNS is FDA approved and effective for treatment-resistant depression:

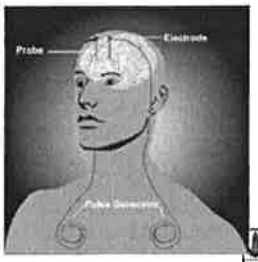




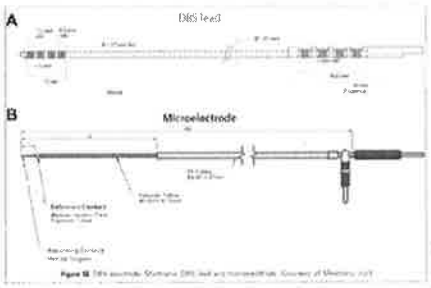
Aaronson et al., Brain Stimulation, 2013

Rush et al., Biological Psych, 2005

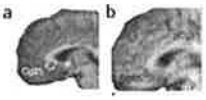
Deep Brain Stimulation



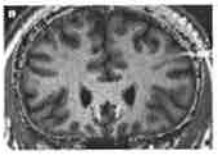
Deep Brain Stimulation



DBS for Depression



Mayberg et al., Biological Psych, 2000



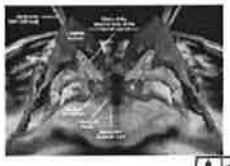
Holtzheimer et al., Arch Gen Psych, 2012

DBS for Depression

First DBS sham-controlled study in depression:

Archival Report

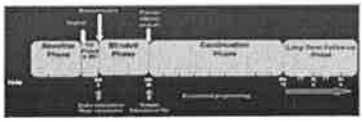
A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression



Dougherty et al., Biol Psychiatry, 2

Reclaim (Medtronic) DBS Study

DBS (VC/VS) for *severe* depression:

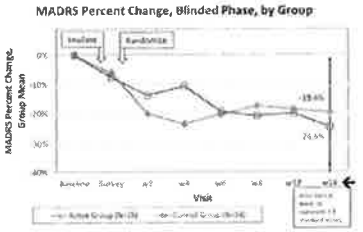


Dougherty et al., Biol Psychiatry, 2

DBS for Depression

DBS for Depression

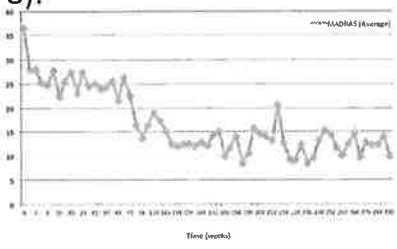
Randomized DBS (VC/VS) for 16 wee



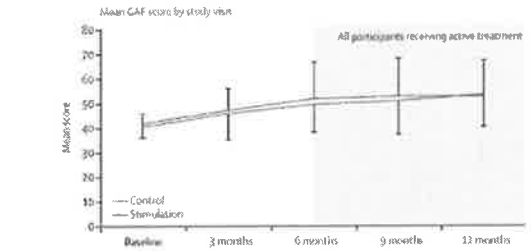
Dougherty et al., Biol Psychiatry, 2

DBS for Depression

Open-label DBS (VC/VS) for >6 years (n=8):



Broaden Study



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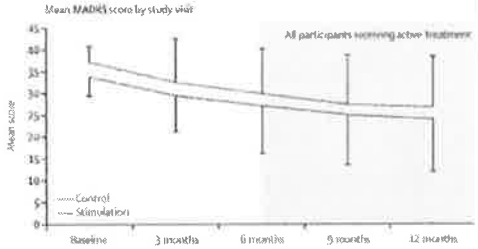
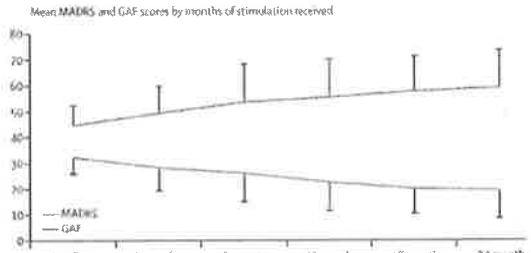
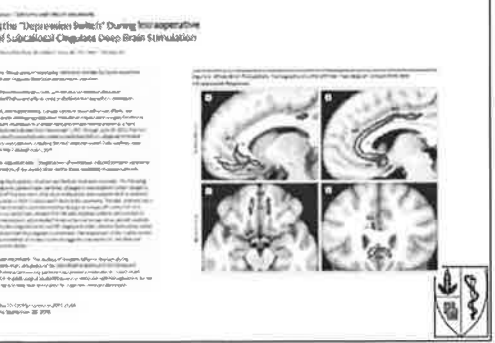


Broaden Study



The Future



The Future

Closed-loop Responsive Neuro

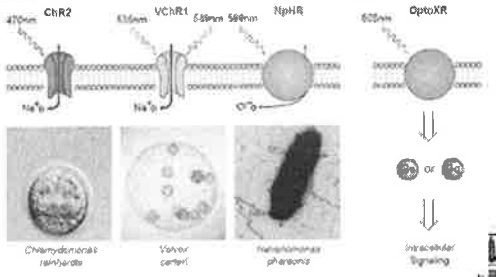
The Future

The developing field of Neuromodulation and Interventional Psychiatry provides opportunities to:

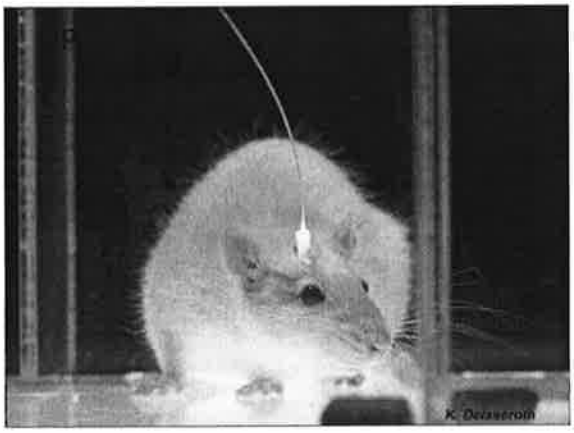
- Directly study human brain-behavior physiology.
- Better define the neurophysiology and functional anatomy of

Optogenetics

In 1979, Francis Crick delineated the major challenges facing neuroscience and called for a technology by which all neurons of just one type could be controlled, "leaving the others more or less unaltered". *Crick, F. H. C. (1979). Thinking about the brain. Scientific American, September, 219-32.*

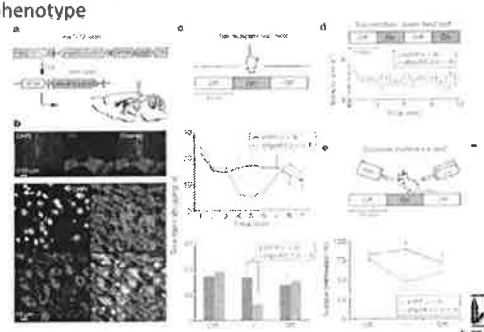


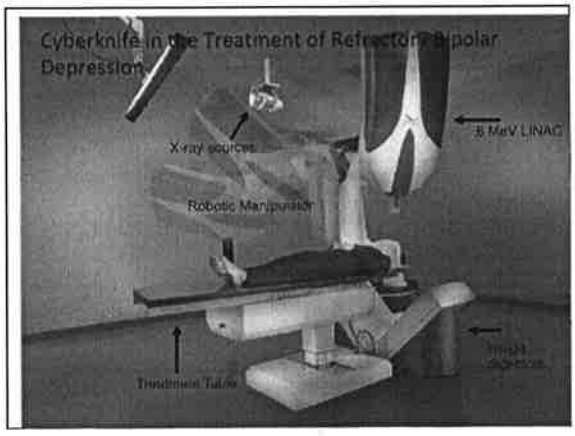
K. Deisseroth



K. Deisseroth

Inhibition of VTA DA neurons induces depressive phenotype

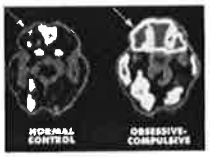




Neuromodulation vs. Ablation

- Cyberknife can decrease firing of specific clusters of neurons
- Evidence of synaptic pruning with low dose radiation (50 rads)
- Has been used in non-ablative treatment of neuropathy

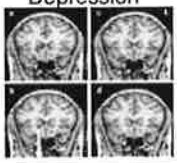
Imaging Correlates of Psychiatric Pathology

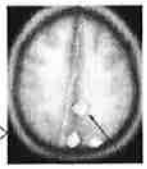


Obsessive-compulsive

SRS Targets?

Depression

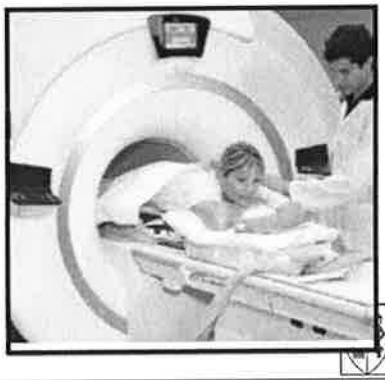




Compulsive Hoarding

Focused Ultrasound

Xalidate table with MRI



Focused Ultrasound

- Noninvasive
- Allows focused heating of tissue
- Used to treat tumors, essential tremor, pain conditions
- Trials in depression and OCD

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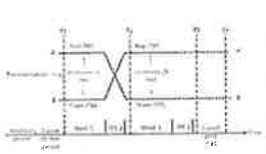
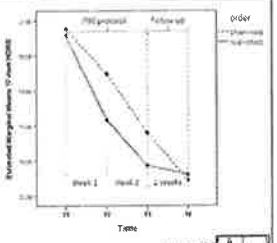
Accelerated Theta-Burst Stimulation for TRD: Results Reported





Target: L DLPFC/ Neuronav
Type: iTBS, 5Hz/50Hz, 54 trains, 8s ITI
Intensity: 110% MT
Pulses: 1,620 pulses/session, 34,200 total
Intersession Interval: 15 minutes

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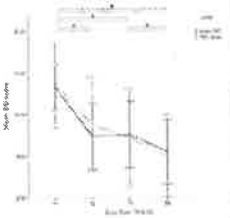
Accelerated Theta-Burst Stimulation for SI: Results Reported



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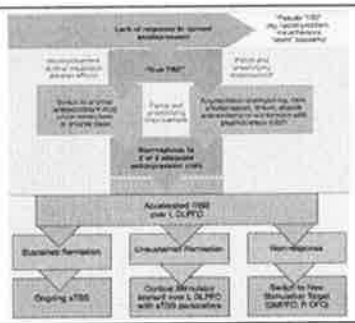
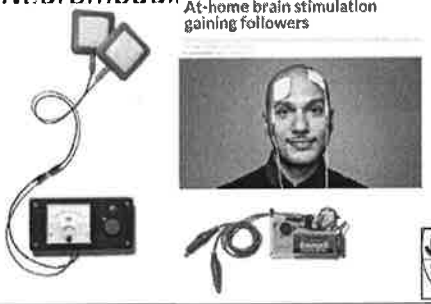
aTBS as a Treatment Predictor



The Future

DIY Neuromodul...

At-home brain stimulation gaining followers



Conclusions

- Neuromodulation is playing a growing role in the treatment of depression
- ECT, TMS are standard treatments
- Our understanding of mood related circuits is slowly increasing
- New technologies may allow noninvasive, precise targeting

Thank you!

ATTACHMENT D

CME SUPPLEMENTAL FORM FOR INDIVIDUAL PRESENTATIONS

Presenter(s): Charles Debattista, MD

Title of Presentation: *Neuromodulation in the Treatment of Resistant Depression*

Date and time of presentation: Saturday, March 24, 2018 – 4:00-4:50pm

Objectives are needed to define the intended outcome and goals of the presentations given. After reviewing the objectives the prospective learner should be able to answer some of these questions: What knowledge will I gain? What skills will I acquire? What attitudes will the program change? What practice outcomes can be expected?

List specific educational objectives for this session:
Review the history of Neuromodulation in Psychiatry
Learn about the current utility and limitations of ECT, VNS, TMS and DBS
Learn about emerging Neuromodulation technologies

Do you anticipate any change in the physician's practice? Please explain:
Clinicians may better understand when to refer a patient for a neuromodulation procedure.

What teaching methodologies will be used? (e.g., lecture, workshop, panel, etc)
Lecture

Content of the session: **Provide an abstract** or outline of **key points to be made**