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Neuromodulation and the Treatment of Refractory Depression

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Disclosures

- ***Research/Grants:*** SAGE Therapeutics – Support for preclinical studies with oxysterols
- ***Consultant:*** Takeda Pharmaceuticals North America, Inc.
- ***Stockholder:*** SAGE Therapeutics
- ***Advisory Board:*** SAGE Therapeutics

Learning Objective 1

Evaluate the efficacy of neuromodulation in managing treatment-resistant major depression (TRMD).

Learning Objective 2

Increase the evidence-based use of neuromodulation in patients who have failed to achieve remission and recovery with conventional pharmacotherapy or psychotherapy.

Treatment-Resistant Major Depression (TRMD): A Significant But Poorly Defined Problem

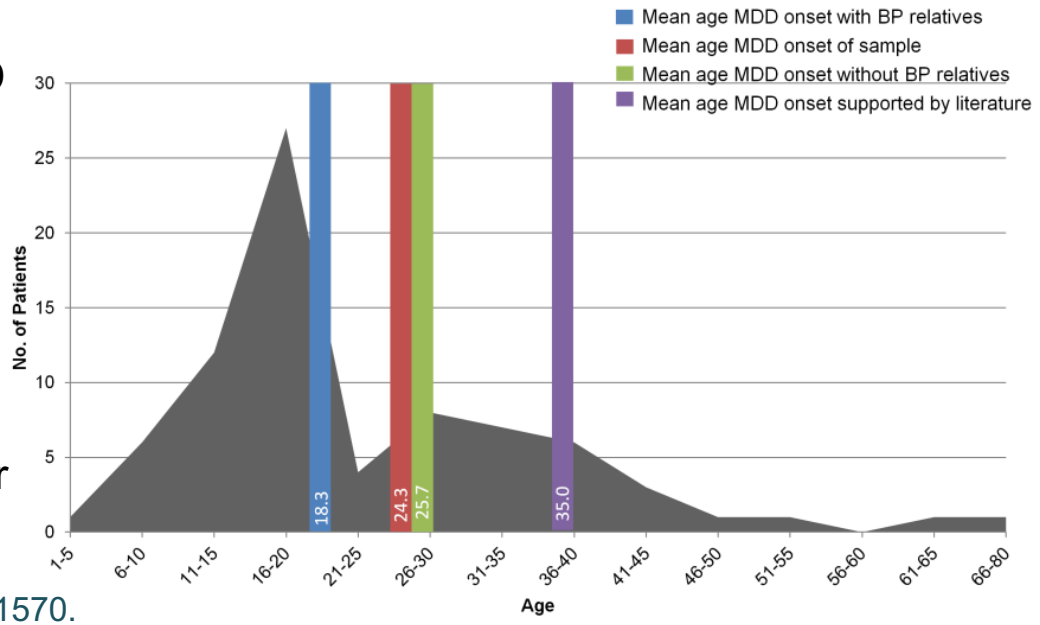
- ~30% of MDD patients
  - High disability → high service utilization
- TRMD = major depression that fails to respond to "x" adequate antidepressant trials
- The "Problem"
  - "Response" vs. "remission?"
  - What is "x?"
  - What is "adequate?"

Zorumski CF, et al. *Front Psychiatry*. 2015;6:172.

Clinical Characteristics of TRMD: Washington University (WU) TRMD Clinic

- **Demographics (n = 79)**
  - Ages: 19-85 (mean 49.3 years)
  - Women > men (2 to 1)
  - Early onset (mean 24.3 years)
  - High family risk for MDD or BD
    - 62% & 14% first degree MDD or BD
- **Course**
  - Average 18.6 years of lifetime depression (range 2-50 years)
  - Recurrent episodes; some have one continuous episode (30%)
  - ~90% with moderate to severe symptoms at index (by MADRS)
  - Average ~8 antidepressant **failures** per subject

- **Outcomes**
  - 27% with suicide attempts (3.4 attempts/attempter)
  - ~63% hospitalized for MDD at some point
  - ~33% on disability

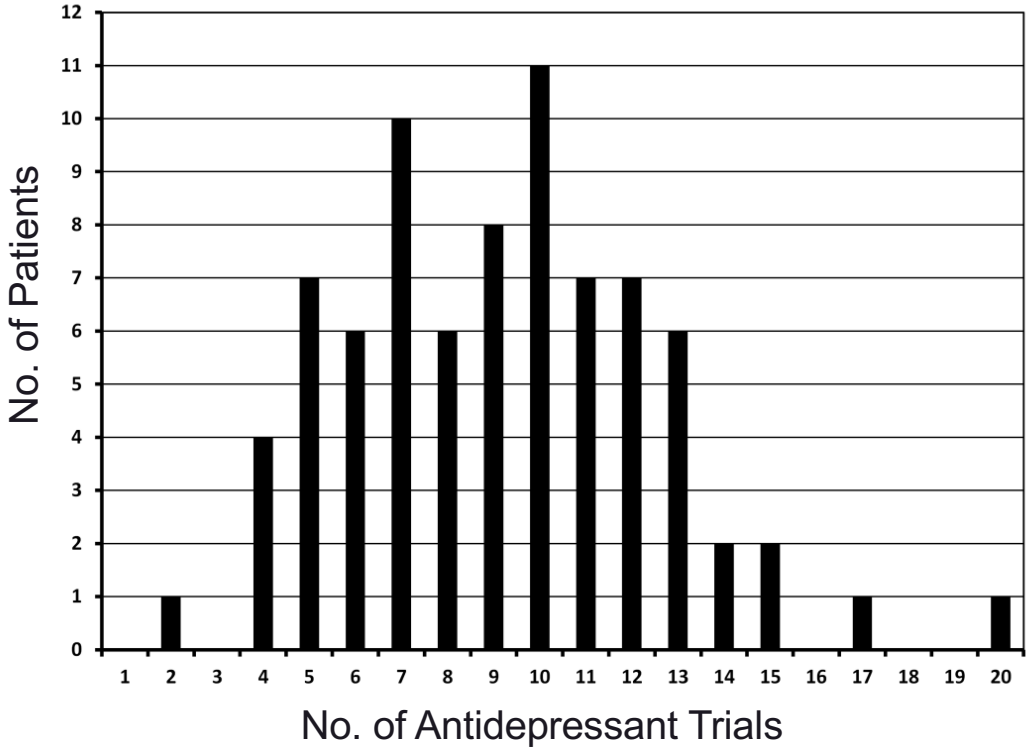


BD = bipolar disorder

Conway CR, et al. *J Clin Psychiatry*. 2015;76(11):1569-1570.

TRMD Prior Treatment: Washington University (WU) TRMD Clinic

- Antidepressant Trials
  - SSRIs (99%)
    - ~3.6 SSRI trials/patient
  - SNRIs (95%)
  - Psychotherapy (93%)
  - Bupropion (89%)
  - ECT (60%)
  - TCAs (57%)
  - Mirtazapine (53%)
  - MAOIs (37%)



Conway CR, et al. *J Clin Psychiatry*. 2015;76(11):1569-1570.

TRMD Prior Treatment: WU TRMD Clinic

- Augmentation Trials
  - Antipsychotics (86%)
    - Aripiprazole/quetiapine > 55% each
  - Lithium (58%)
  - Stimulants (54%)
  - Thyroid (34%)
  - Buspirone (23%)

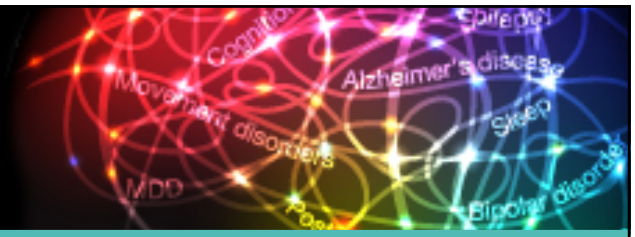
Conway CR, et al. *J Clin Psychiatry*. 2015;76(11):1569-1570.

TRMD Proposed Definition

- STAR*D remission rates[1]
  - Remission rates at the four stages of treatment
    - 37% → 31% → 14% → 13%
  - Remission + maintenance x 1 year
    - 26% → 14% → 5% → 3%
- Two-stage TRMD definition[2]
  - Stage 1 TRMD: Failure of 2 adequate trials
  - Stage 2 TRMD: Failure of > 2 adequate trials

1. Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917; 2. Conway CR, et al. *JAMA Psychiatry*. 2017;74 (1):9-10.

TRMD Stages & Treatment



- Stage 1 TRMD (2 failures)
  - Less invasive, novel mechanism treatments
    - Repetitive transcranial magnetic stimulation (rTMS), ketamine*, buprenorphine*
    - Consider electroconvulsive therapy (ECT)
- Stage 2 TRMD (3 or more failures)
  - More invasive interventions likely required
    - ECT, VNS, DBS?

*ketamine and buprenorphine are not FDA-approved for TRMD

Conway CR, et al. *JAMA Psychiatry*. 2017;74(1):9-10.

TRMD and Neuromodulation

- Electroconvulsive therapy (ECT)
- Vagus nerve stimulation (VNS)
- Repetitive transcranial magnetic stimulation (rTMS)
- Investigational methods

Level of Evidence of Neuromodulation

Treatment	Invasive	Chronic Treatment	Acute Efficacy	Long-Term Efficacy	Safety
ECT		Maintenance treatment optional	Level 1	Level 1	Level 2
Magnetic Size Therapy (MST)*		Maintenance treatment optional	Level 3	Level 3	Level 3
Repetitive Transcranial Magnetic Stimulation (rTMS)			Level 1	Level 3	Level 1
Vagus Nerve Stimulation (VNS)	X		Level 2	Level 2	Level 2
Deep Brain Stimulation (DBS)*	X		Level 3	Level 3	Level 3

*MST and DBS are not FDA-approved for treatment refractory depression.

Bewernick B, et al. *F1000Res*. 2015;4 pii:F1000 Faculty Rev-1389.

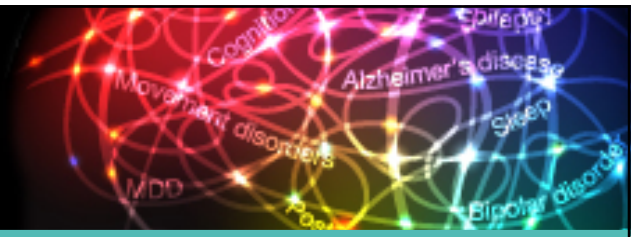
ECT

- Oldest & best studied of neuromodulation methods in psychiatry
- A standard for hospitalized patients with severe depression
- Long track record in severe & refractory depression
- A lot known about optimal use
- But – major side effects and stigma

Key Factors Contributing to the Benefits of ECT

- Generalized CNS seizure
- Electrical dose

Electrical Dosing



- High dose = more benefit AND more side effects
  - Unilateral ECT at 6X seizure threshold is more effective than unilateral ECT at 1.5X or 2.5X threshold AND is as effective as bilateral ECT
- Pulse width matters
  - Unilateral: Ultrabrief pulses (< 0.5ms) provide benefit + fewer side effects, but may be less effective and slower in response than brief pulse
  - Bilateral: Ultrabrief pulses may be less effective

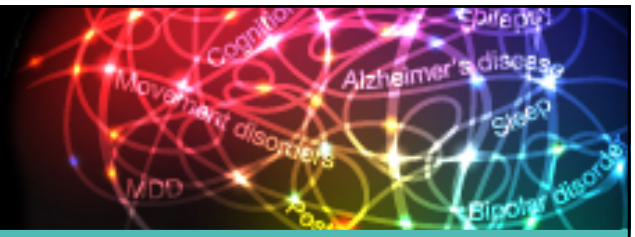
Sackeim HA, et al. *Brain Stimul.* 2008;1(2):71-83. Tor PC, et al. *J Clin Psychiatry*. 2015;76(9):e1092-e1098.

Effective Use of ECT

- Optimize acute course by adjusting electrode placement, stimulus parameters, charge, number of treatments, and perhaps seizure length
  - Concurrent psychotropic medications may improve outcome but may add to memory problems
- Sequence of treatment
  - Right Unilateral (RUL) with ultrabrief pulses @ 6X threshold → Max charge RUL → 1.5-2.5X threshold bilateral with brief pulses → Max Bilateral
  - ECT "Failure" = Failure of Max Charge Bilateral ECT
- Identify effective maintenance treatment

Sackeim HA, et al. *Arch Gen Psychiatry*. 2009;66(7):729-737.

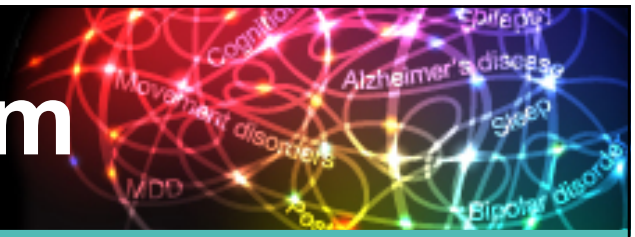
What to Expect from ECT?



- Acute clinical response
  - Good effect size: 0.9 vs. sham; 0.8 vs. meds, overall remission rate: ~60+%
  - Medication failures: ~50% initial response rate + high rates of early relapse
- Side effects
  - Headaches, nausea, muscle soreness
  - Acute confusion
  - Memory impairment (bilateral >> unilateral)

UK ECT Review Group. *Lancet.* 2003;361(9360):799-808; Sackeim HA. *JAMA Psychiatry*. 2017;74(8):779-780.

Maintenance: A Big Problem



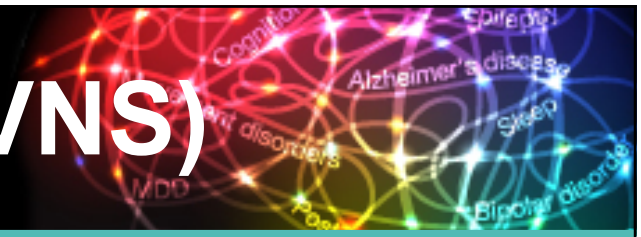
- Many ECT failures = failures of maintenance
  - Without successful maintenance, most patients will relapse in 6 weeks – 6 months
    - 84% (placebo); 60% (nortriptyline); 39% (lithium + nortriptyline)
- Maintenance strategies
  - Medications (different classes, combinations)
  - Evidence-based psychotherapies
  - Maintenance ECT
  - rTMS / VNS (?)

Sackeim HA, et al. *JAMA*. 2001;285(10):1299-307. Tew JD, et al. *Ann Clin Psychiatry*. 2007;19(1):1-4. Jelovac A, et al. *Neuropsychopharmacology.* 2013;38(12):2467-74. Kellner CH, et al. Am J Psychiatry. 2016; 173(11):1110-1118.

Beyond ECT

- Vagus nerve stimulation (VNS)
- Repetitive transcranial magnetic stimulation (rTMS)
- Investigational neuromodulation methods

Vagus Nerve Stimulation (VNS)

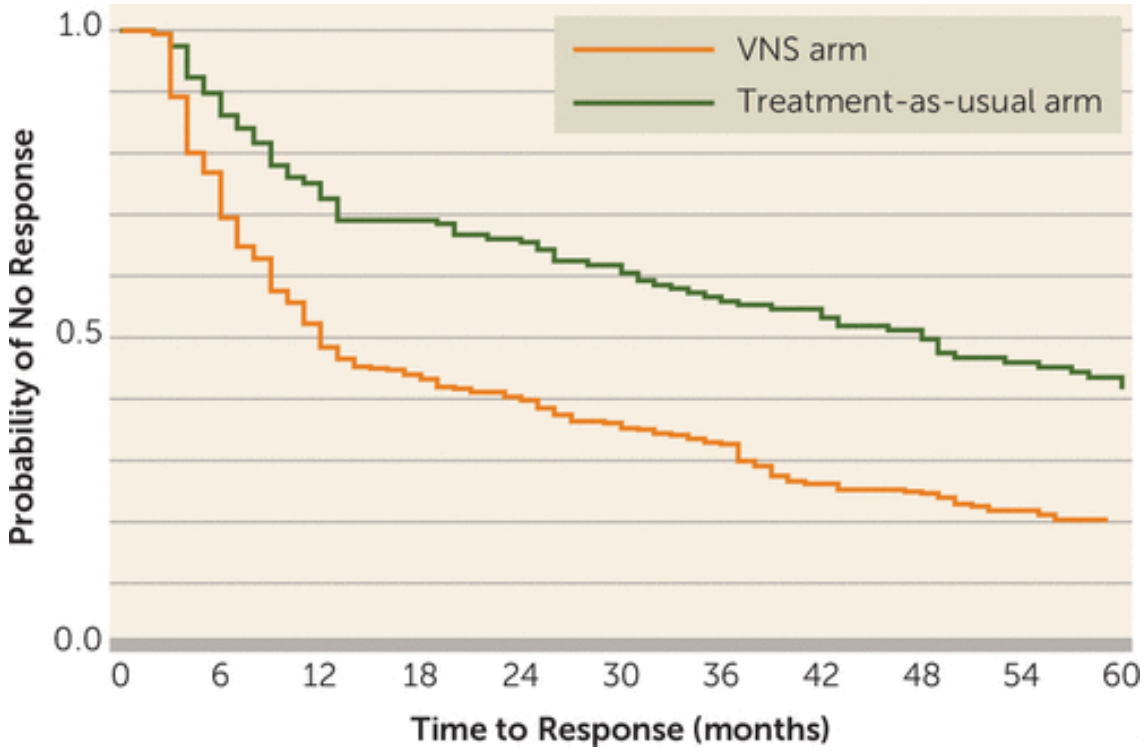


- Approved for epilepsy in 1997
  - Stimulus parameters reasonably well-defined
- Use in psychiatry consistent with effects of other anticonvulsant treatments (including ECT)
- Requires surgery & pulse generator in chest
- Approved by FDA for refractory depression in 2005
  - Stimulation parameters not as well-defined
  - 0.5 ms, 0.25 mA pulses @ 20-30Hz x 30 s q 5 min

Aaronson ST, et al. *Am J Psychiatry*. 2017;174(7):640-648.

VNS and TRMD: 5-Year Observational Study

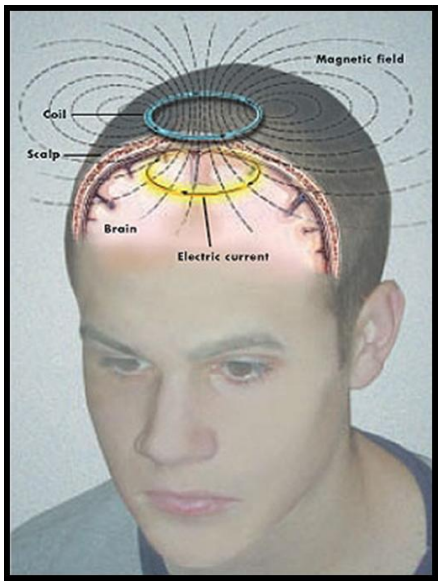
- Non-psychotic TRMD patients (N = 795)
- Unipolar or bipolar depression
- Episode of ≥ 2 years + ≥ 3 episodes
- Failed ≥ 4 treatments (including ECT)



Aaronson ST, et al. *Am J Psychiatry*. 2017;174(7):640-648.

Repetitive Transcranial Magnetic Stimulation (rTMS)

- Electromagnetic coil generates a fluctuating field to induce currents in neocortex
  - Penetrates ~ 2-3 cm into cortex
  - 4 devices FDA approved since 2008
- Stimulation parameters
  - 1-3k 0.1 ms pulses/day
  - @ 90-120% motor threshold
  - x 15-20 days (5x/wk)
  - Left DLPFC = 10-20 Hz
  - Right DLPFC = 1 Hz

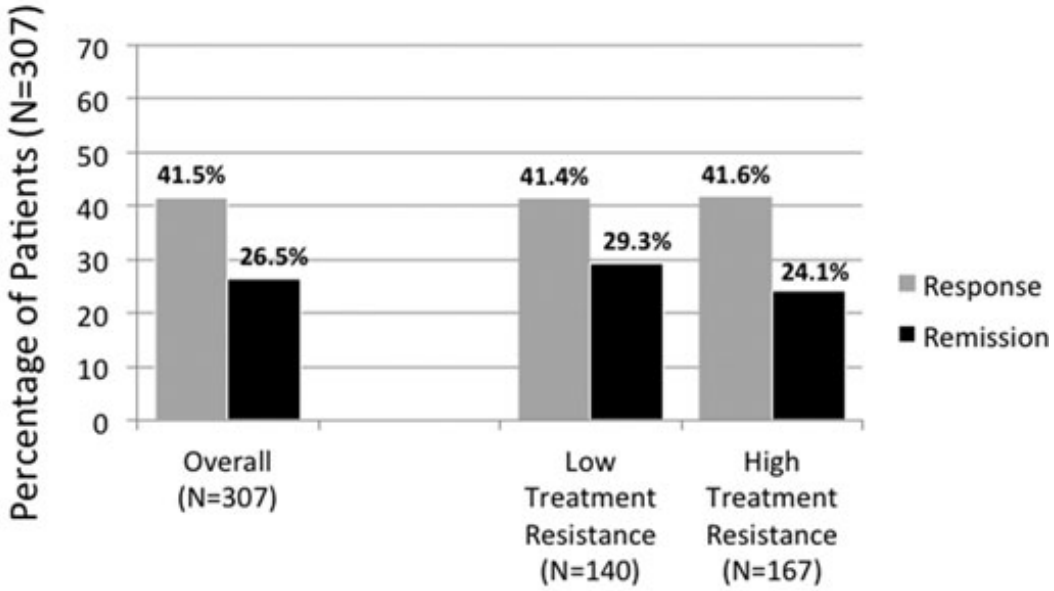


DLPF = dorsolateral prefrontal cortex

Teng S, et al. *Eur Psychiatry*. 2017;41:75-84.

Efficacy of TMS in TRMD: IDS-SR Outcomes

	Baseline	Week 2	Acute Phase
IDS-SR Total Scores mean (SD)	45.7 (11.0)	35.2 (13.2)	27.4 (15.8)
Change from Baseline		-10.7 (10.0)	-18.3 (14.9)
p value		< .0001	< .0001



IDS-SR, Inventory of Depressive Symptoms – Self-Report
IDS-SR response = ≥ 50% drop in endpoint score compared to baseline; remission = endpoint score < 15

Carpenter LL, et al. *Depress Anxiety*. 2012;29(7):587-596; Dunner DL, et al. *J Clin Psychiatry*. 2014;75(12):1394-1401.

rTMS: Current Status

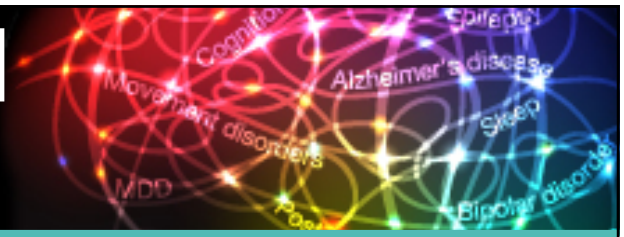
- Optimal parameters not defined
  - Multiple stimulation paradigms appear to have benefit
    - Bilateral, priming low frequency, high frequency, low frequency, theta-burst stimulation (TBS) >> SHAM = accelerated, synchronized and deep
  - WU: 10Hz x 40, 0.25 ms pulses to Left-DLPFC q 30s (3000/day) @ 120% MT x 15-20 days; 5 days/week
- Effectiveness in “refractory” depression is uncertain
  - Modest effects but may be comparable to meds
    - ~15% acute remission on HAM-D for 2-3 prior failures
    - Effect size 0.42 (2-4 failures); 0.83 (1 failure)
- May have some unique uses
  - Patient preference, postpartum depression, pregnancy

Brunoni AR, et al. *JAMA Psychiatry*. 2017;74(2):143-152; Lisanby SH, et al. *Neuropsychopharmacology*. 2009;34(2):522-534.

Investigational Methods

- Magnetic seizure therapy (MST)
- Focal electrically administered seizure therapy (FEAST)
- Transcranial direct current stimulation (tDCS)
- Others: cranial electrotherapy stimulation (CES), epidural prefrontal cortical stimulation (EpCS), low field MR stimulation
- Deep brain stimulation (DBS)
- Infusion/inhalation methods
  - NMDA antagonists; GABAergics (neurosteroids)

The Future: Imaging-Based Subtypes of Depression

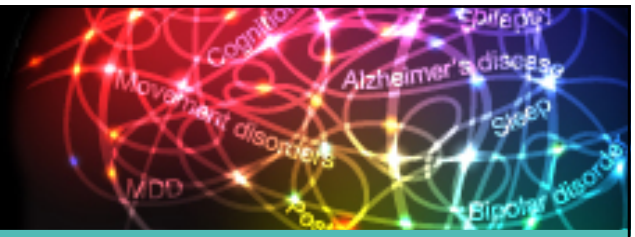


- Clinical & imaging clusters
  - Anxiety → ↓ fronto-amygdala connectivity
  - Anhedonia/slowing → ↑ thalamic-fronto-striatal connectivity
  - Anergia/fatigue → ↓ anterior cingulate cortex/orbital frontal cortex connectivity
- Depression subtypes
  - Bio 1: Anxious – anergic (25%)
  - Bio 2: Anergic (22%)
  - Bio 3: Anhedonic (20%)
  - Bio 4: Anxious – anhedonic (33%)

Response to dorsomedial prefrontal cortex rTMS
1 (83%) > 3 (61%) > 2~4 (25-30%)

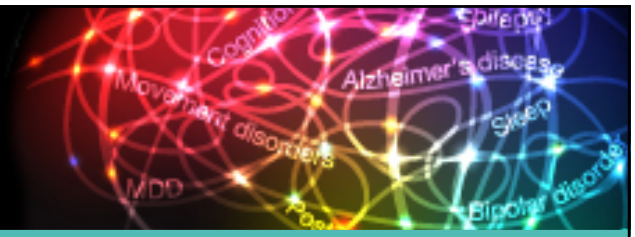
Drysdale AT, et al. *Nat Med*. 2017;23(1):28-38.

Summary



- TRMD is a major clinical problem
- ECT remains the gold standard for TRMD
- VNS, rTMS and DBS are intriguing but remain works in progress
- Infusion treatments are gaining traction, but are works in progress

Call to Action



- Improve clinical outcomes in individuals with TRMD by incorporating neuromodulation strategies into treatment protocols
- Remain abreast of clinical trial updates on neuromodulation strategies for TRMD to optimize individualized treatment selection

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.