Stanford MEDICINE | BRAIN STIMULATION LABORATORY

Rapid-Acting Antidepressants: Deconstructing One and Constructing Another

NOLAN WILLIAMS, M.D.
Assistant Professor
Department of Psychiatry
Stanford University

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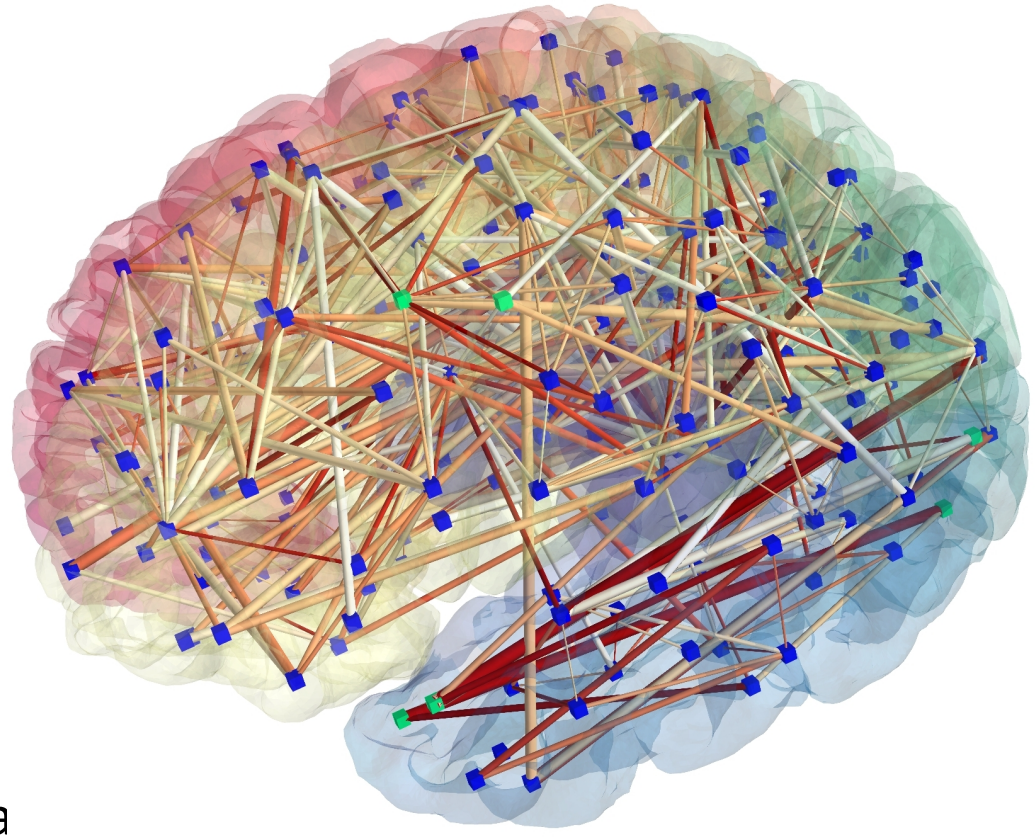
Goals of Talk

- To provide a historical background for interventional psychiatry.
- To demonstrate a novel technique for starting to deconstruct ketamine into its mechanistic components.
- To demonstrate new brain stimulation method with preliminary evidence of efficacy as a rapid-acting antidepressant intervention.

All Neuropsychiatric Diseases Are Disorders of Distributed Neural Networks

"Neurological Conditions"

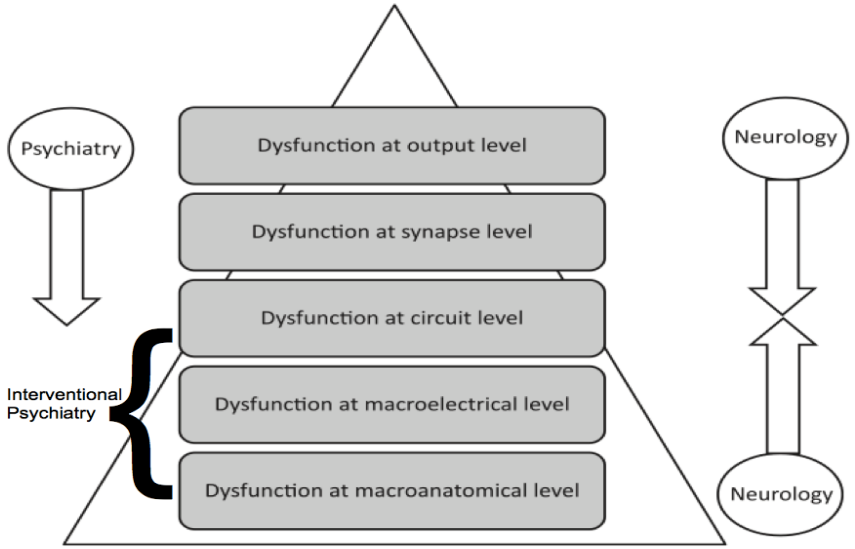
- Parkinson's disease
- Tourette syndrome
- Alzheimer's disease
- Generalized Dystonia



"Psychiatric Conditions"

- Major Depression
- Bipolar Disorder
- Obsessive-Compulsive Disorder
- Post Traumatic Stress Disorder

Networks Can Be Recorded and Modulated

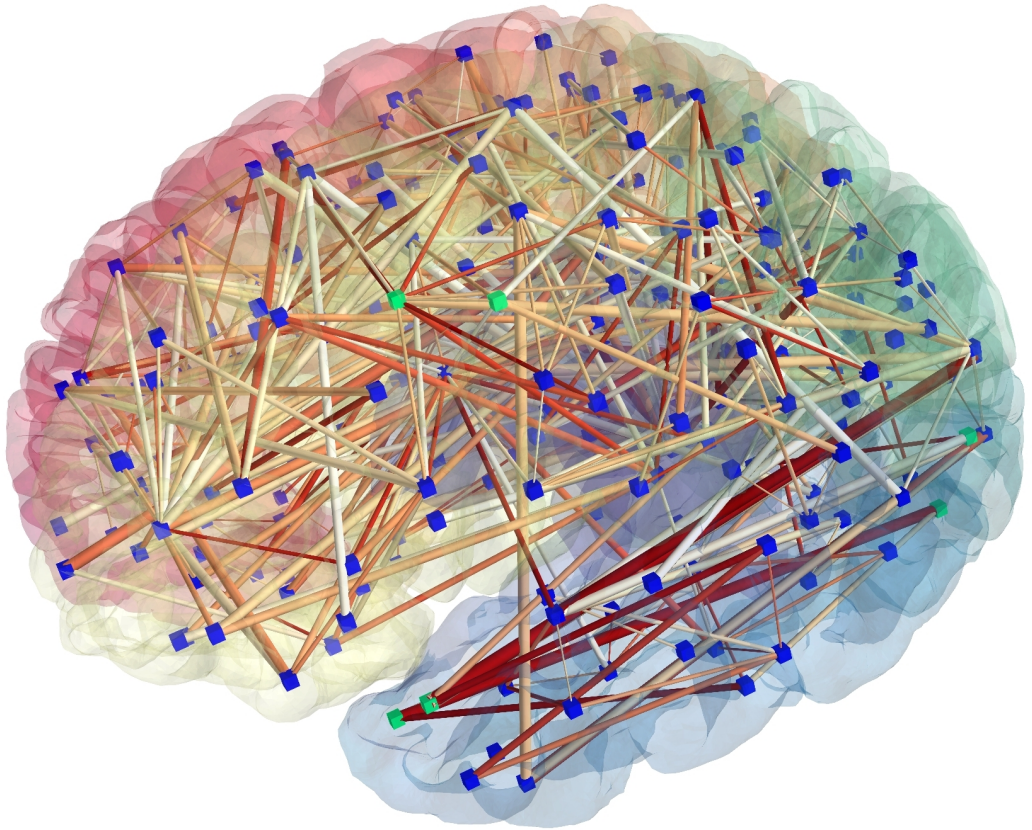


Interventional Psychiatry: The Time is Now

- Interventional psychiatry is an emerging subspecialty that utilizes neurotechnologies to identify dysfunctional brain circuitry underlying neuropsychiatric disorders and apply neuromodulation to modulate that circuitry.

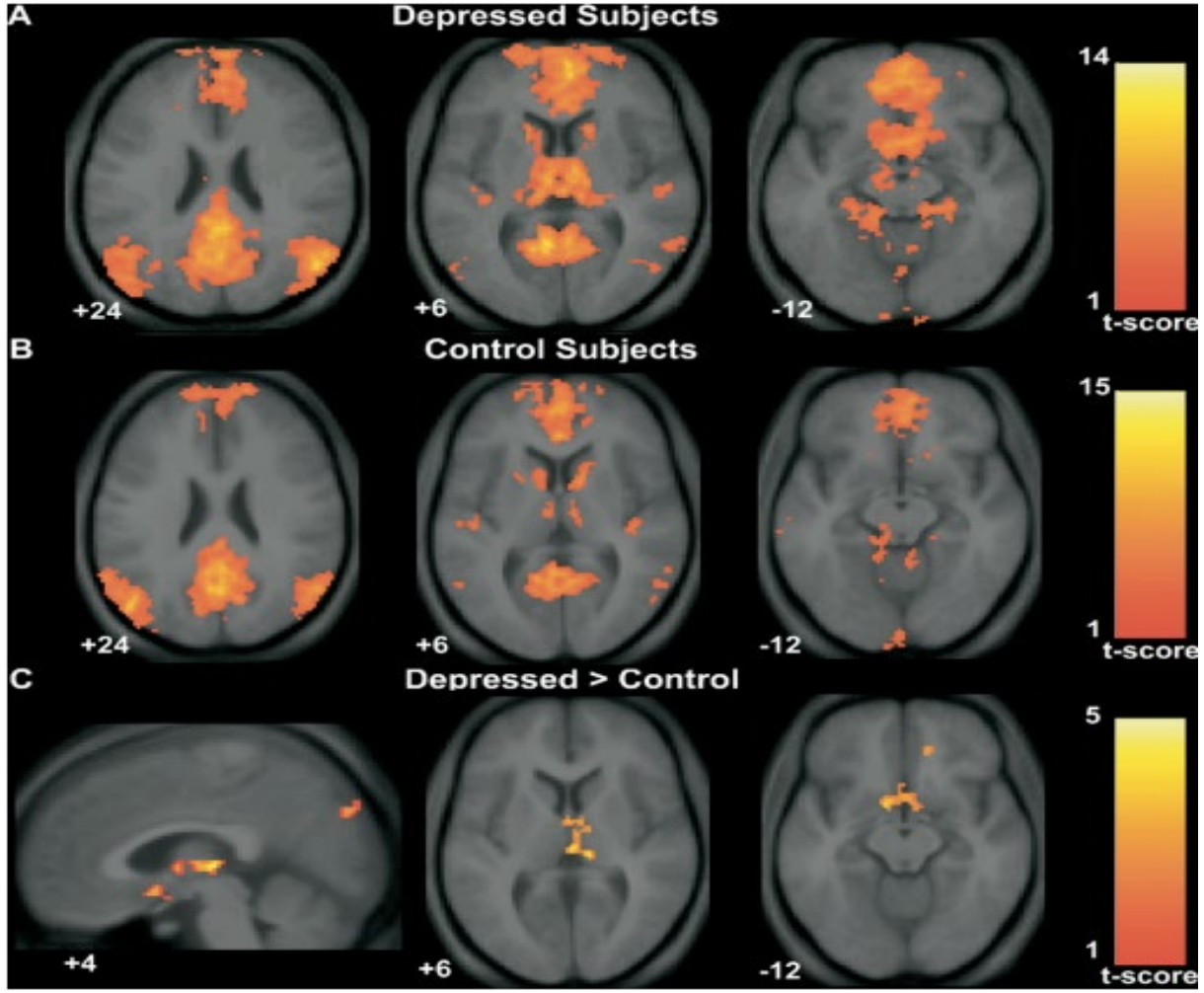
- Within the last 50 years, and particularly the last decade, these classical techniques have been refined, new treatments have been developed, and novel therapeutic targets have been explored.

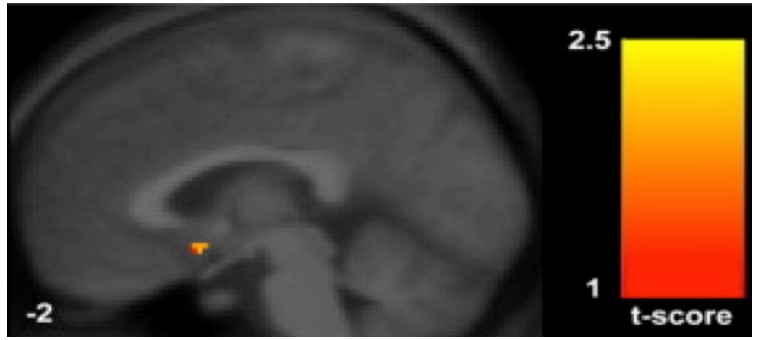
- Nearly a dozen forms of brain stimulation are in development or currently US FDA–approved for a variety of neuropsychiatric indications.

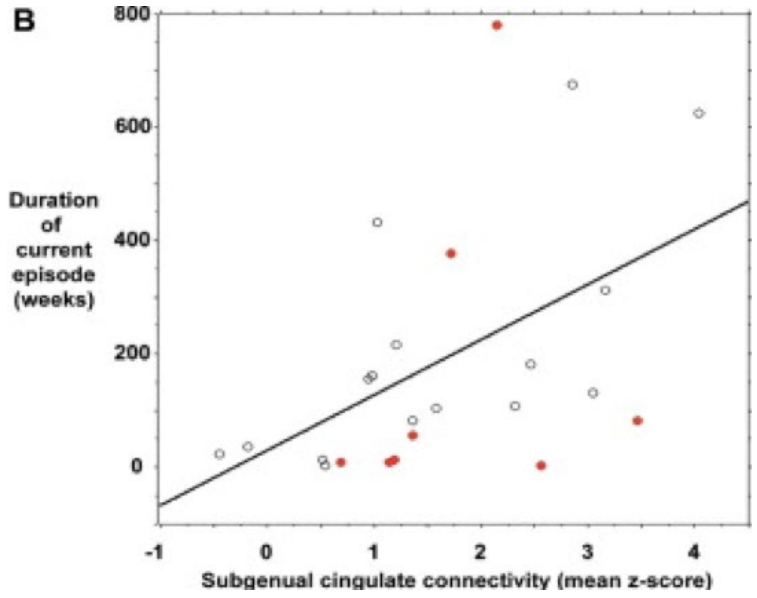


Williams, JCP, 2014

Depression is a Disorder of Large Scale Functional Networks







Greicius, Biol Psych, 2007

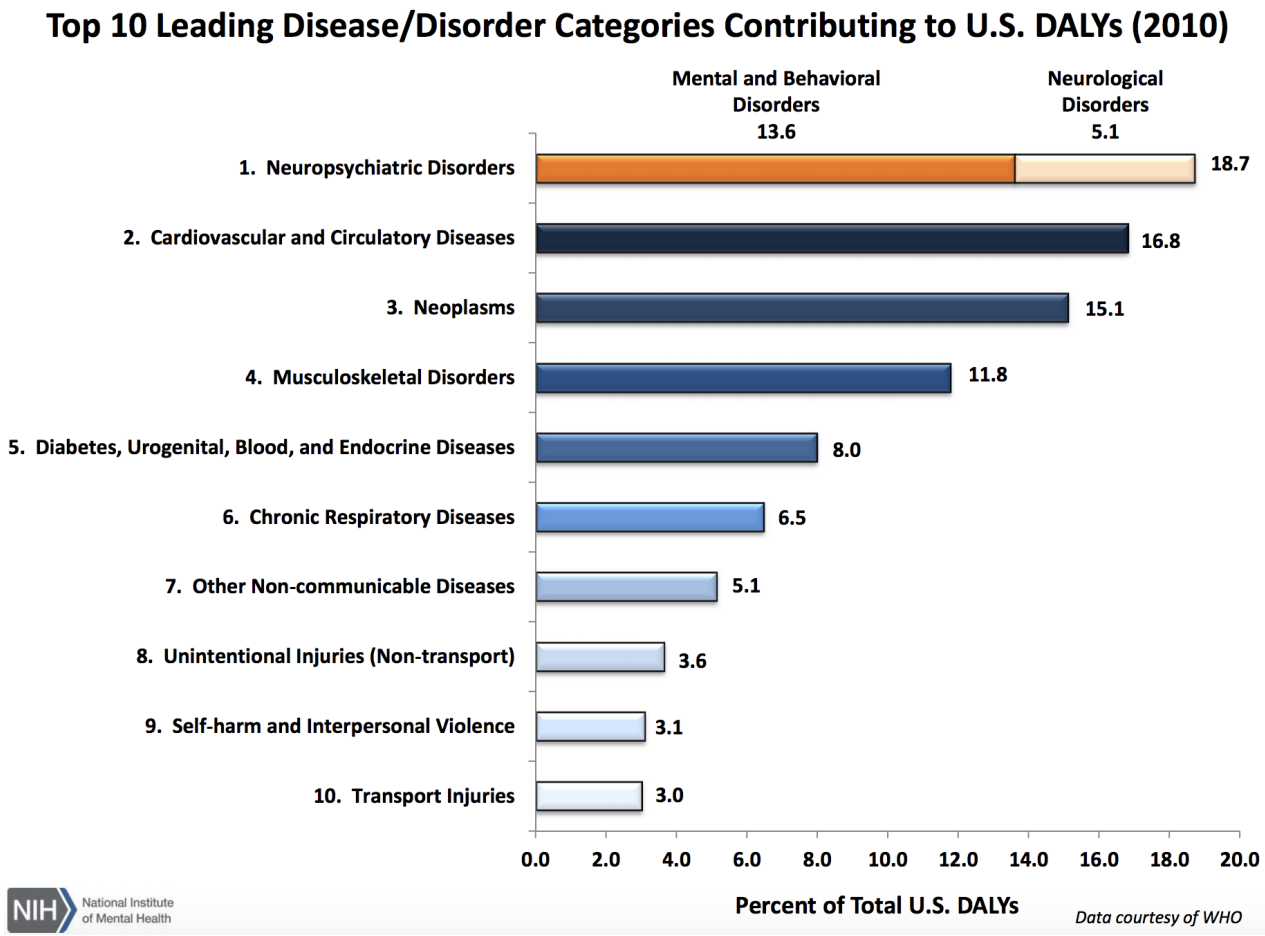
What is Treatment-Resistant Depression and How is it Measured?

- Approximately 30% of patients with MDD have a failed response to antidepressant medications or psychotherapy and are referred to as having "treatment-resistant depression (TRD)."

- There are a number of measures for capturing TRD including:
- Antidepressant Treatment History Form (ATHF)
- Thase-Rush Staging Model (TRSM)
- European Staging Model (ESM)
- MGH General Hospital Staging model (MGH-S)
- Maudsley Refractoriness Scale

Why Treatment-Resistant Depression?

- Depression has now become the most disabling condition world-wide.
- Depression is now one of the four major risk factors for heart disease which is the number two most disabling condition.
- Depression is the most well-studied condition for non-invasive neuromodulation therapies.
- Depression is co-morbid with most major psychiatric and neurological conditions.



Maudsley May Reflect Underlying Circuitopathy

Behavioral Baseline -> fc Changes

- HDRS17
- Maudsley score

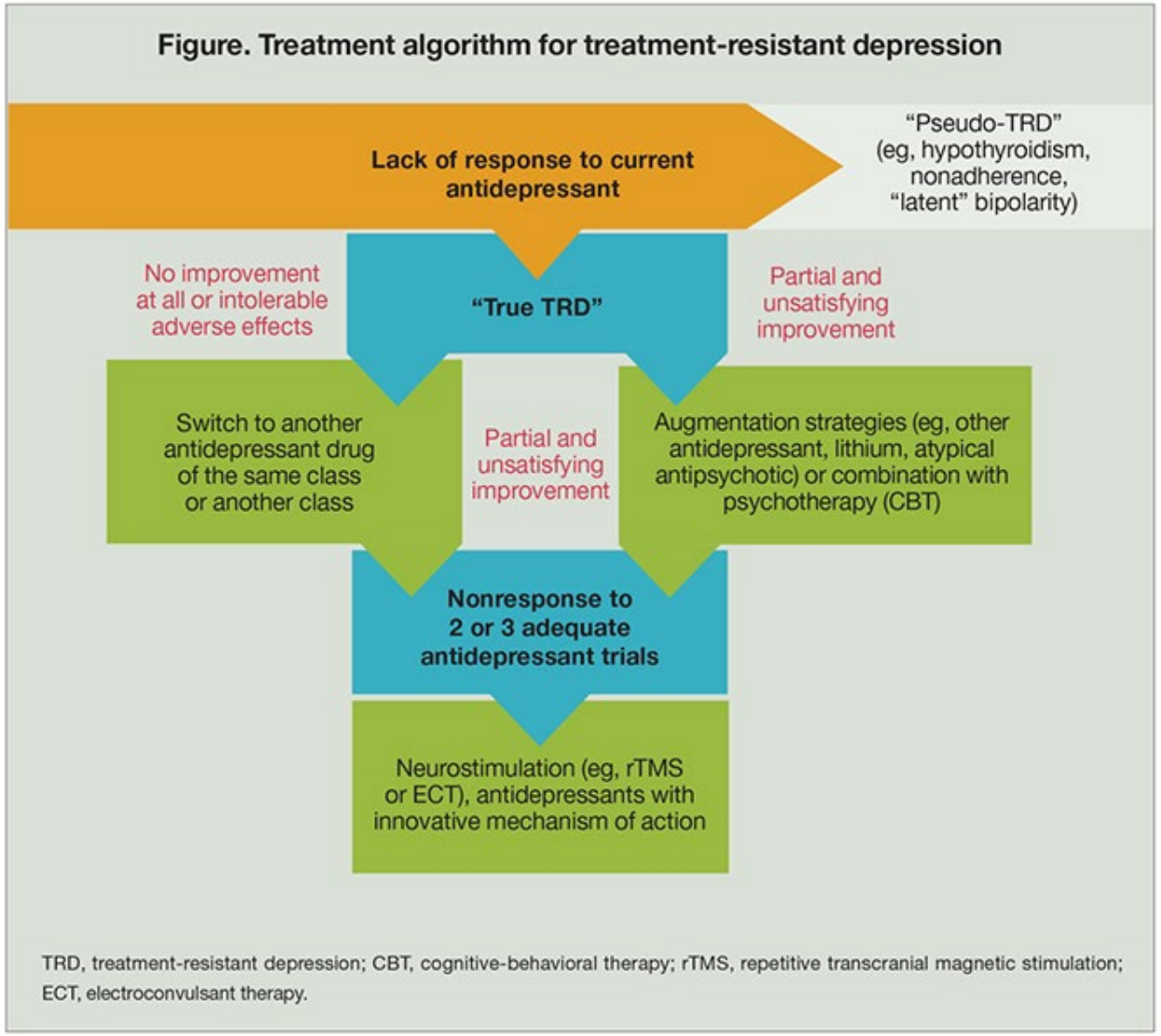
fc diff ~ HDRS17 baseline			
	SCC	Vstriatum	Amygdala
LDLPFC	0.06(.36)	0.04(.48)	0.03(.53)
SCC		0.05(.42)	0.03(.52)
Vstriatum			0.03(.52)

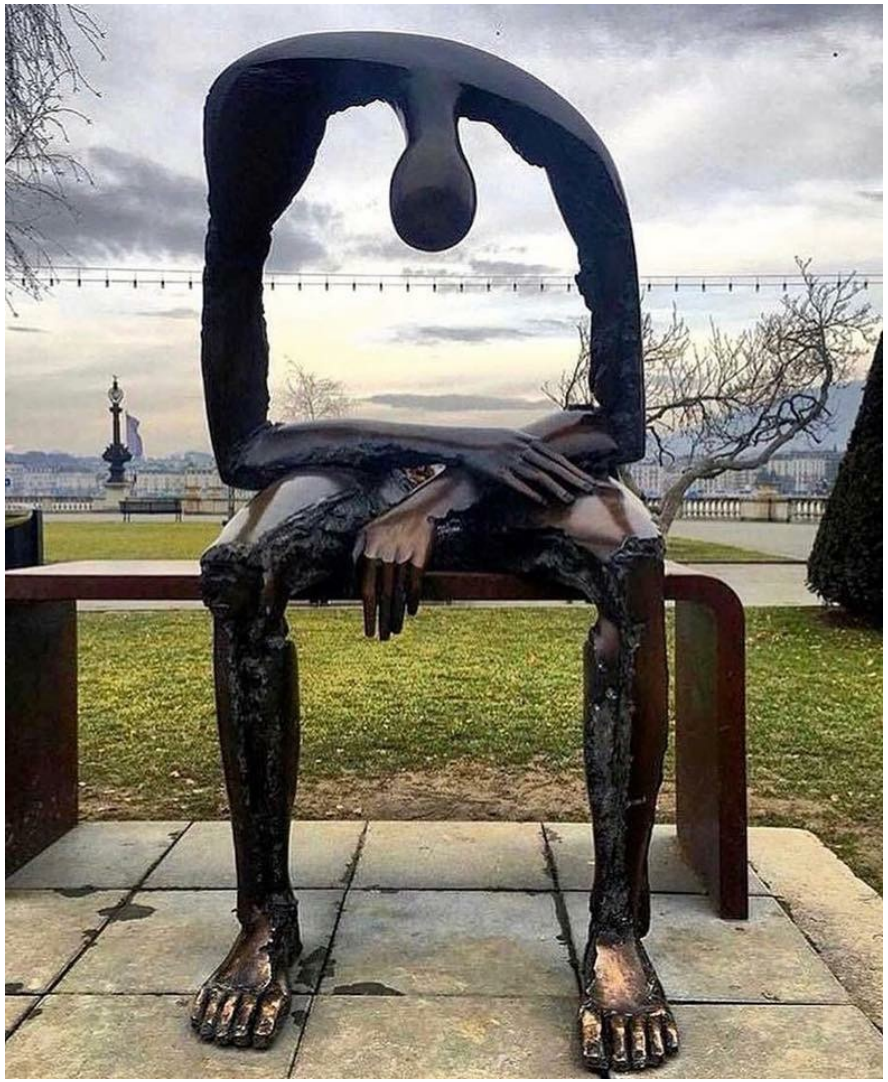
fc diff ~ Maudsley			
	SCC	Vstriatum	Amygdala
LDLPFC	0.25(.048)	0.21(.078)	0.24(.054)
SCC		0.23(.060)	0.26(.046)
Vstriatum			0.22(.067)

*R^2(p)

*Bonferroni correction $p < .05/6 = .008$

Current State of the Art for TRD





Melancholy by Albert György

History of Convulsive Therapy

1924

EEG

Hans Berger invented the electro-encephalogram (EEG).

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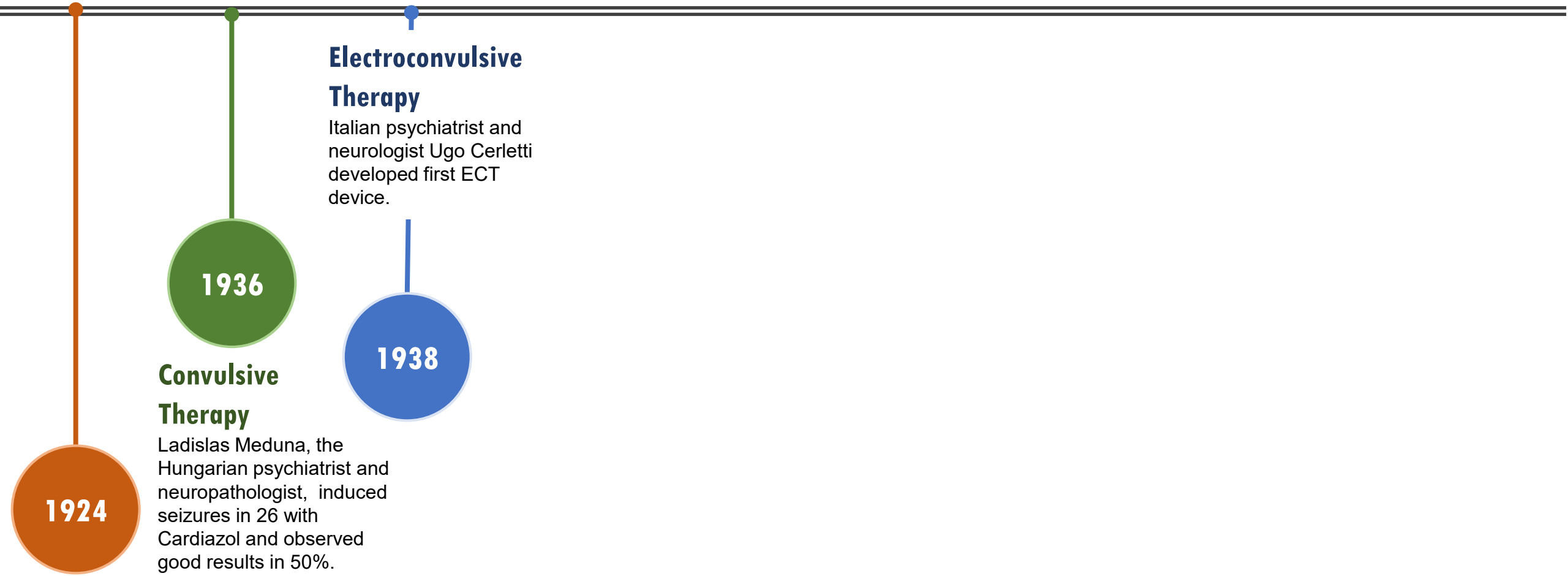
Convulsive Therapy

Ladislas Meduna, the Hungarian psychiatrist and neuropathologist, induced seizures in 26 with Cardiazol and observed good results in 50%.

History of Convulsive Therapy



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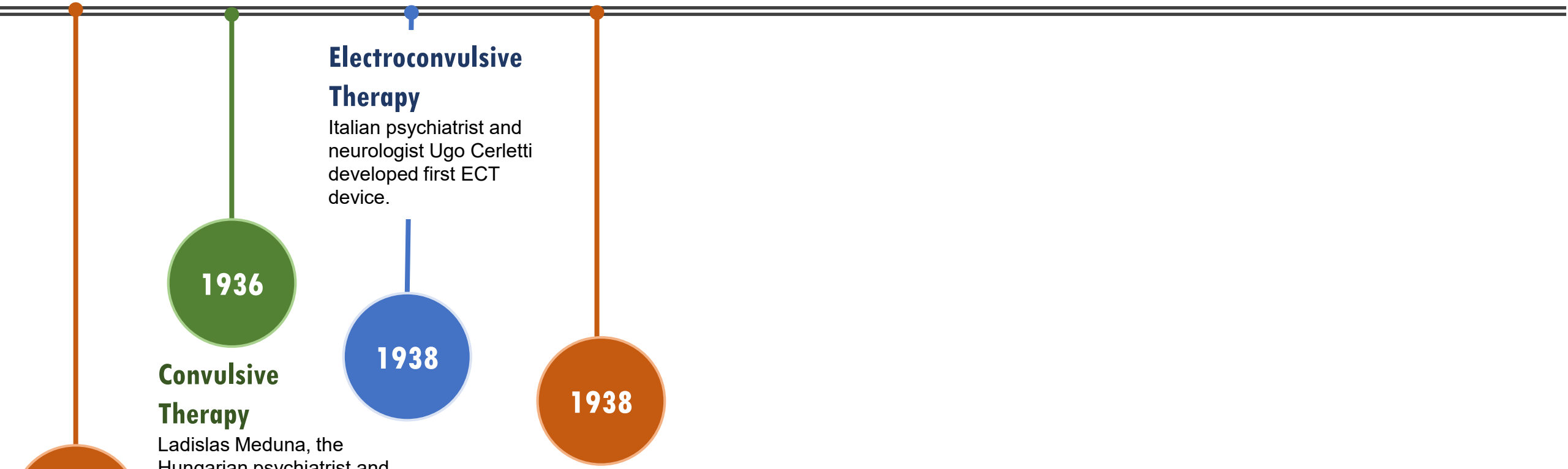

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Electroconvulsive Therapy

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When the opposition in my own country mounted and psychiatrists were attacking even my personal honesty, two years after the discovery of the convulsive treatment.

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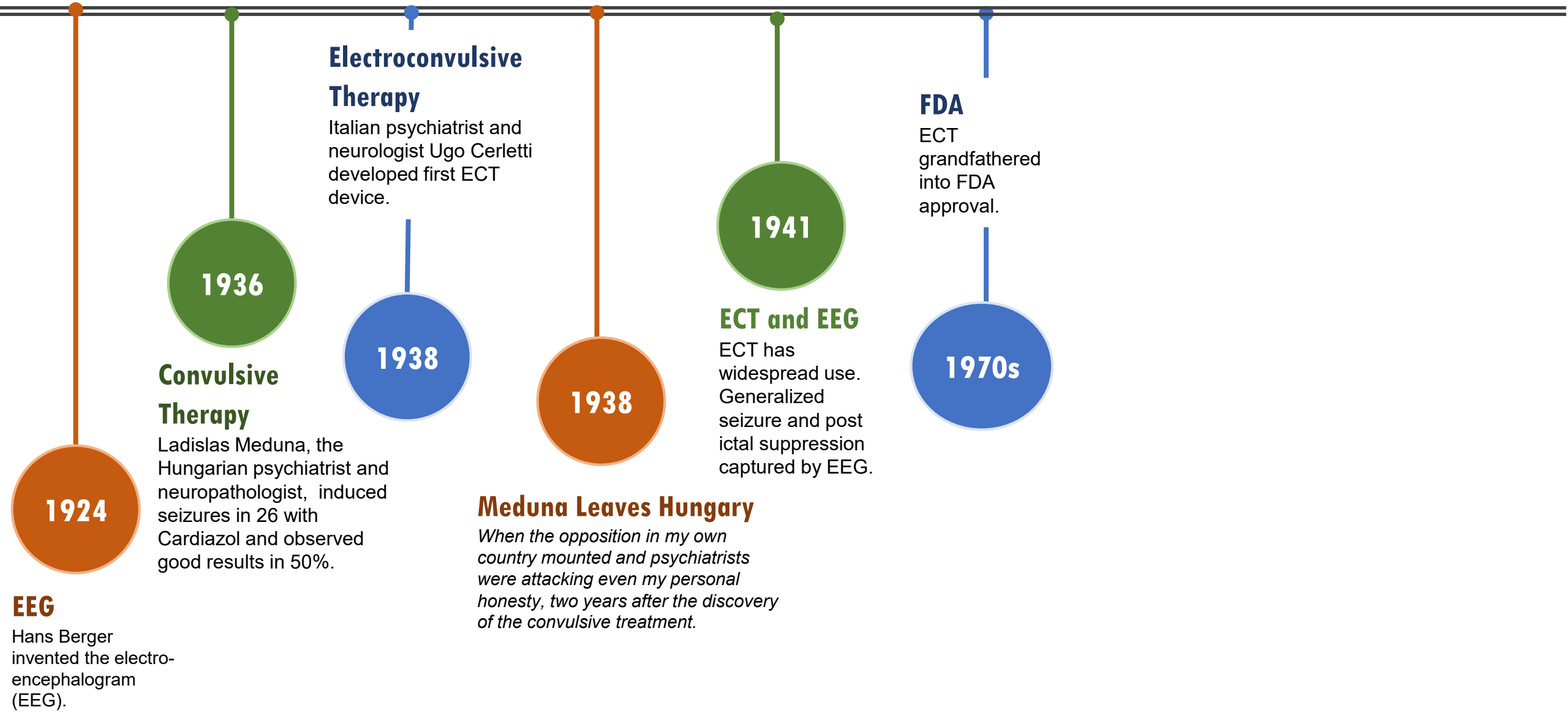
1941

ECT and EEG

ECT has widespread use. Generalized seizure and post ictal suppression captured by EEG.

History of Convulsive Therapy



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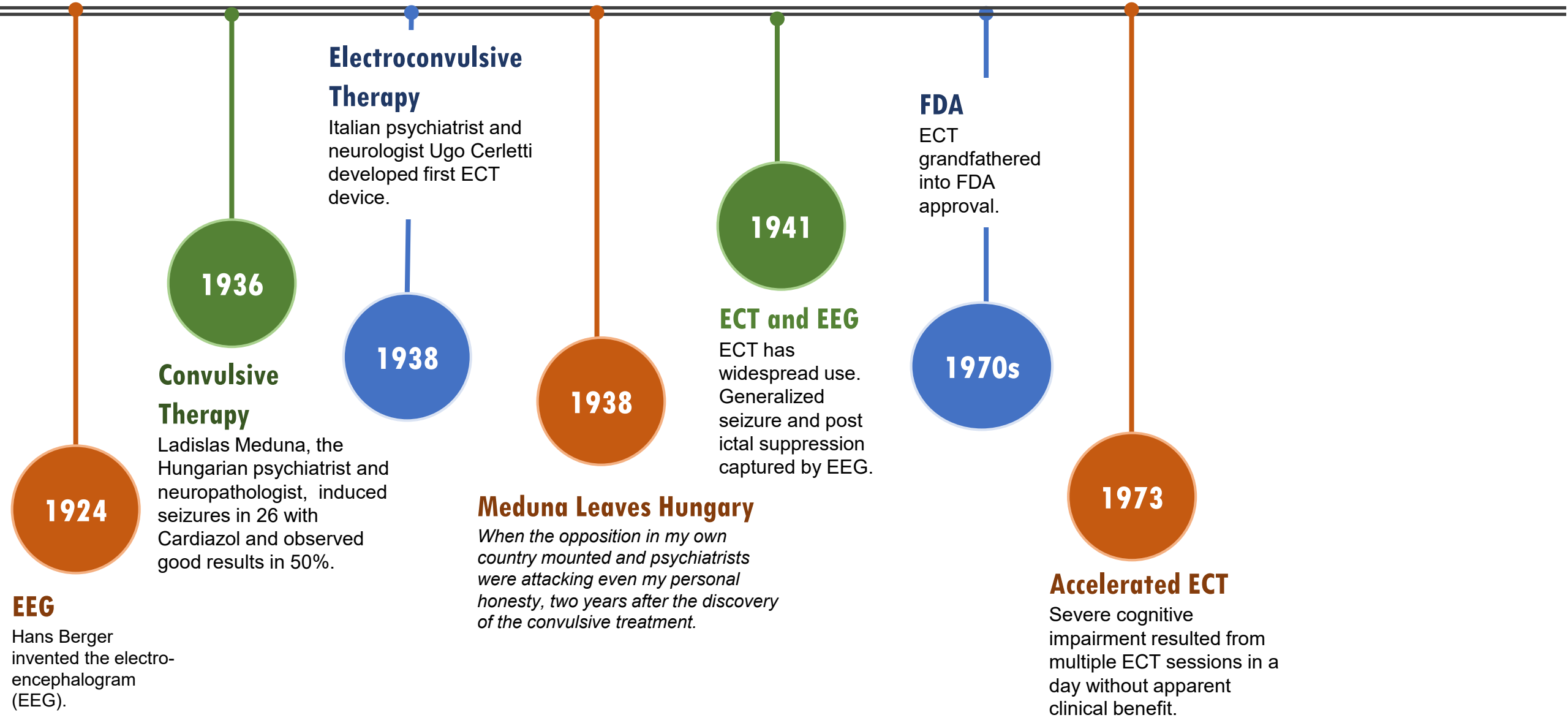

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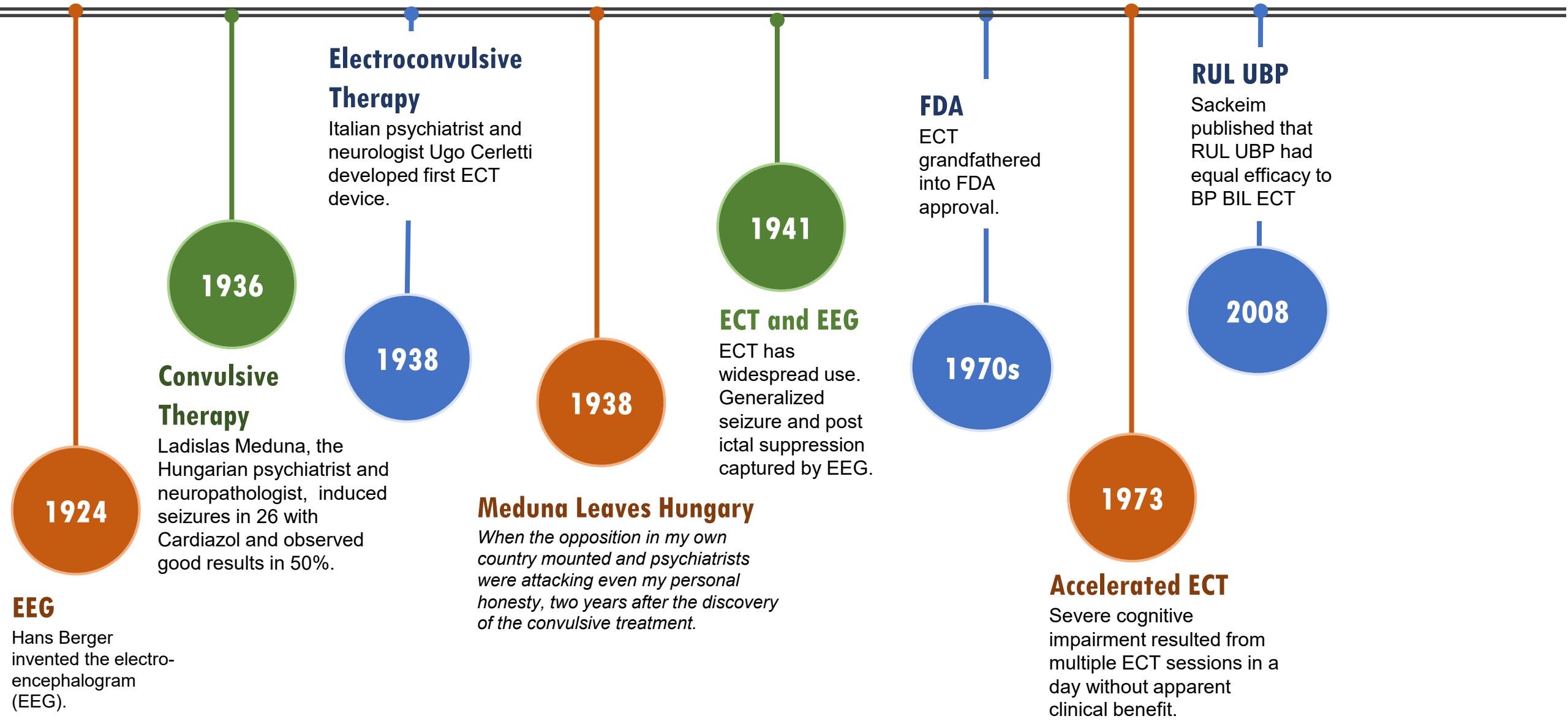

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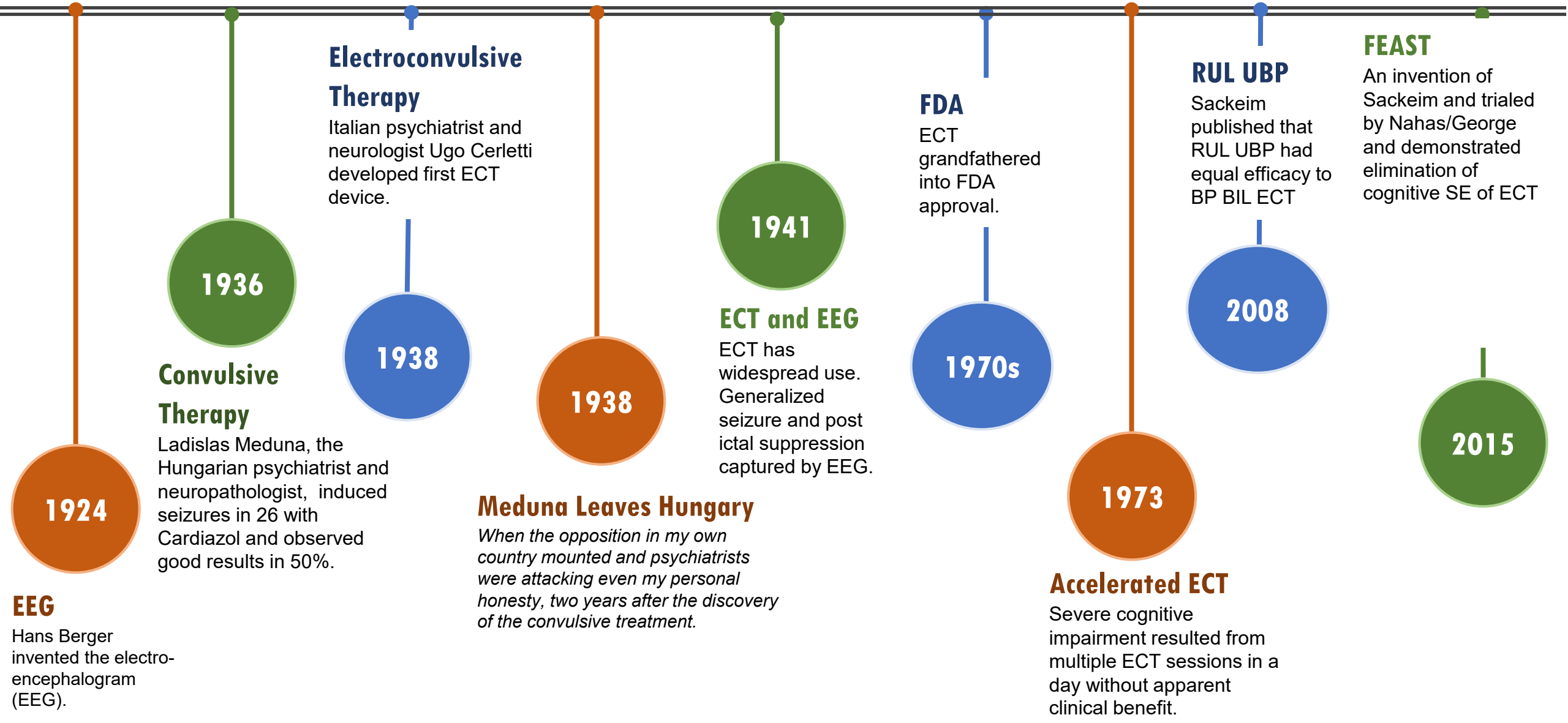
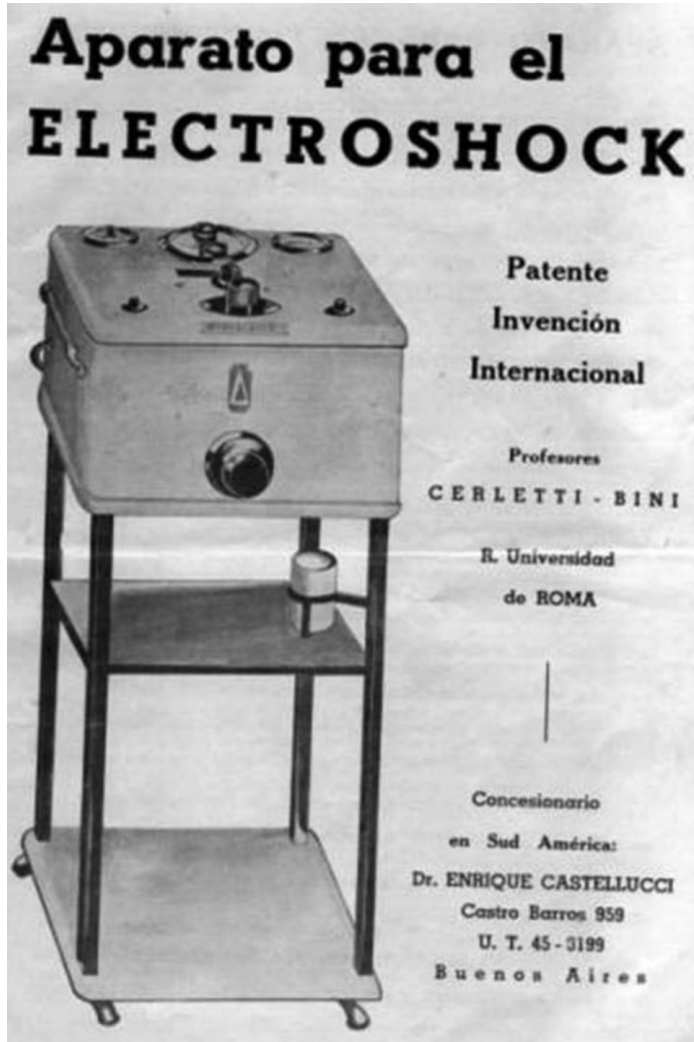


Efficacy of Electroconvulsive Therapy (ECT)

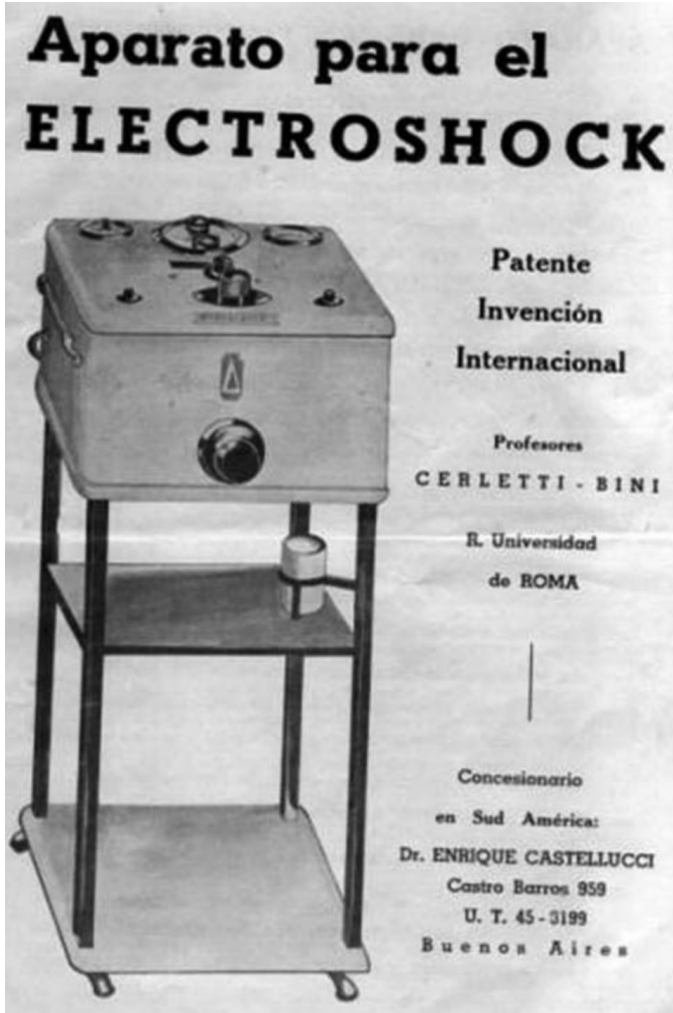
- ECT has an avg remission rate of 48% in treatment-resistant depression (TRD) versus 64.9% in treatment naïve depression in open-label samples according a recent meta-analysis (Heijnen 2010).

- In the pooled sample for the 2 studies (n = 250), 63.2% of the high suicide risk patients had complete resolution of suicidality after the course of ECT (Fink 2014).



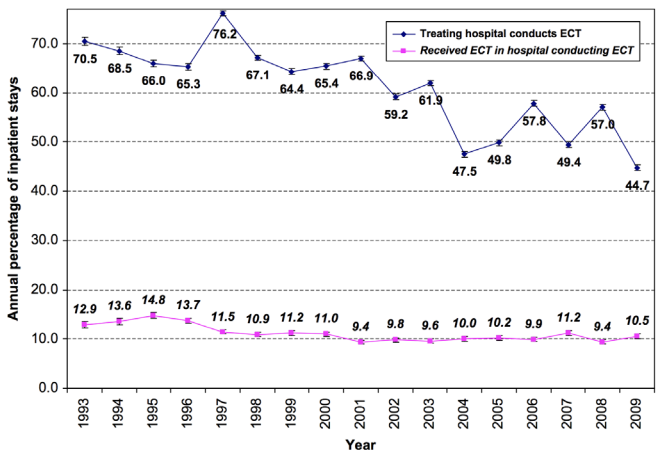
Efficacy of Electroconvulsive Therapy (ECT)

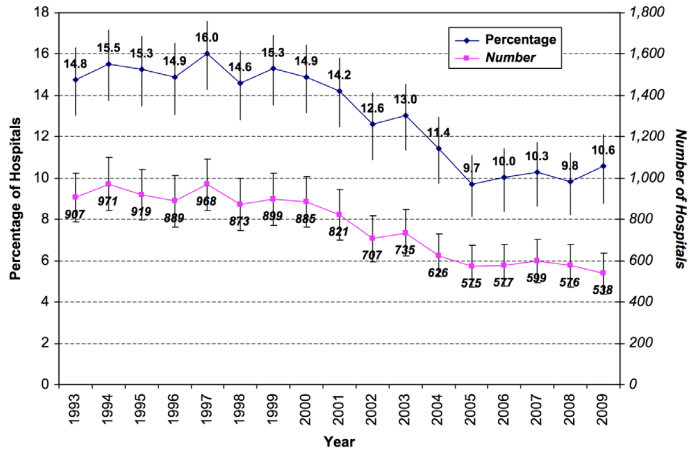
- Generally, ECT has a relapse rate of 62.7% at 3 months and 78% at 6 months for all patients in modern ECT trials, but this includes medication naïve patients in a recent meta-analysis (Jelovac 2013).
- In a study of ECT for TRD, 25% of TRD patients relapsed by 1 week without continuation ECT (Prudic 1996).
- For TRD patients, the average length of wellness is 8.6 weeks after an acute ECT course (Prudic 2004).
- Continuation and maintenance ECT have been demonstrated to extend this period.

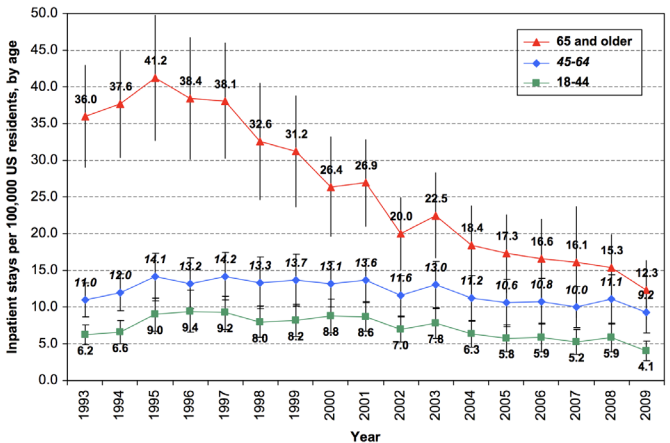


The Use of Electroconvulsive Therapy

- ECT is not used during inpatient care in ~9 of 10 US hospitals, and its use in these settings has declined over the past 2 decades (Case 2013).
- In 2017, all hospital inpatient admission data from 9 states demonstrated that 1.5% of all depressed inpatients eligible to receive ECT receive it (Slade 2017).
- ECT was demonstrated to be associated with a readmission rate of 6.6% versus 12.3% for individuals not receiving ECT (Slade 2017).

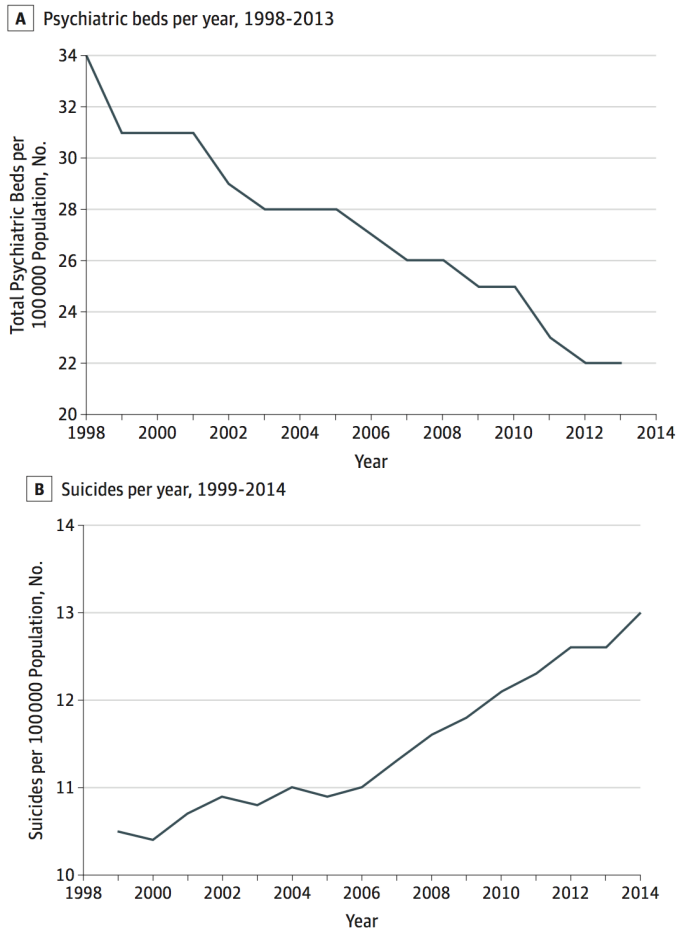




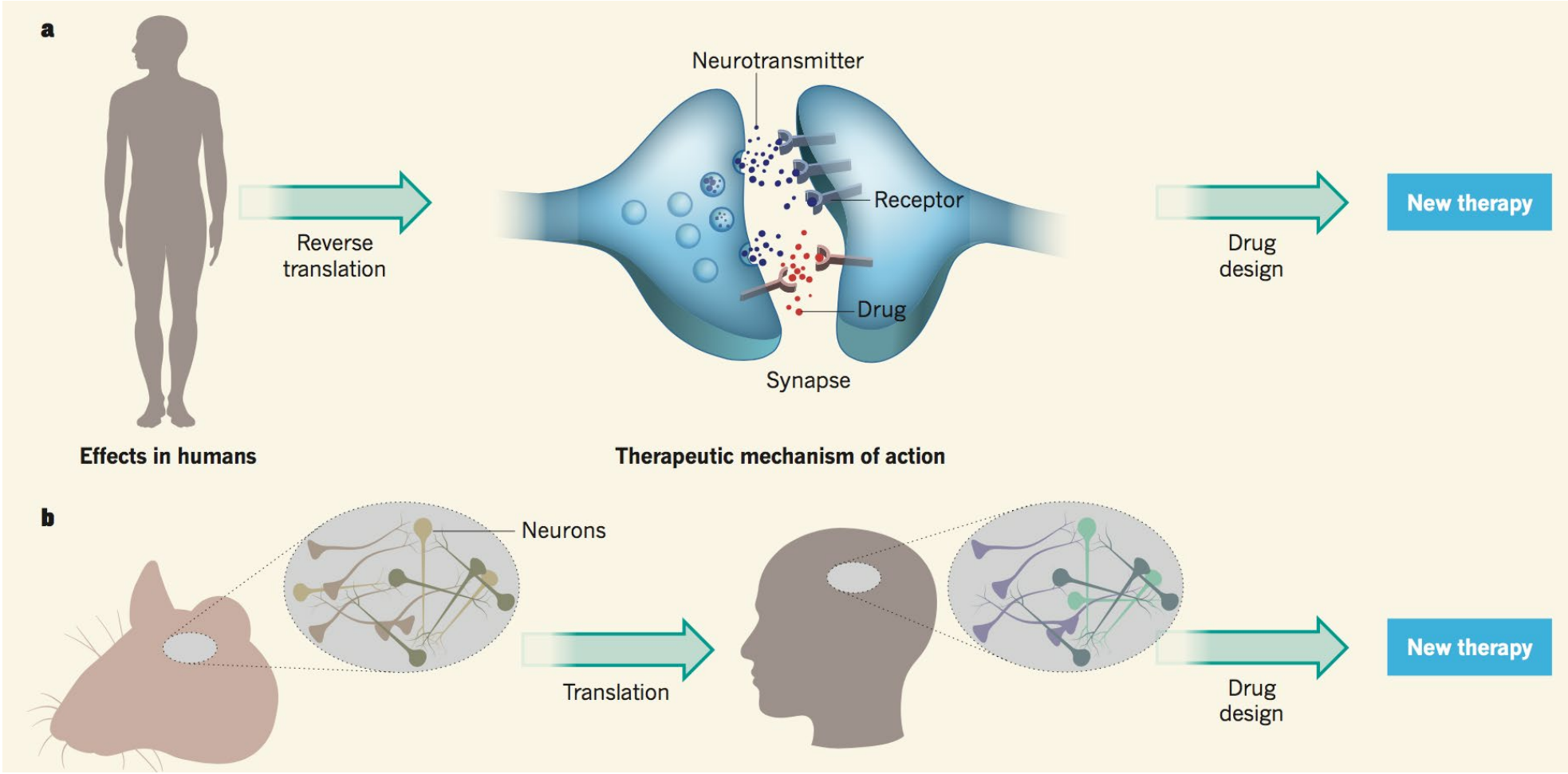


Decline of the Psychiatric Asylum: Suicide Rates Drive Need for Rapid-Acting Interventions

- U.S. suicide rates are increasing while the number of psychiatric beds is decreasing.
- The average length of stay is 10.0 ± 3.0 days (Lee 2012).
- There have been calls to increase the number of psychiatric hospital beds in an attempt to reduce suicide rates.
- The highest risk for completion of suicide is 1-3 months after first psychiatric hospitalization (Chung 2017.



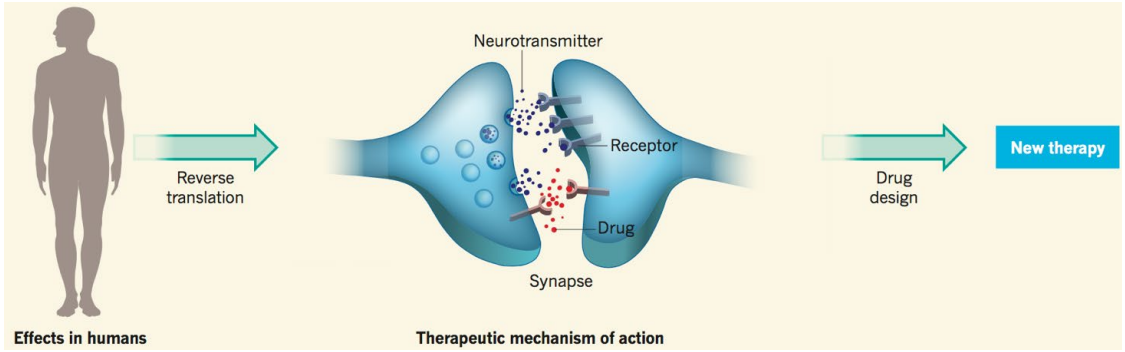
Therapeutic Development for Depression in the 21st Century: *The Best Way Forward*

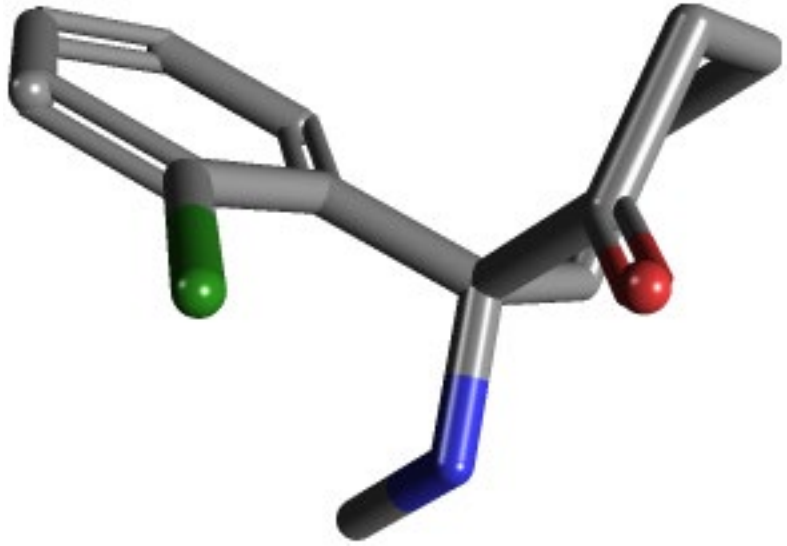


Monteggia, Deisseroth, Malenka, Nature, 2014

Therapeutic Development for the 21st Century: *Therapies First*

- Antidepressants that are effective in humans can be reverse translated in the laboratory, to infer how treatments can be improved.
- The MoA of ketamine is deconstructed, to give a biochemical understanding of how ketamine exerts its effects at synapses.
- Acquired knowledge can then be used to identify new targets for treatment.

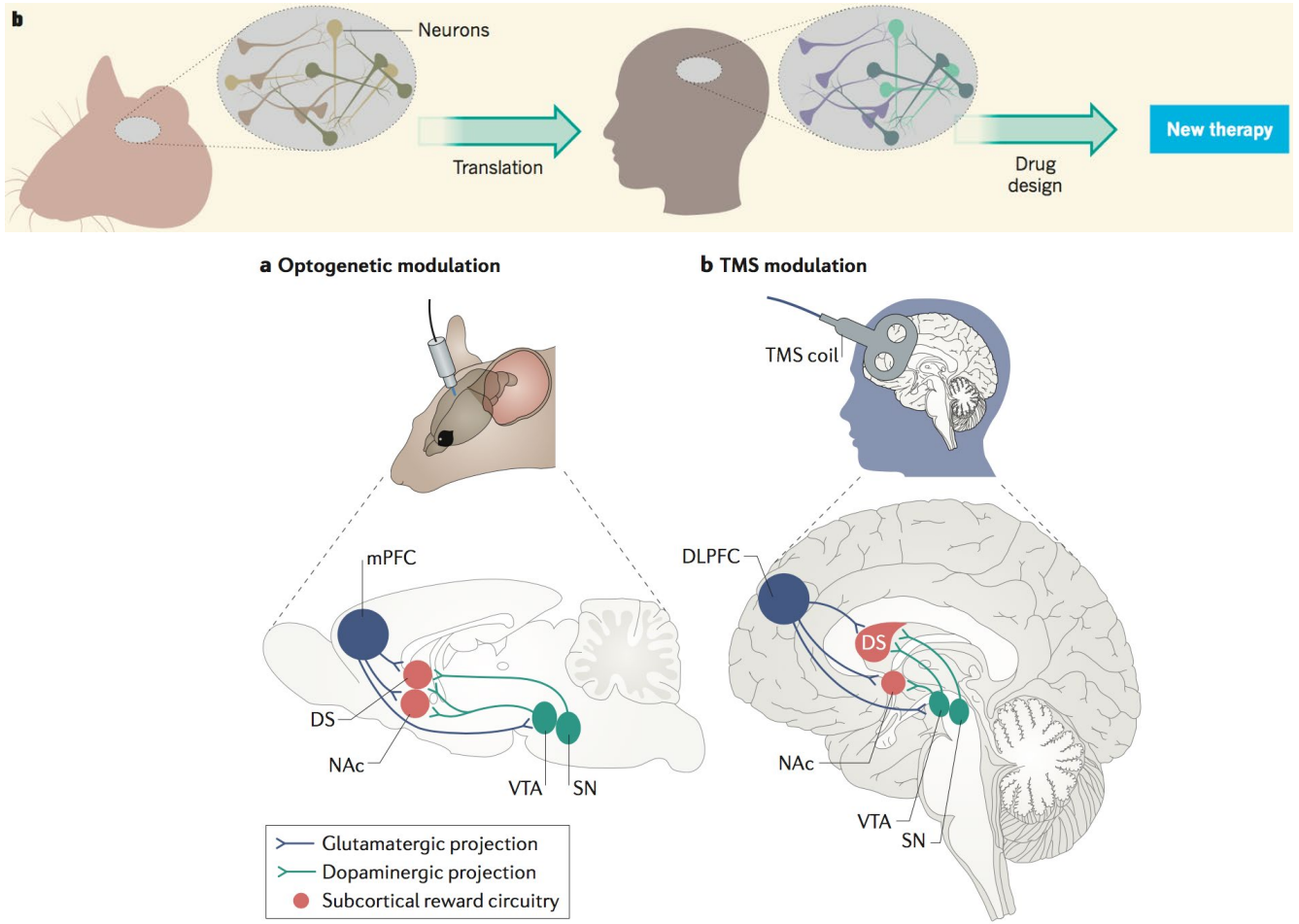




Monteggia, Nature, 2014

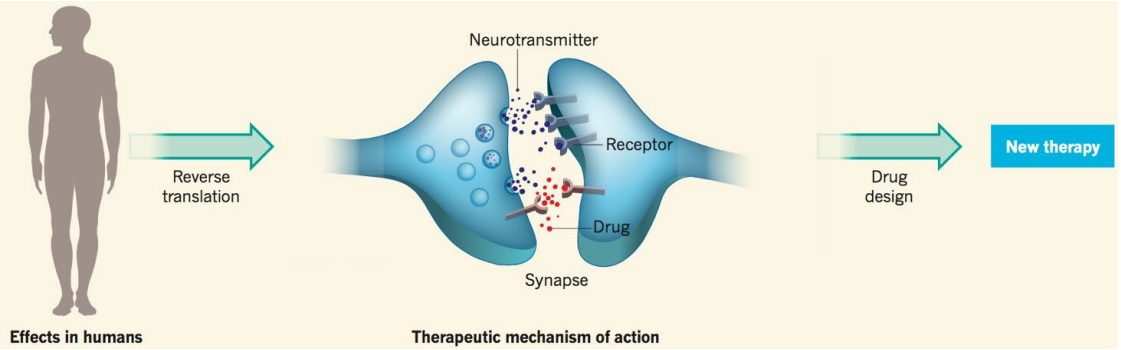
Therapeutic Development for the 21st Century: *Circuits First*

- An alternative approach is to dissect the neuronal circuitry that malfunctions in animals showing symptoms of depression.
- Once a dysfunctional circuit has been identified, the same circuit can be analyzed in humans.
- In this way, putative therapeutic targets can be defined and tested in a reliable animal model, and then tested in humans.



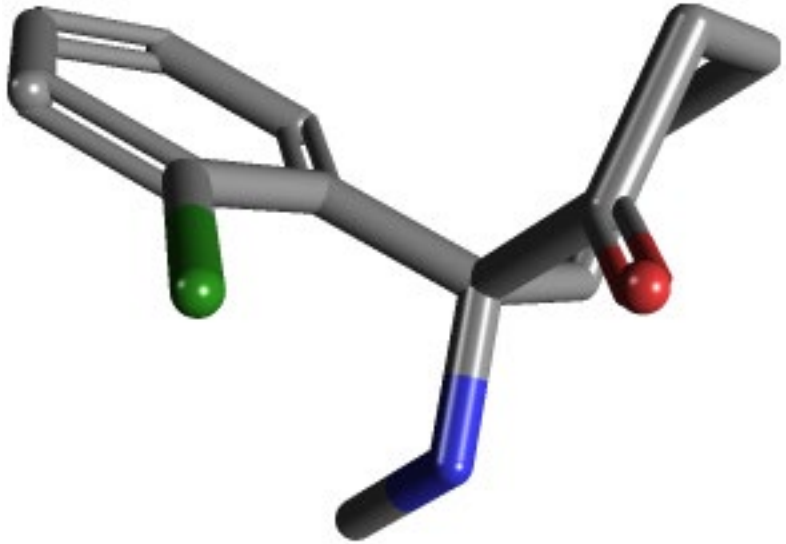
Deisseroth, Malenka, Nature, 2014

Therapeutic Development for the 21st Century: Ketamine



"Recent data suggest that **ketamine**, given intravenously, might be the ***most important breakthrough in antidepressant treatment in decades***."

Former NIMH Director Thomas Insel, MD

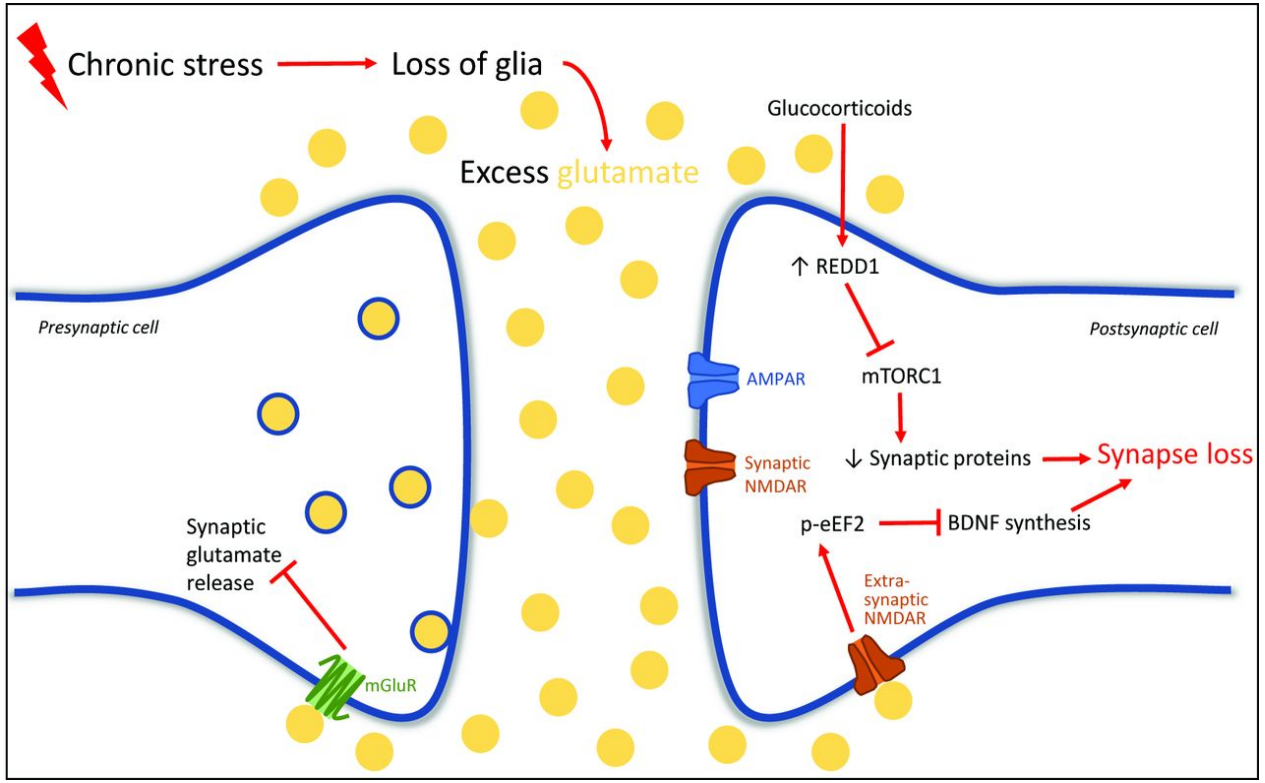


Ketamine Antidepressant Efficacy

- First study of ketamine as an antidepressant demonstrated a 50% response rate (Berman 2000).
- A recent meta-analysis demonstrated response and remission rates for ketamine at 24 and 72 h, and day 7 of 52.2% and 20.6%; 47.9% and 23.8%; and 39.8% and 26.2%, respectively (Han 2016).
- A recent study demonstrate anti-suicide response rate of 55% for IV ketamine (Grunebaum 2017).
- Until recently, there have been no human studies demonstrating the mechanism of action for ketamine as an antidepressant (Williams 2016).

The Effects of Chronic Stress

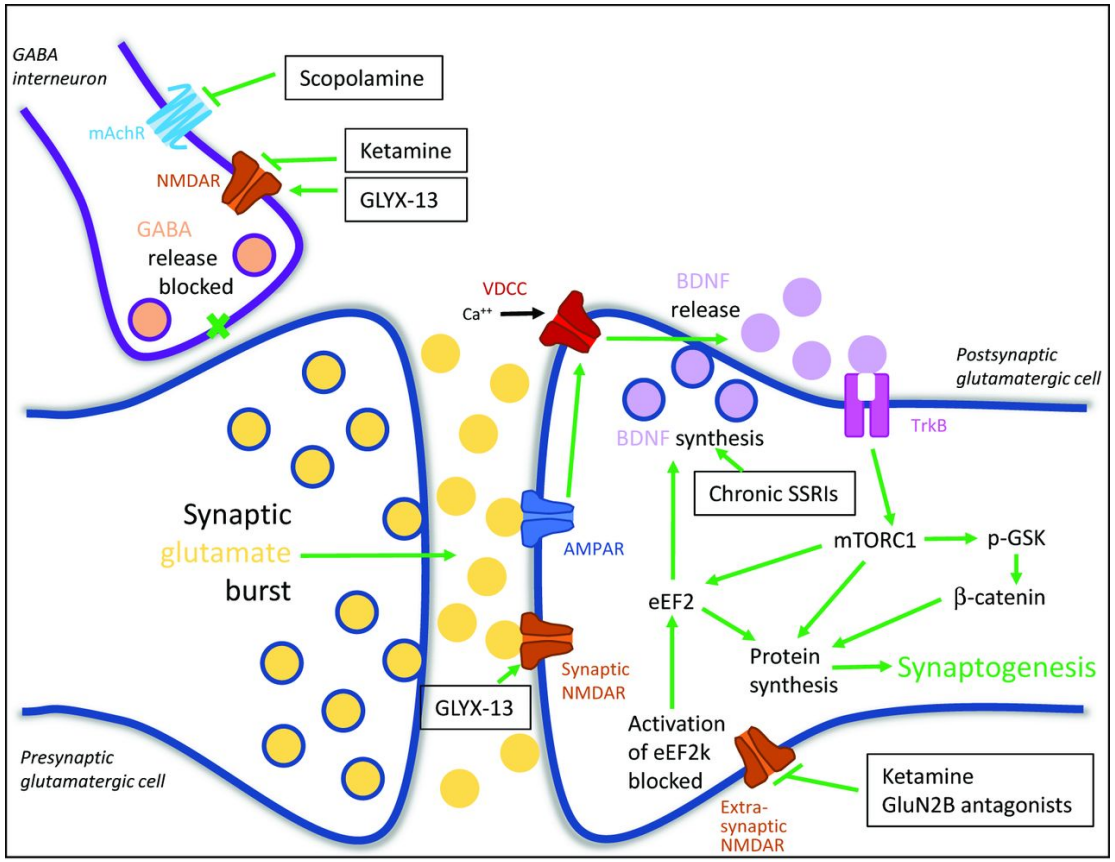
- Stress-induced loss of glia leads to excess extracellular glutamate.
- Glutamate binds to presynaptic mGluRs that inhibit synaptic glutamate release.
- Glutamate binding to extrasynaptic $NMDA_R$ leads to phosphorylation of eEF2, which inhibits synthesis of BDNF.
- Stress also inhibits the mTORC1 pathway.
- mTORC1 promotes the translation of synaptic proteins necessary for new dendrite formation.



Hare, Duman, 2017

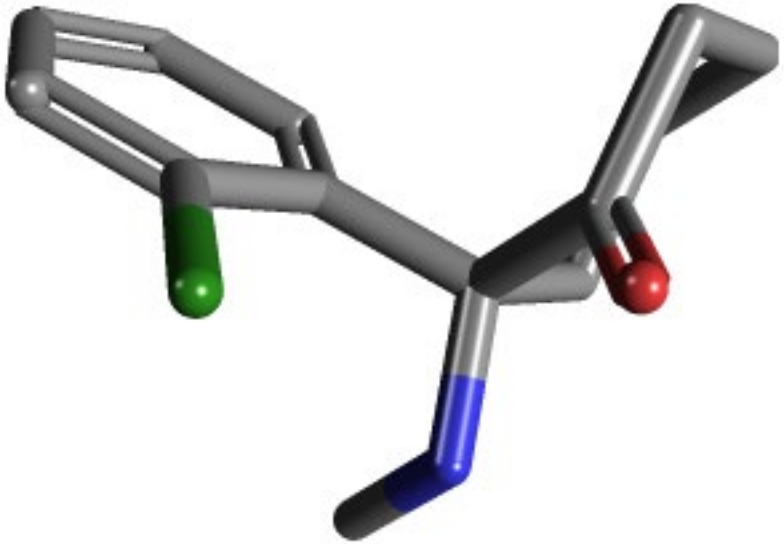
Proposed Effects of Ketamine on Glutamate System

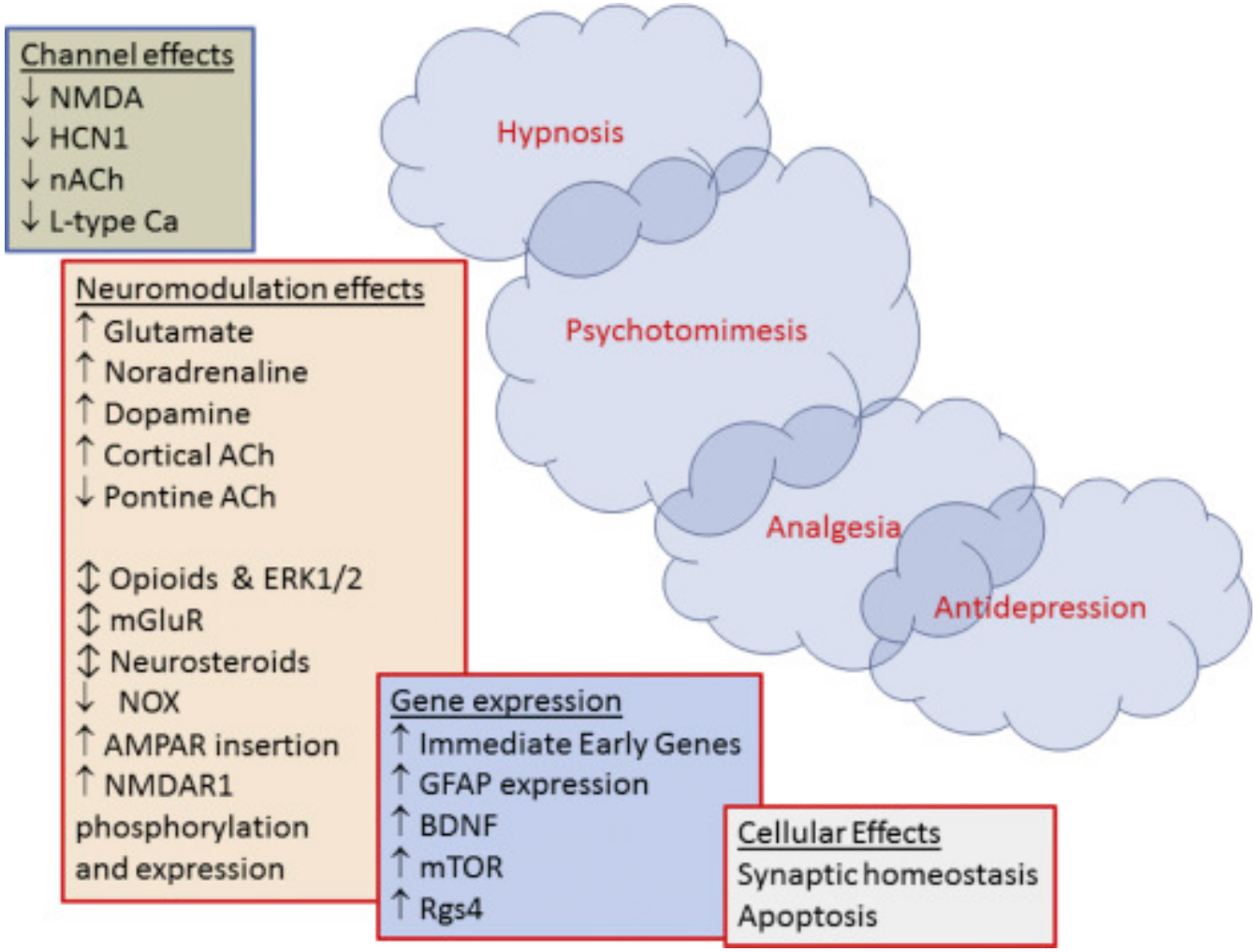
- Ketamine blocks the activity of the $NMDA_R$.
- The glutamate burst activates synaptic AMPA receptors (AMPARs) triggering the release of BDNF, which binds to tropomysin receptor kinase B (TrkB) and induces mTORC1 signaling.
- This leads to activation of elongation factor 2 kinase (EF2k), which inhibits eEF2; blockade of extrasynaptic $NMDA_R$ induce BDNF synthesis and other protein synthesis via eEF2.



Hare, Duman, 2017

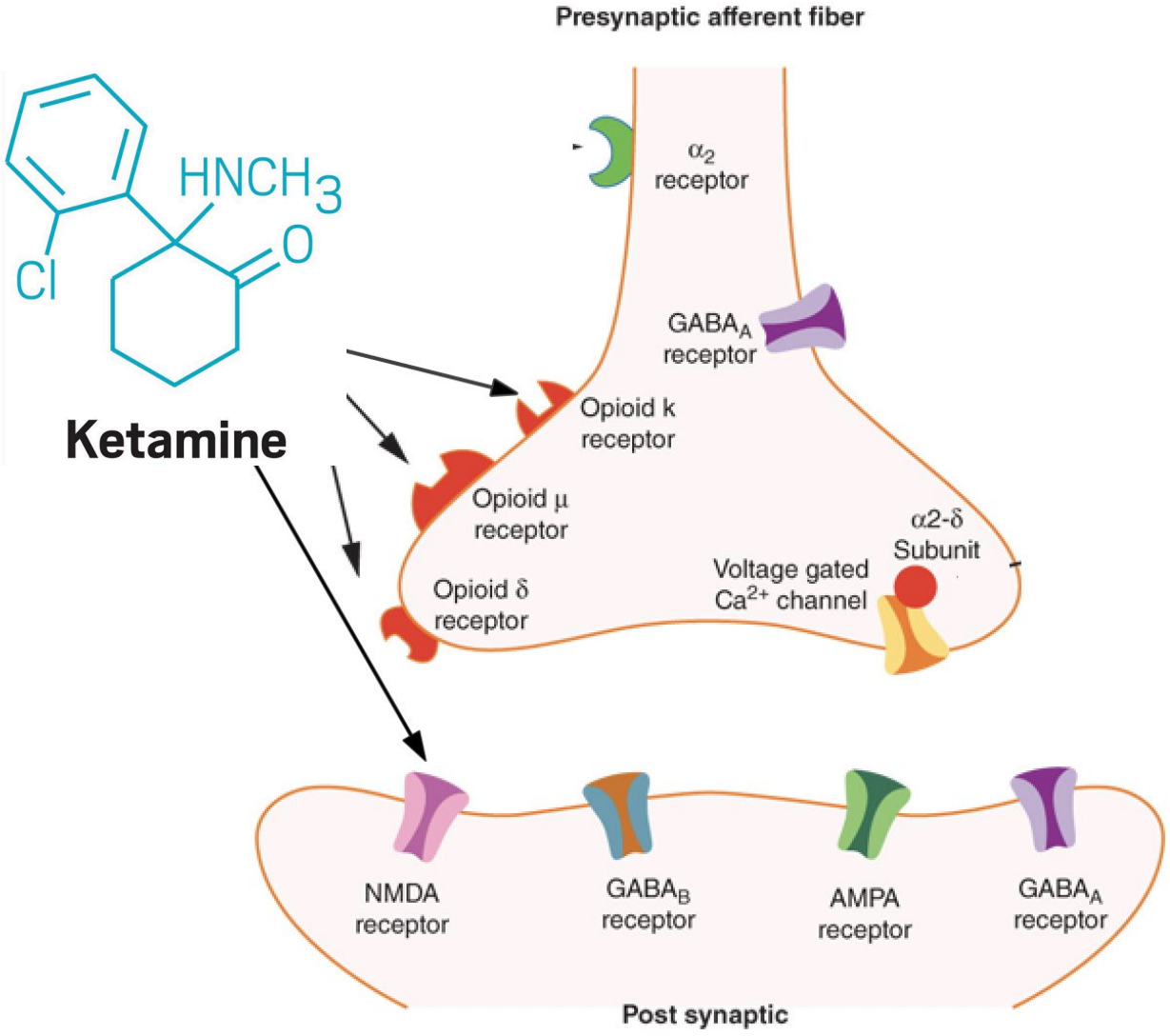
Ketamine Affects Many Neurotransmitter Systems





Ketamine Interacts with the Opioid System

- Human and preclinical studies have found that ketamine:
  - Substantially potentiates the analgesic effect of opioids (Baker et al, 2002).
  - Produces opioid-receptor dependent analgesia (Ryder et al, 1978; Sarton et al, 2001; Pacheco et al, 2014).
  - Reduces opioid tolerance and opioid-induced hyperalgesia to opioids (Koppert et al, 2003).
  - Produces an MOR-dependent respiratory depression (Sarton et al, 2001).



Ketamine Interacts with the Opioid System

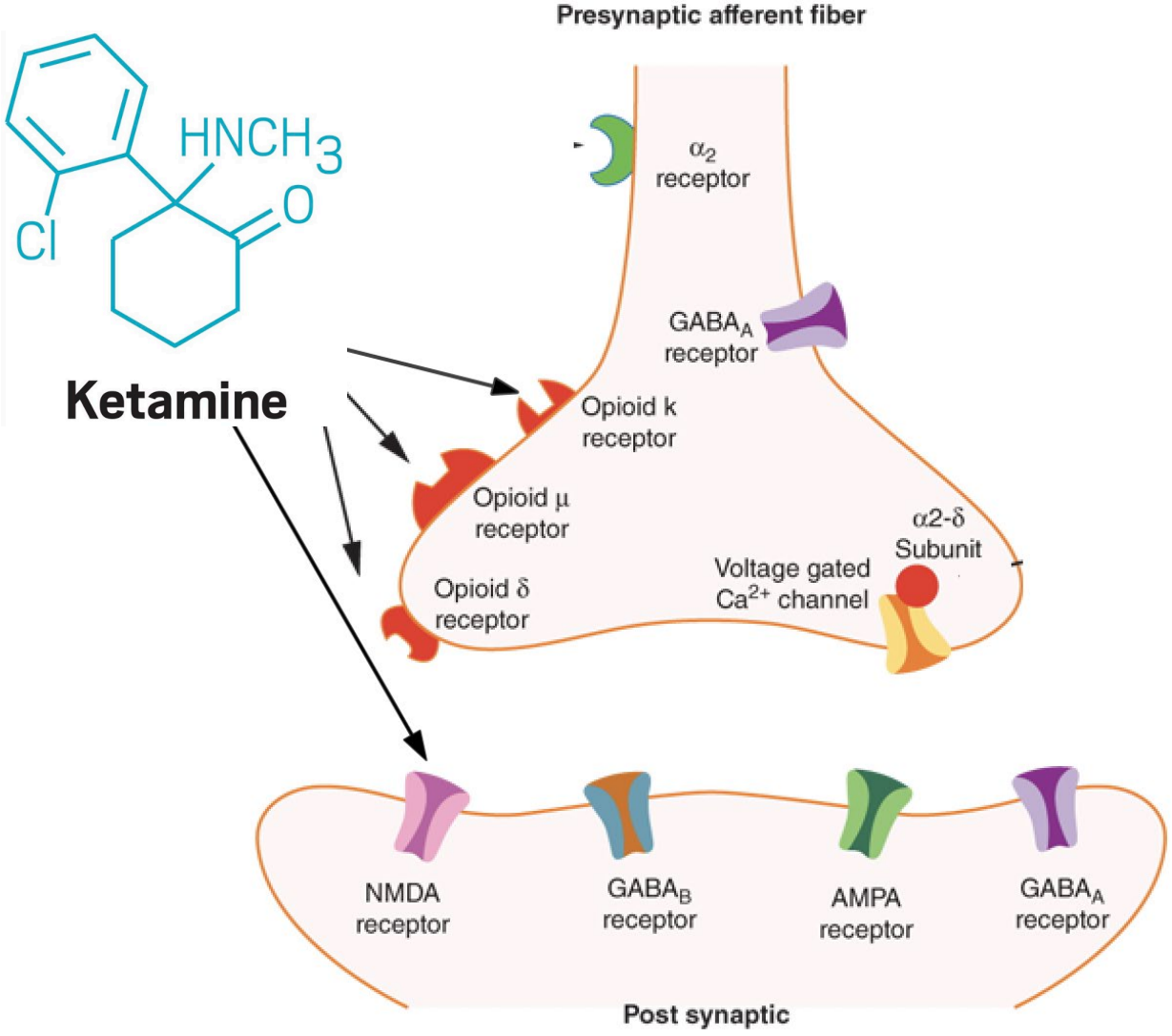
- Meta-analyses consistently show that ketamine has a clinically significant opiate-sparing effect for acute postoperative pain (Jonkman et al, 2017).

- Ketamine-mediated analgesia involves either:

  - A direct action at MORs (Finck, 1982; Smith, 1987; Hirota et al, 1999; Salat, 2015)

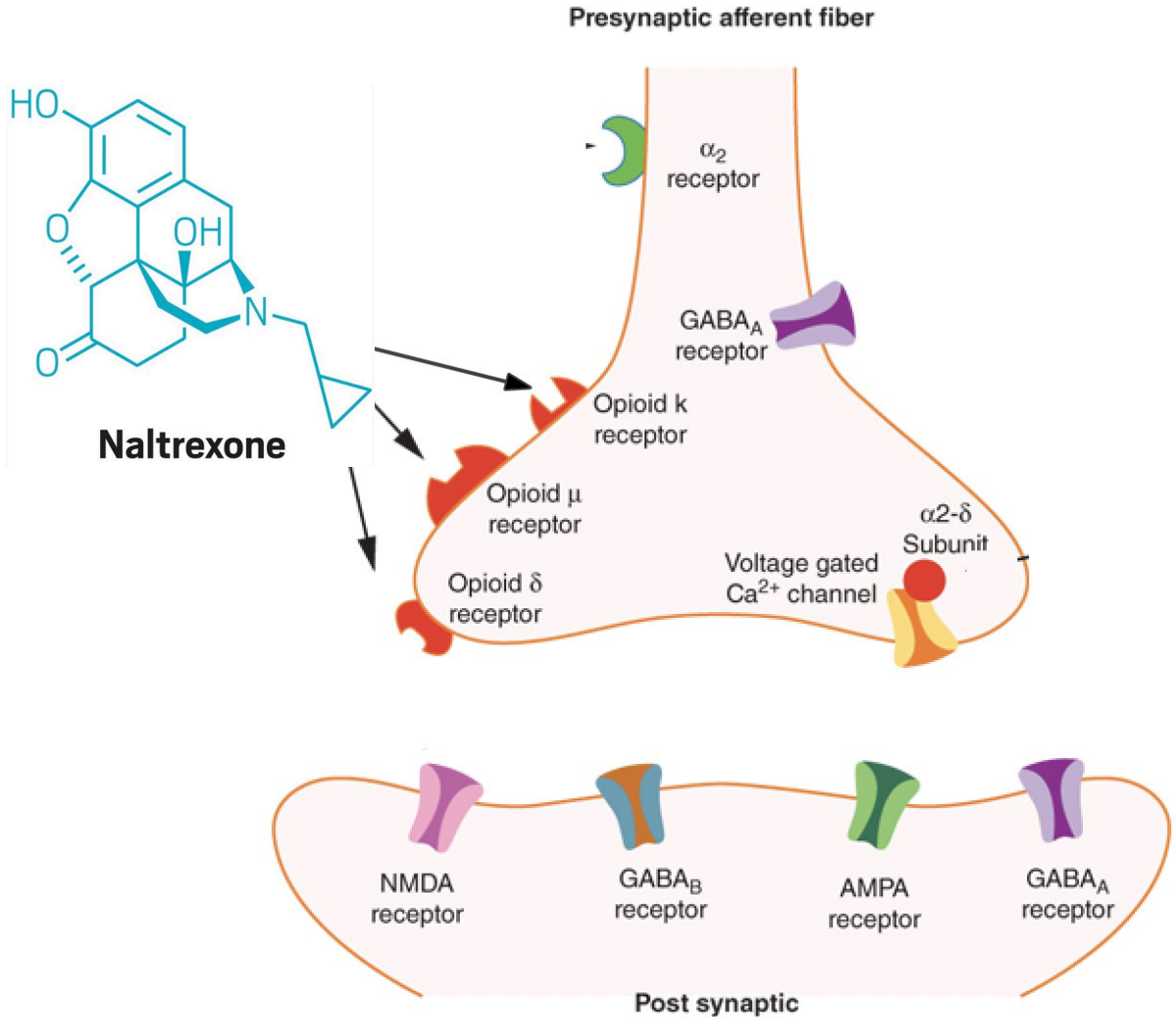
    -AND/OR-

  - An interaction between NMDARs and MORs (Commons et al, 1999; Glass et al, 2009; Rodriguez-Munoz, 2012; Chartoff, 2014).



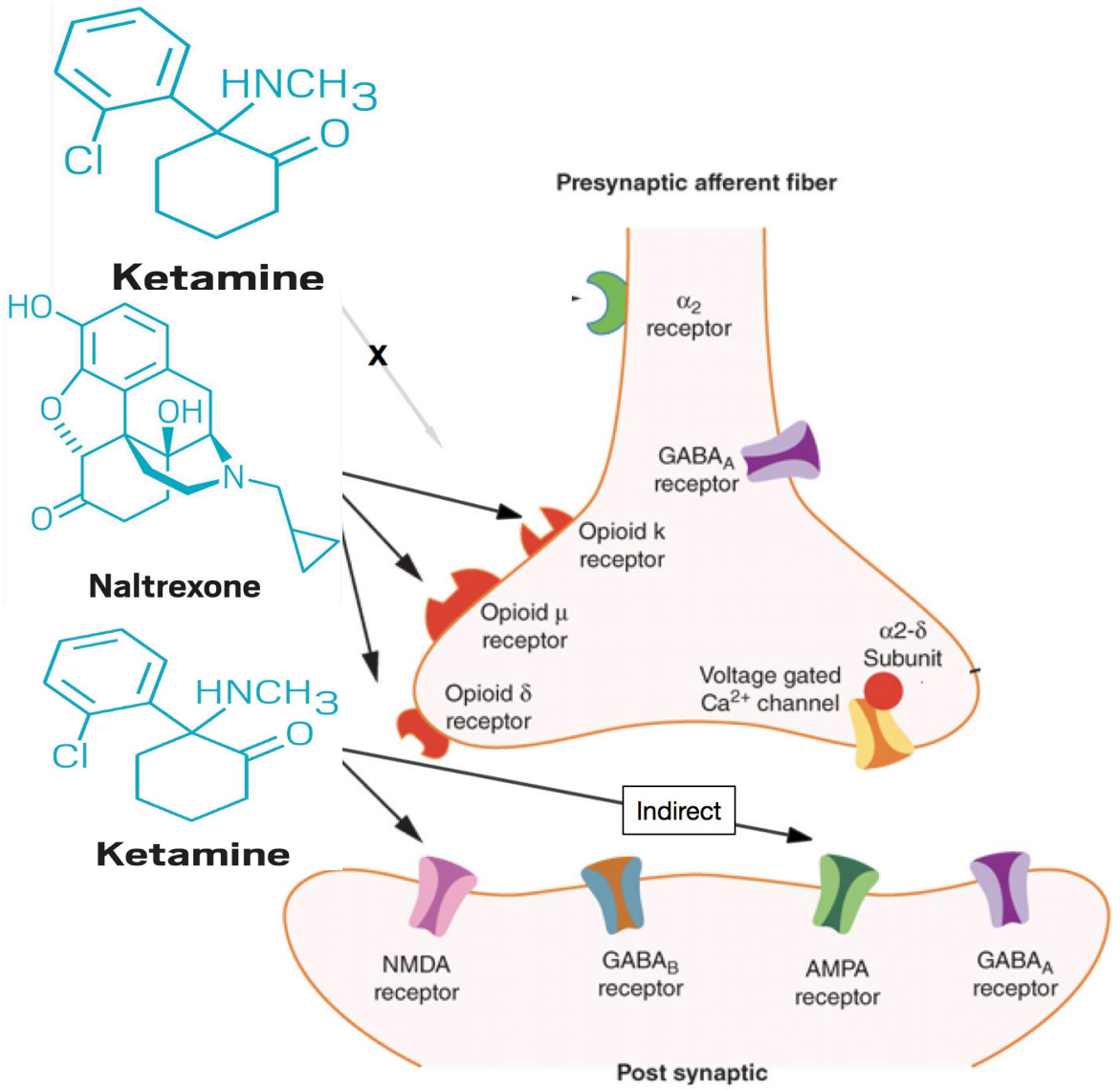
Naltrexone Antagonizes the Opioid System

- Naltrexone is an opioid receptor antagonist (Resnick et al. 1974).
- Naltrexone has no known effects on $NMDA_R$.
- Naltrexone has a 4 hour plasma half-life and its major metabolite, beta-naltrexol, has a 12 hour plasma half-life (Meyer et al. 1984).
- Naltrexone at 50mg oral doses provides complete blockade of the MOR and has a 96 hour half-life in the human brain (Lee et al. 1988).
- Naltrexone pretreatment attenuates the acute psychoactive effects of methamphetamine (Ray et al. 2015).



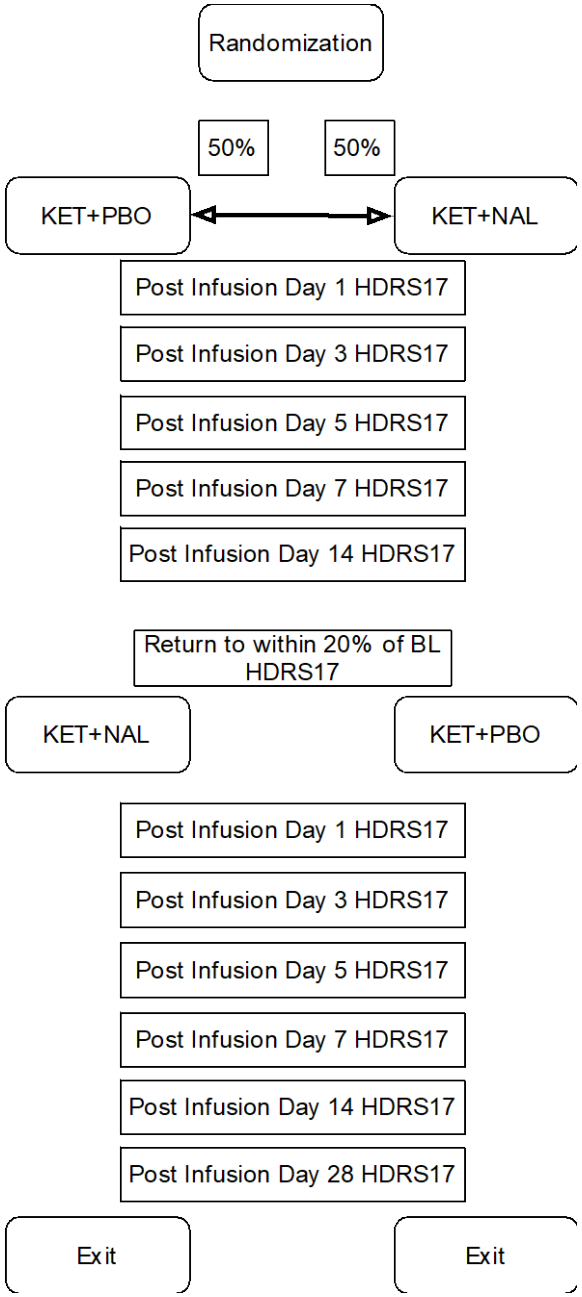
Theoretical Underpinnings of Study Design

- $NMDA_R$ antagonists are not effective antidepressants (Williams 2016).
- Some opioids are effective antidepressants (Pecina 2018).
- Ketamine has opioid effects (Jonkman 2017).
- Naltrexone has not been demonstrated to negatively affect mood (Zaaijer 2015).
- Concurrent administration of naltrexone should only attenuate the antidepressant effects of ketamine if the MoA for ketamine is opioid system mediated.



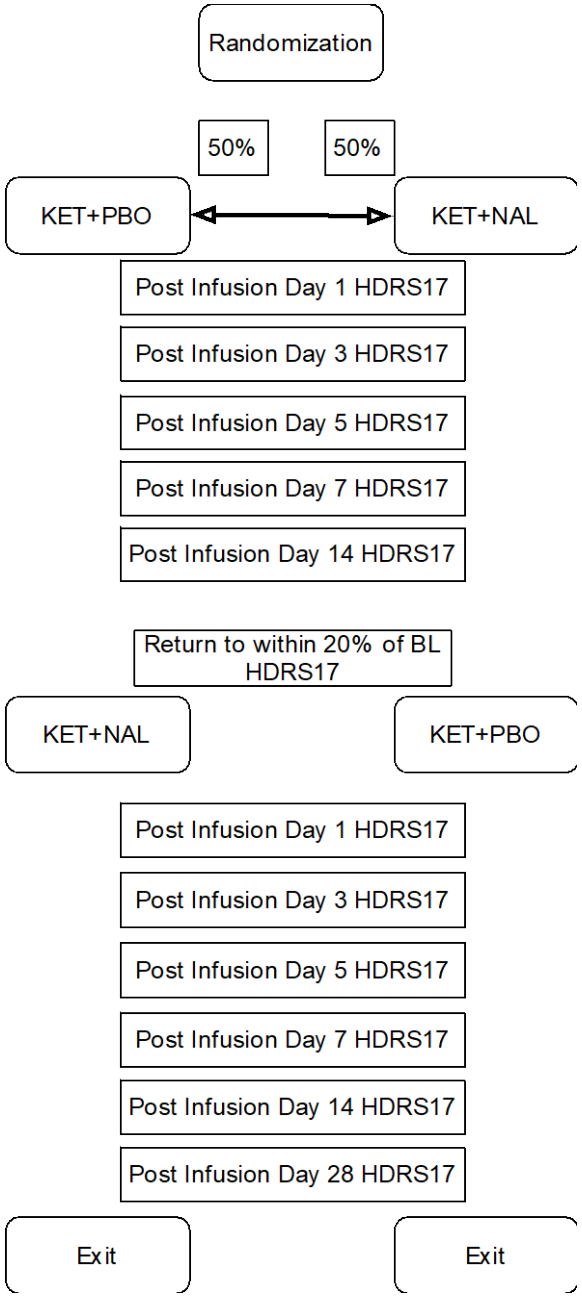
Study Design

- Inclusion criteria included a current diagnosis of a non-psychotic, non-atypical major depressive episode (MDE) as part of either bipolar II disorder or major depressive disorder (MDD), defined by DSM-5 criteria.
- For the initial enrollment, all participants needed a score ≥20 on the 17-item Hamilton Rating Scale for Depression (HRSD17).
- Each needed to:
  - Have not benefited sufficiently from trials of at least 4 different classes of antidepressant medications or other somatic treatments as defined by the Antidepressant History Treatment Form (ATHF) criteria -AND-
  - A minimum of 6 weeks of prior psychotherapy during any MDE prior to intervention.



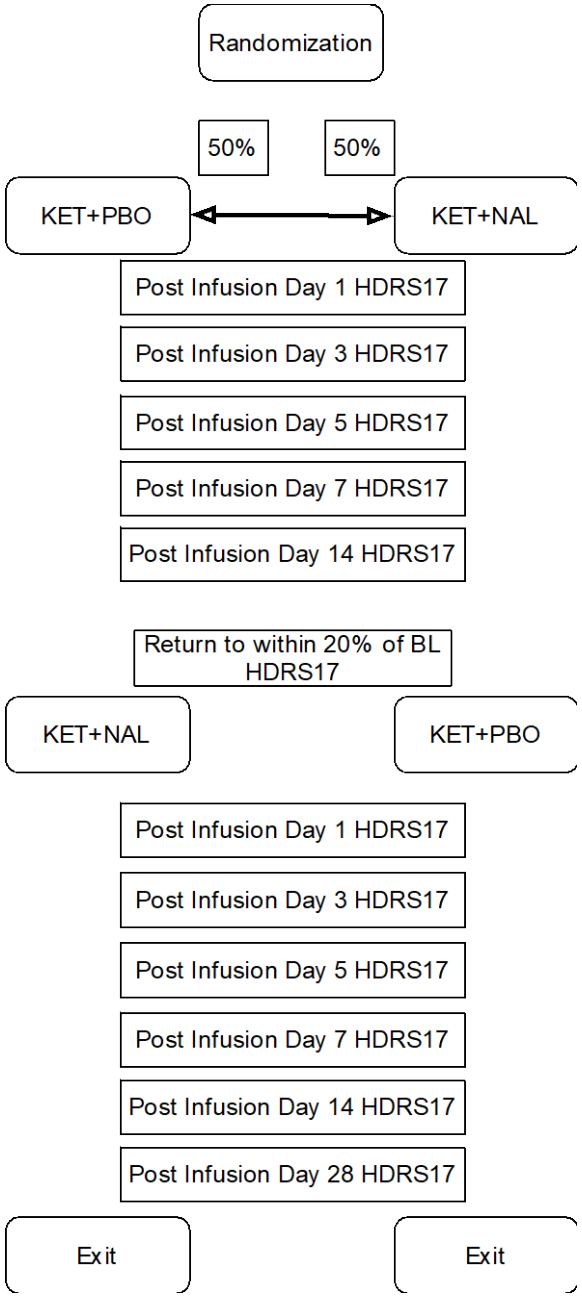
Study Design

- The study utilized a double-blinded crossover design with two treatment conditions:
  - A 0.5mg/kg infusion of ketamine plus oral placebo.
  - A 0.5mg/kg of ketamine plus oral naltrexone (50mg).
- Order of treatment was counterbalanced and the pills were identical in appearance.
- Investigators and participants were blinded to the order of treatments received.
- Oral medication was given 45 min prior to ketamine infusion.
- Ketamine 0.5mg/kg was administered intravenously over 40 minutes.

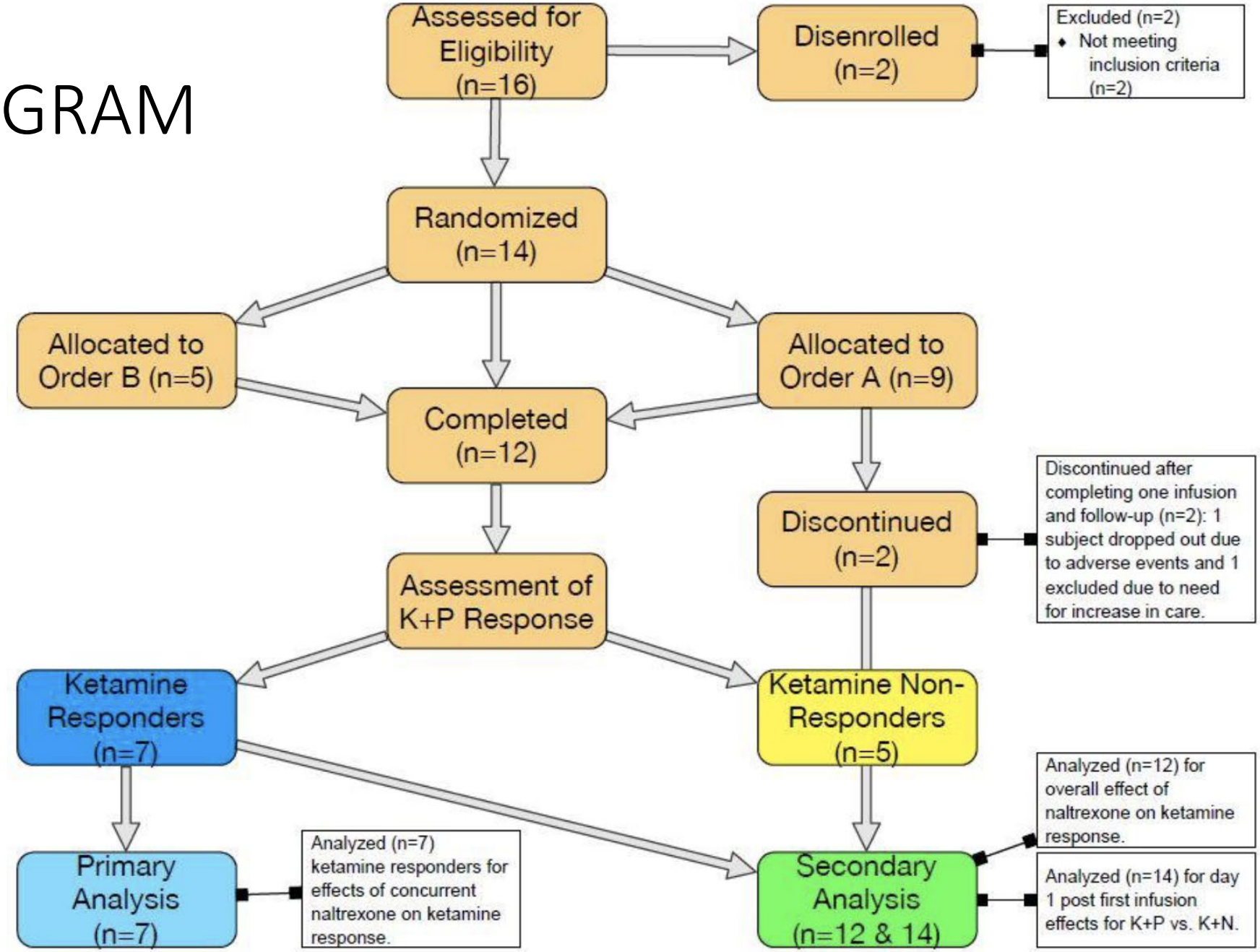


Study Design

- The primary efficacy measure was the total depression score from the Hamilton Depression Rating Scale 17-item (HDRS-17) at day 1.
- Outcome measures were also administered on days 3, 5, 7, 14.
- In the first treatment condition, patients were assessed 15 then 30 days post-infusion to evaluate relapse, defined a priori as having an HDRS-17 total score within 20% of their baseline score, and to determine eligibility for entering the second treatment condition.
- Once relapse was determined, participants crossed over and received the second treatment condition (i.e., patients randomized to ketamine + placebo in their first treatment received ketamine + naltrexone in their second treatment).



CONSORT DIAGRAM

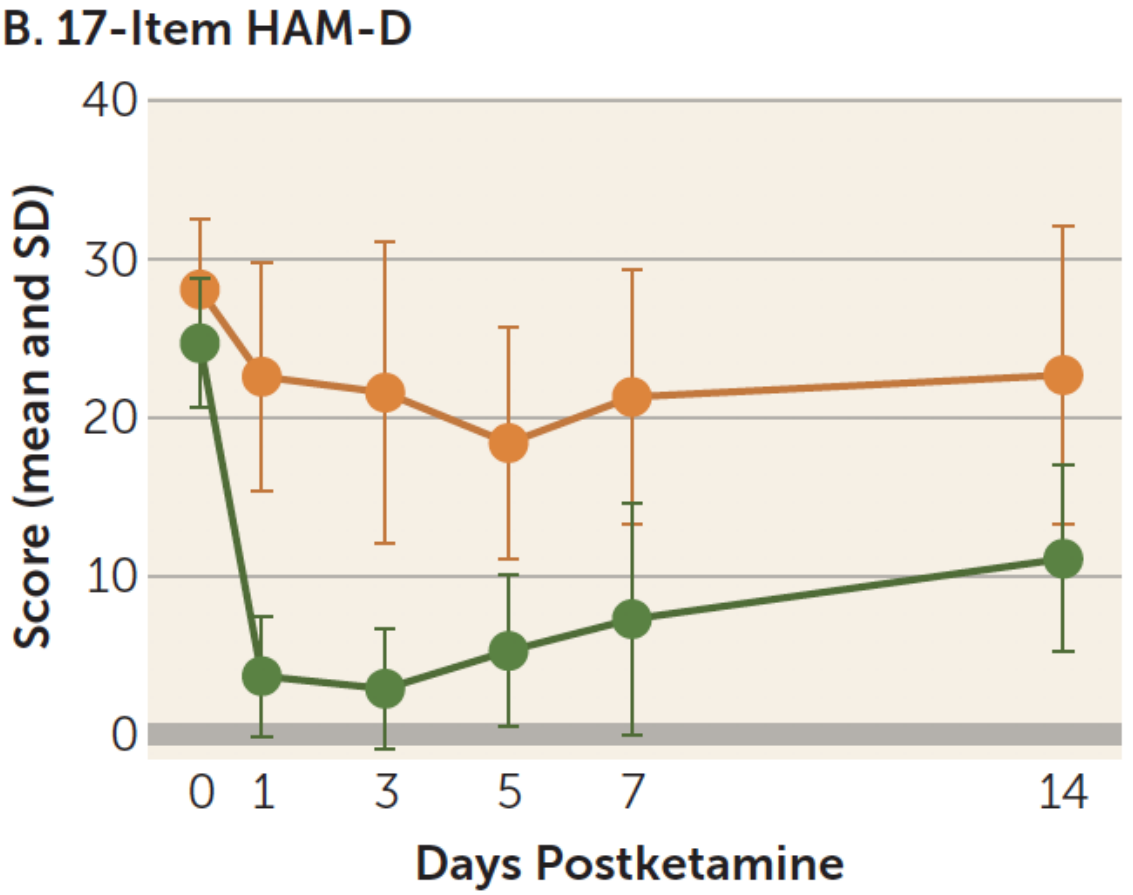


Demographics for Ketamine Study

	All		Responder		Non-Responder	
	Mean	SD	Mean	SD	Mean	SD
Current Age	41.3	11.8	39.8	8.2	44.4	18.2
Age at MDD onset	17.3	4.3	16.3	3.2	17.8	5.8
Length of Illness (years)	24.1	10.6	23.5	9.2	26.6	14.6
Current Depressive Episode (years)	8.6	7.4	7.7	8.3	10.2	6.8
Total med failures in current episode	8.4	8.7	6.6	7.3	7.8	7.0
Antidepressant failures in current episode	4.4	3.2	3.7	3.0	4.0	1.9
Total number antidepressants, lifetime	7.1	3.8	7.4	4.2	5.6	3.4
	N	%	N	%	N	%
Gender (Female)	6	42.9	4	57.1	1	20.0
Diagnosis Recurrent MDD	12	85.7	7	100.0	4	80.0
Previous Brain Stimulation Therapies (ECT or TMS)	6	42.9	2	28.6	2	40.0
Past Psychotherapy	11	78.6	6	85.7	3	60.0
Family History of Depression	5	35.7	3	42.9	2	40.0
	Mean	SD	Mean	SD	Mean	SD
HDRS Score (17 item), Baseline	25.9	4.6	26.0	4.3	26.6	5.8
MADRS, Baseline	35.3	4.9	35.1	3.8	35.6	4.8
CGI-S, Baseline	5.1	0.5	5.1	0.4	5.0	0.7
BDI-II Self report, Baseline	30.1	10.5	29.1	9.5	28.8	9.8

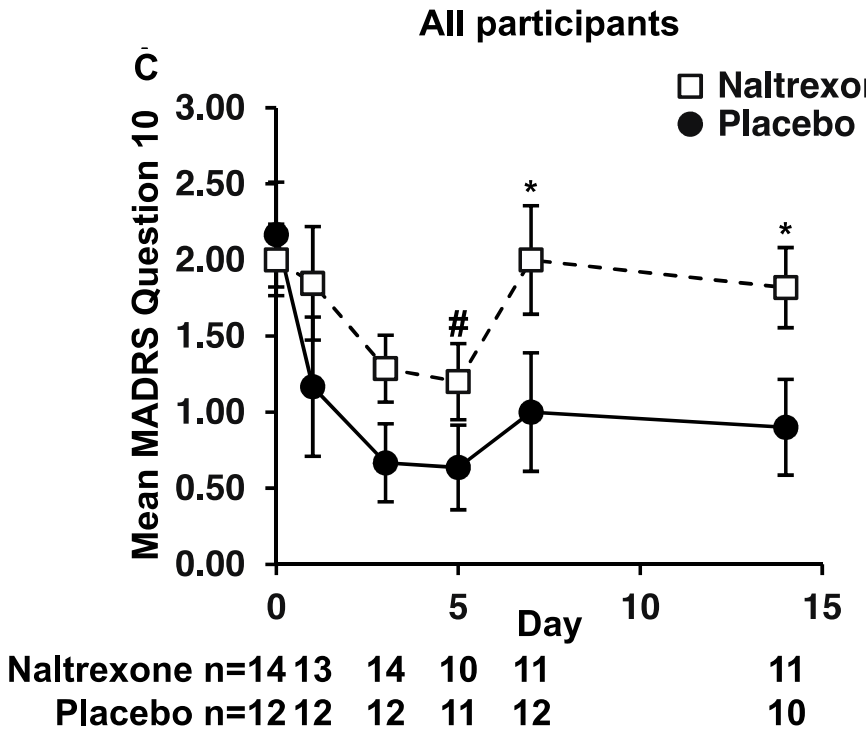
Naltrexone Pretreament Blocks Ketamine's Antidepressant Effect in Ketamine Responders

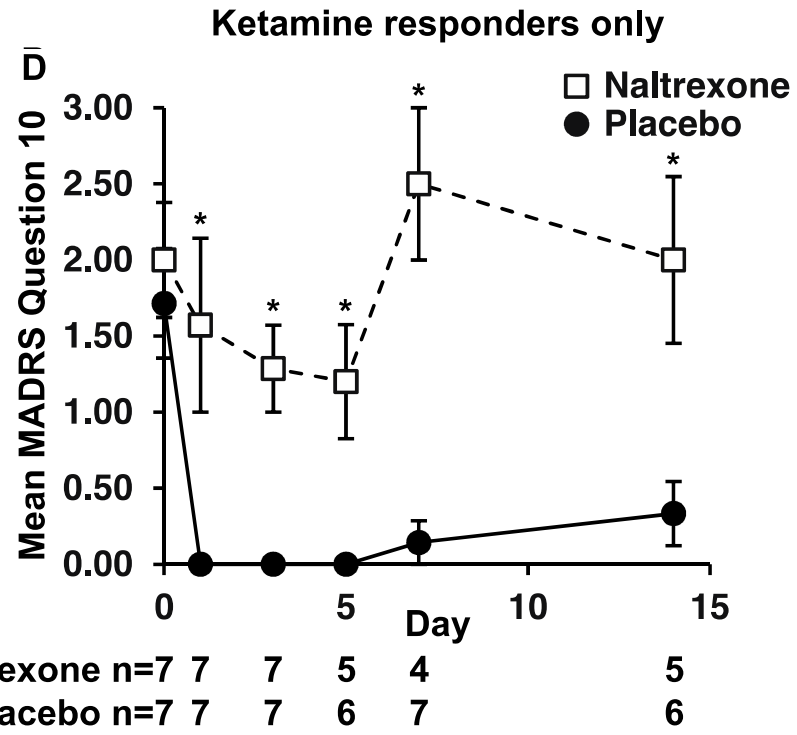
- Time course of HDRS17 scores (mean ± SEM) for patients in 2 conditions ketamine + placebo (KET+PBO) and ketamine + naltrexone (KET+NAL).
- KET+NAL scores were significantly attenuated at Day 1 and Day 3 compared to KET+PBO (p=0.0006).
- 6 of 7 patients were remitters (HDRS17≤ 7) at Day 1 with KET+PBO and 0 of 7 patients were responders at Day 1 with KET+NAL.



Williams, AJP, 2018

MADRS Question 10





0 = Enjoys life or takes it as it comes.

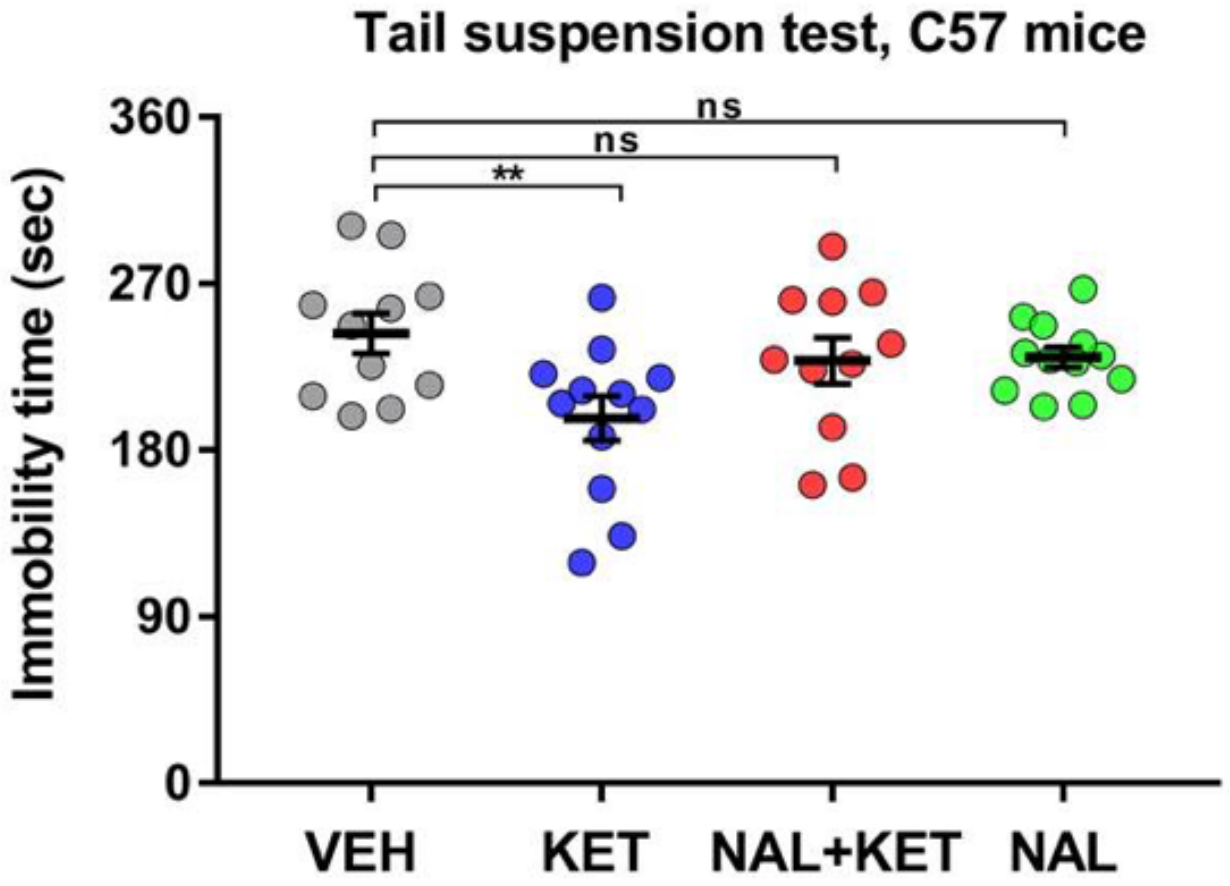
2 = Weary of life. Only fleeting suicidal thoughts.

4 = Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.

6 = Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Mice Pretreated with Naltrexone Do Not Demonstrate Reduced Immobility on TST

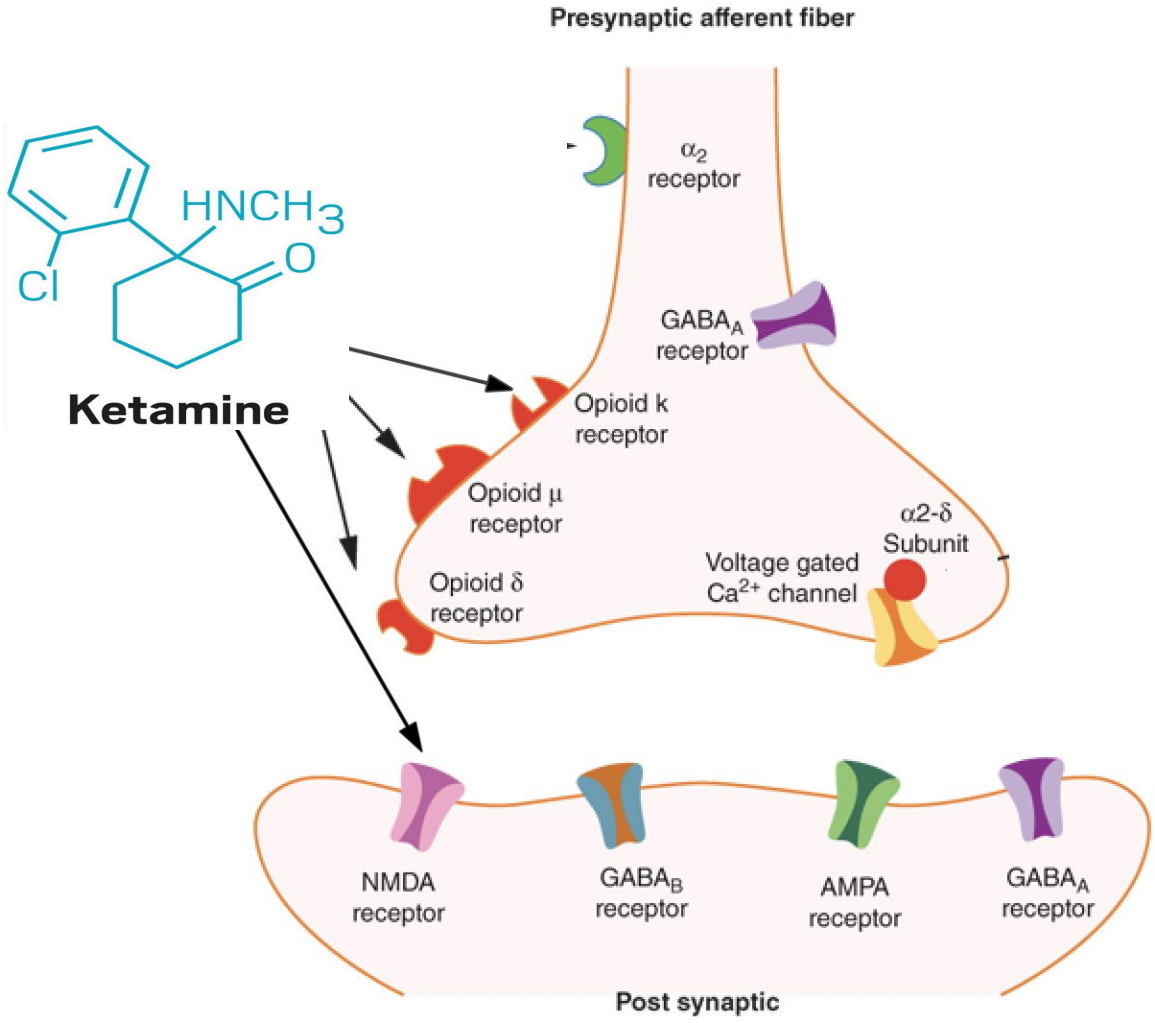
- We conducted a parallel animal model study to determine if naltrexone blocks the ketamine-induced antidepressant effects in mouse.
- Immobility time on Tail Suspension Test (TST) significantly reduced with ketamine (KET) compared to vehicle (VEH) injection.
- Naltrexone (NAL) and naltrexone + ketamine (NAL+KET) were not significantly different than VEH.



Williams, Molecular Psych, in prep

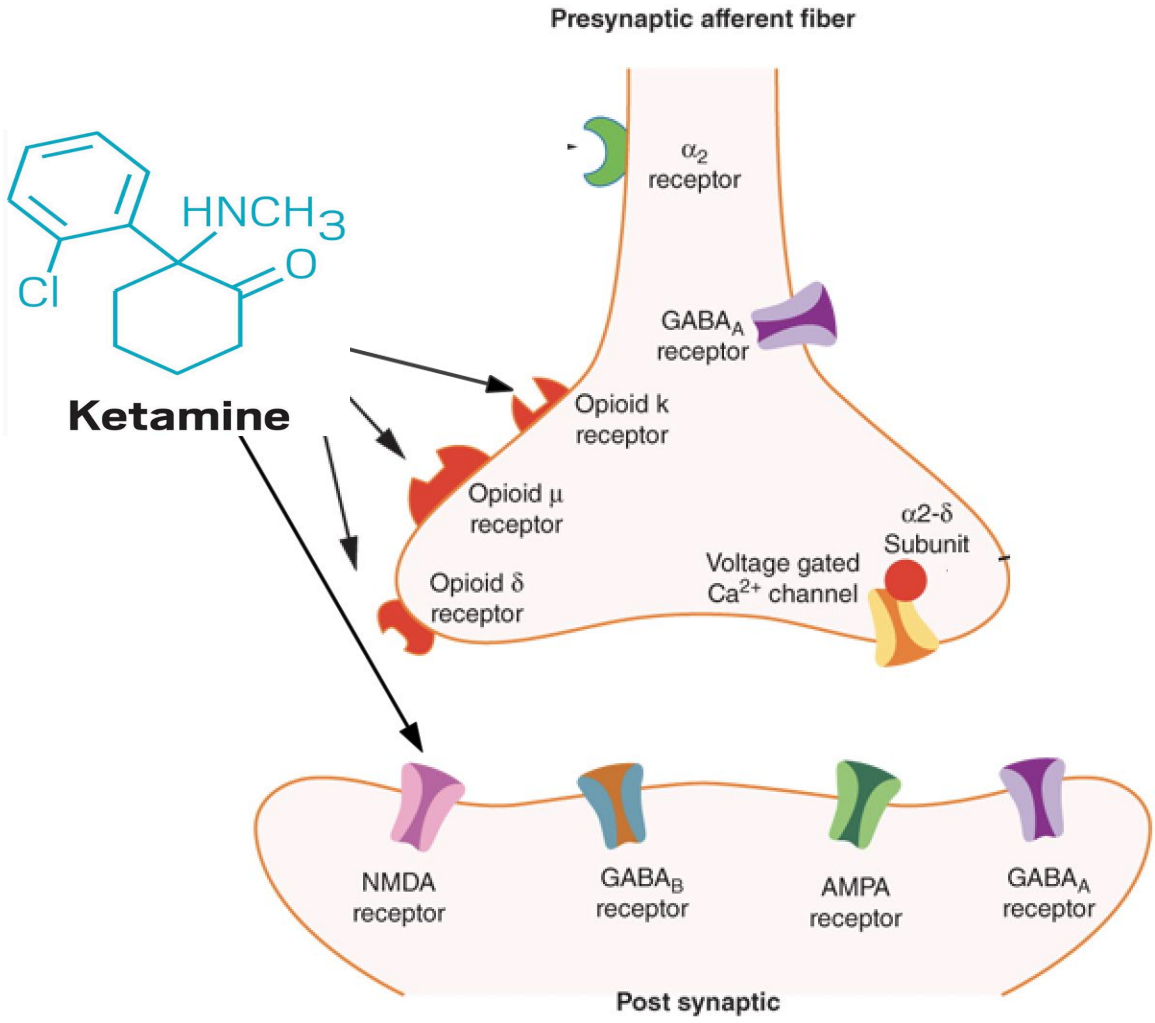
Conclusions

- This is the first study examining the ***opioid properties of ketamine as necessary*** in producing its rapid antidepressant effects.
- The naltrexone blockade of antidepressant response in ketamine alone responders clearly demonstrated that the ***OR agonism is necessary*** to produce the dramatic antidepressant effects observed with intravenous infusion of ketamine.

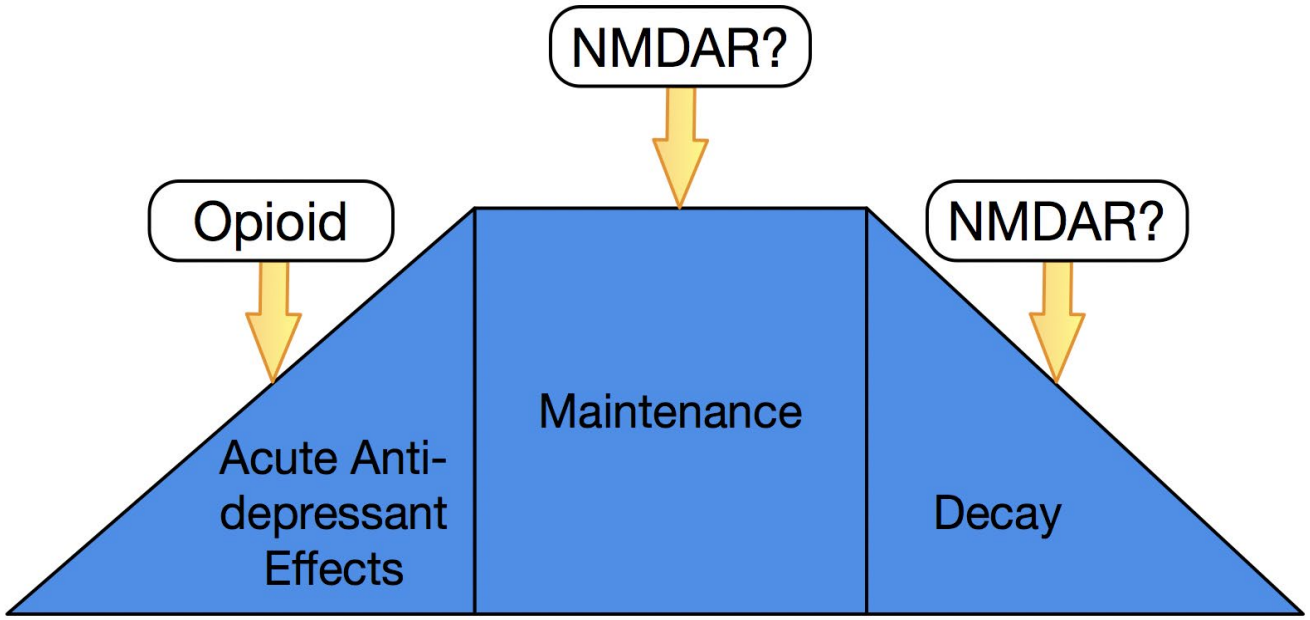


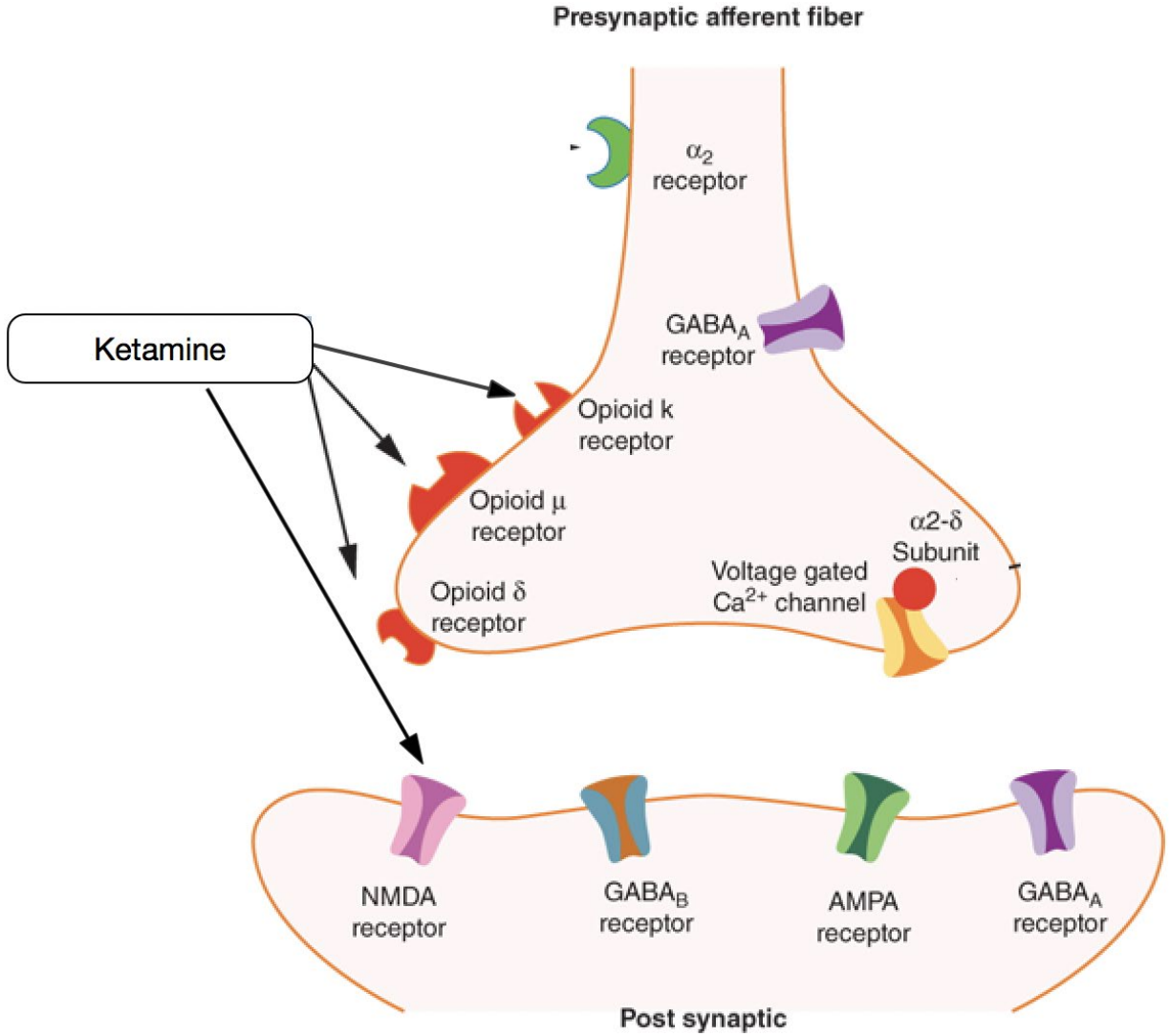
Conclusions

- Our results also demonstrate that the dissociation observed during the ketamine infusion is not due to OR agonism and appears to ***not mediate*** the antidepressant effects of ketamine nor is it ***sufficient*** to produce an antidepressant response.
- This study also suggests that the NMDA and AMPA mechanisms of ketamine alone *are* ***not sufficient*** to produce the dramatic antidepressant effects of ketamine.
- It is conceivable that NMDA antagonism may account for prolonged effects via enhancing synaptic plasticity post initial MOR agonism.

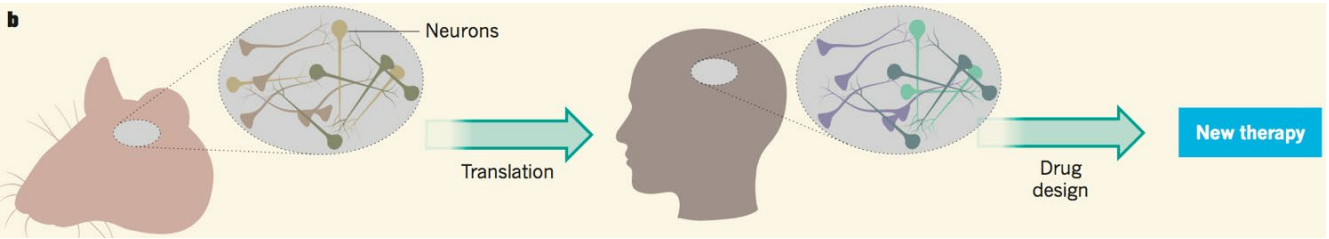


Hypothetical Framework

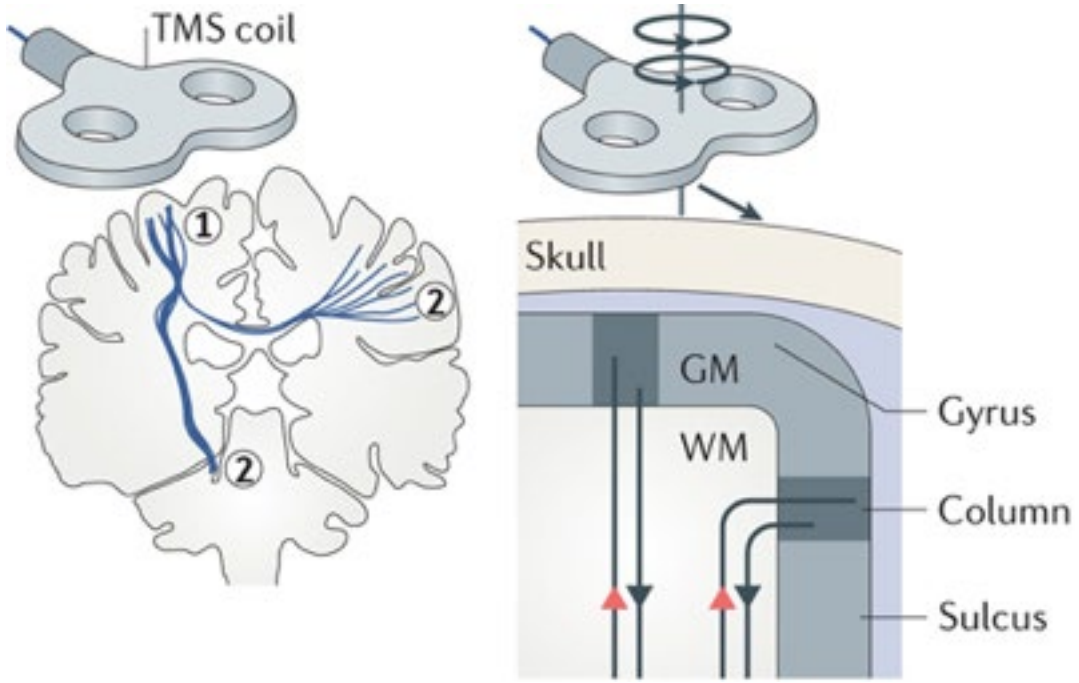




Therapeutic Development for the 21st Century: Constructing a New Path

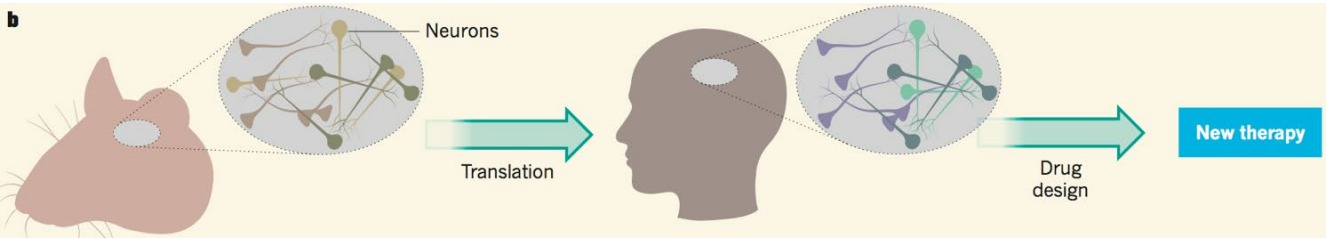


Is >90% remission possible in treatment-resistant depression?



Diana, Nat Rev Neuro, 2017

Therapeutic Development for the 21st Century: Constructing a New Path



Is >90% remission possible in brain disorders?

History of Repetitive Transcranial Magnetic Stimulation

1985

TMS

Tony Barker published first TMS study demonstrating motor evoked potential.

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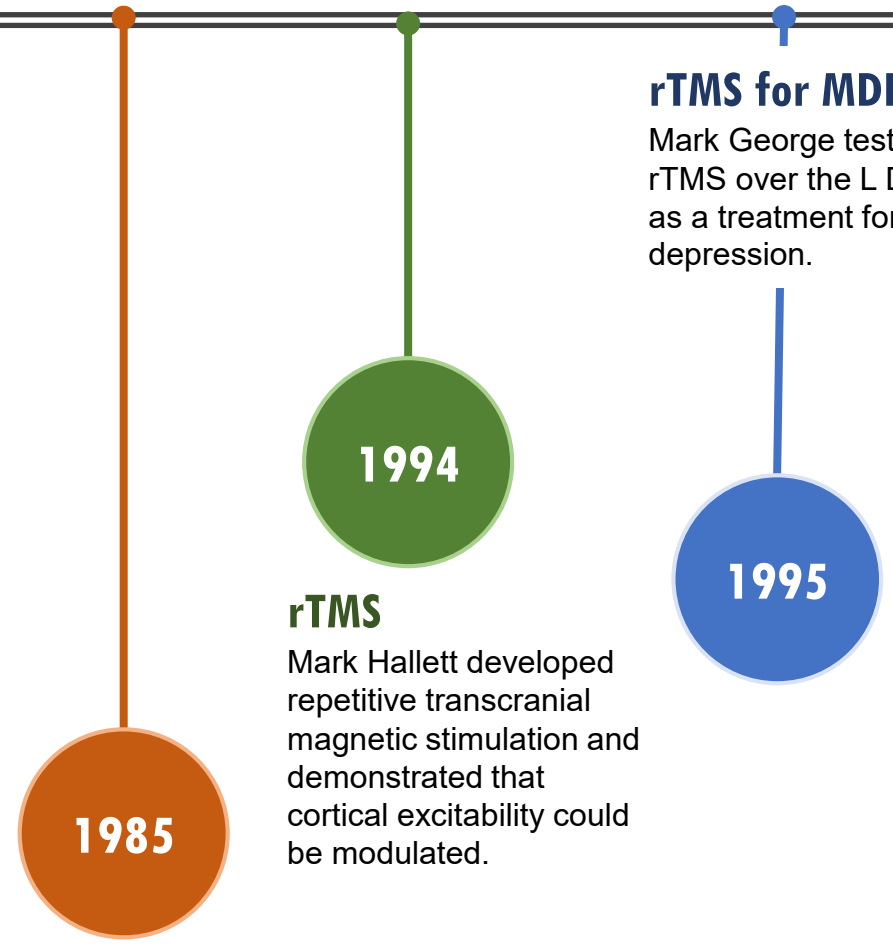
Tony Barker published first TMS study demonstrating motor evoked potential.

1994

rTMS

Mark Hallett developed repetitive transcranial magnetic stimulation and demonstrated that cortical excitability could be modulated.

History of Repetitive Transcranial Magnetic Stimulation



TMS

Tony Barker published first TMS study demonstrating motor evoked potential.

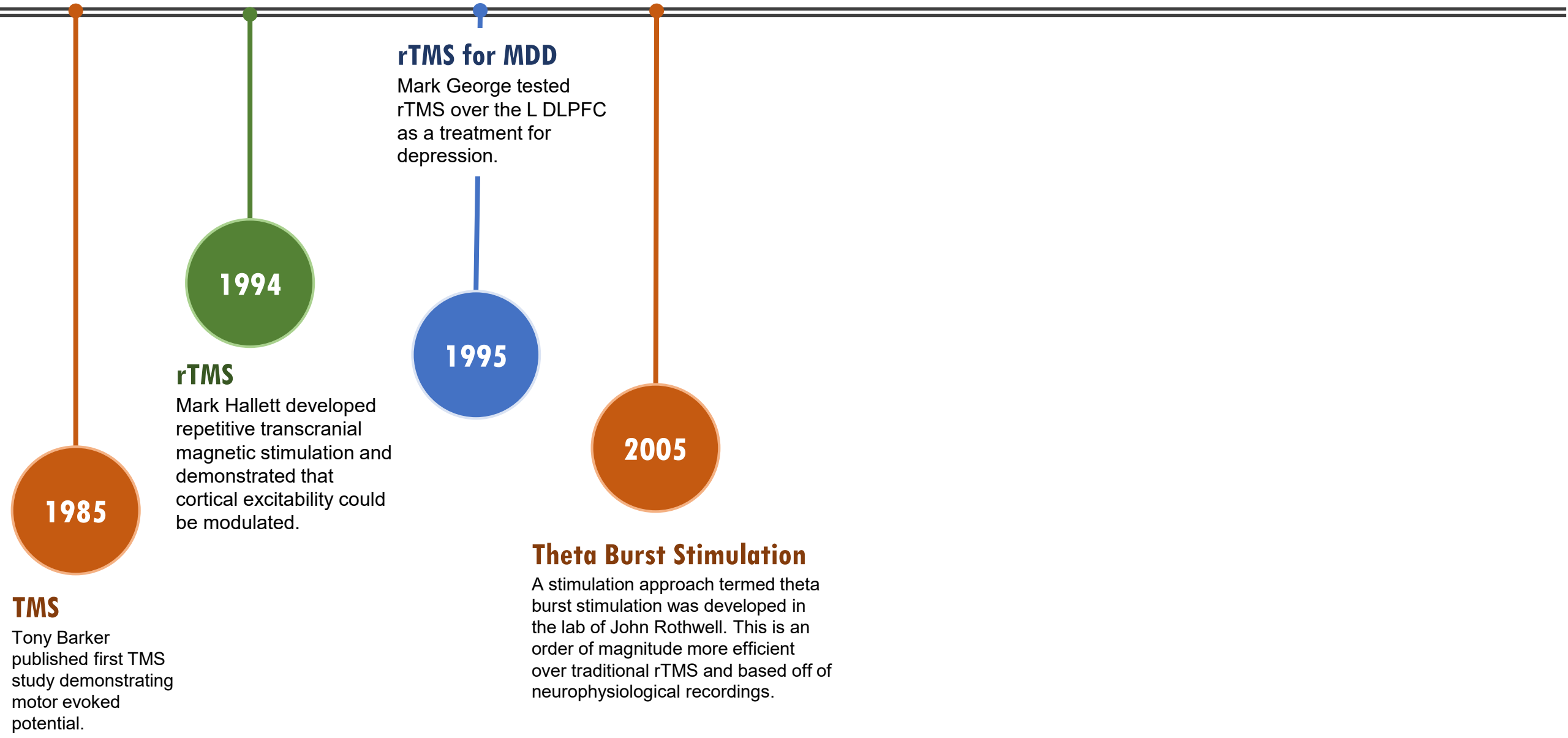
rTMS

Mark Hallett developed repetitive transcranial magnetic stimulation and demonstrated that cortical excitability could be modulated.

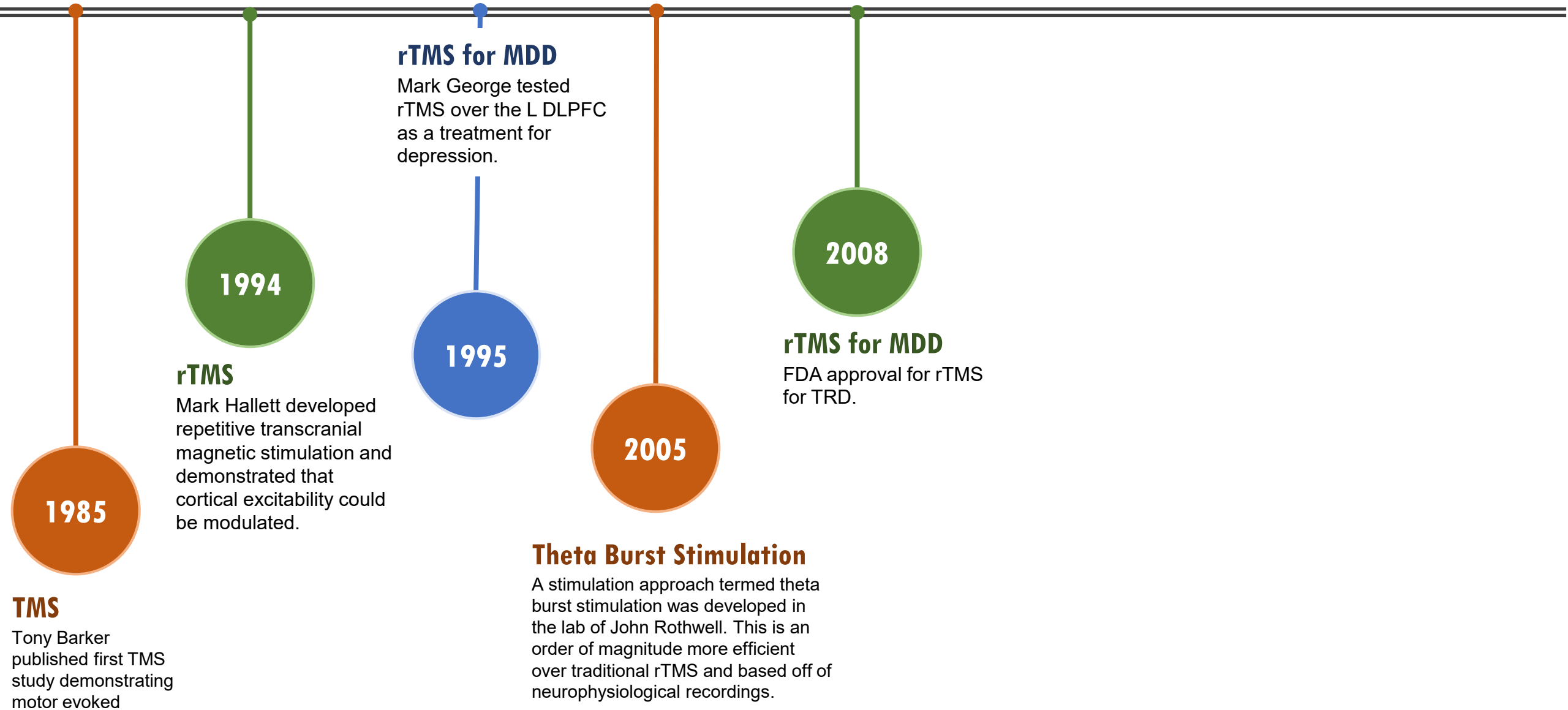
rTMS for MDD

Mark George tested rTMS over the L DLPFC as a treatment for depression.

History of Repetitive Transcranial Magnetic Stimulation



History of Repetitive Transcranial Magnetic Stimulation



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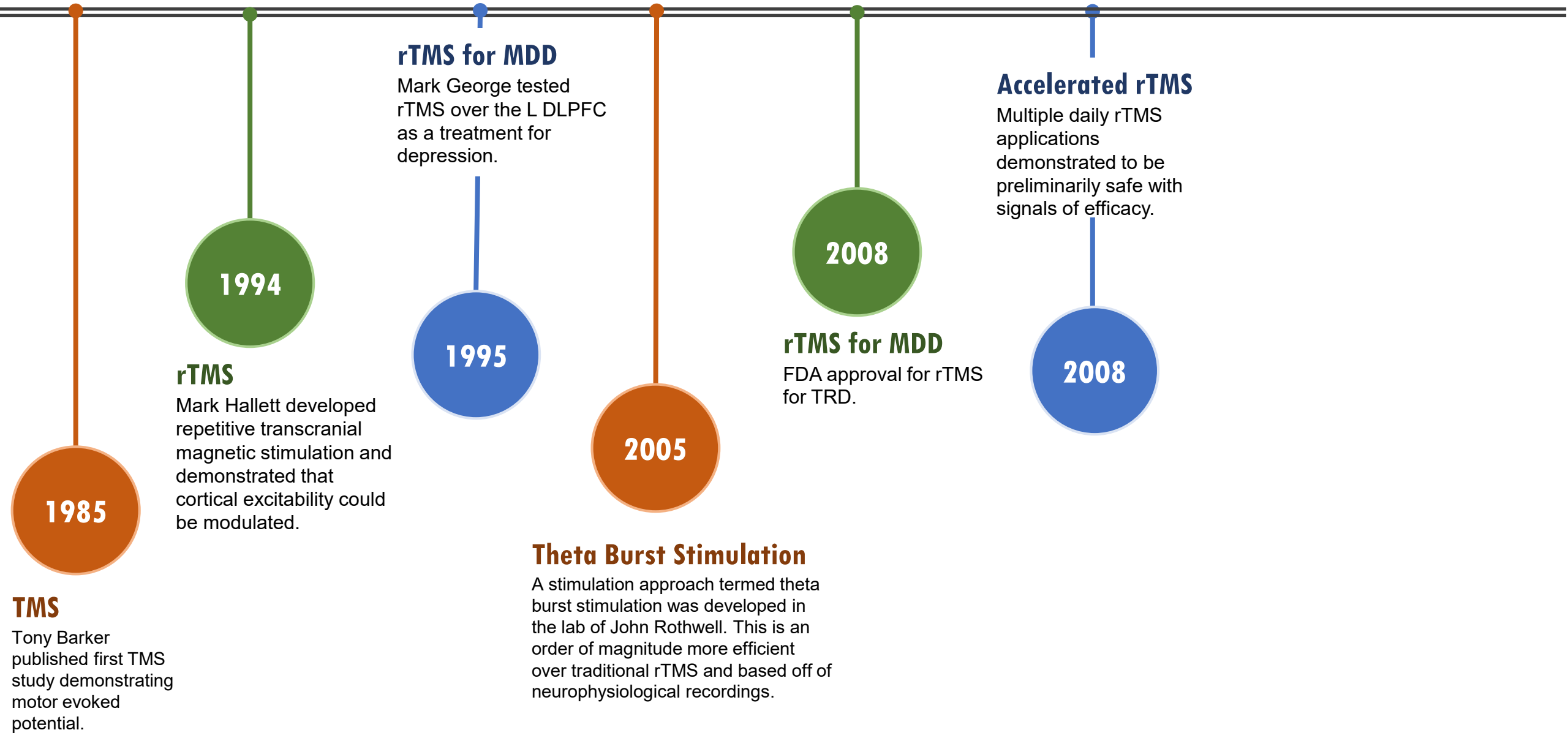

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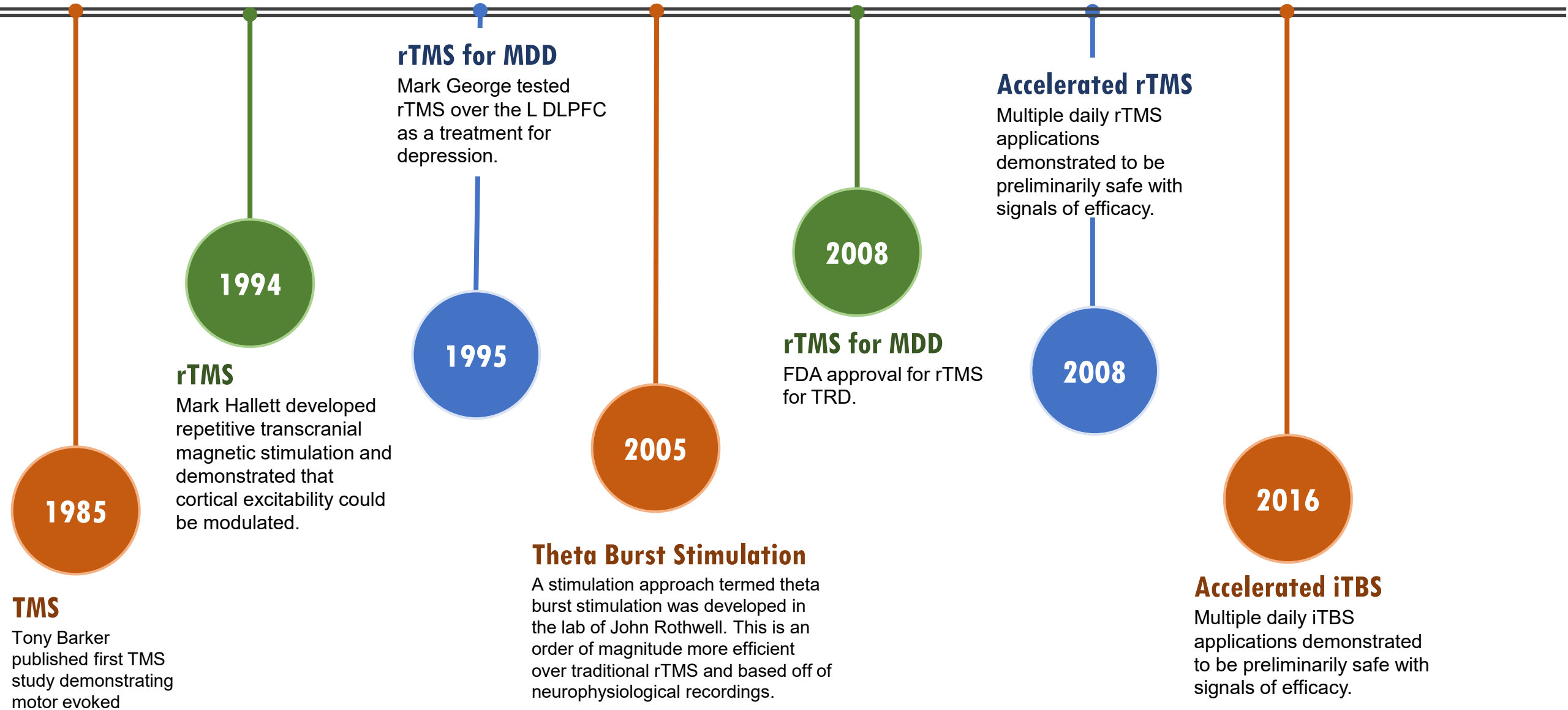

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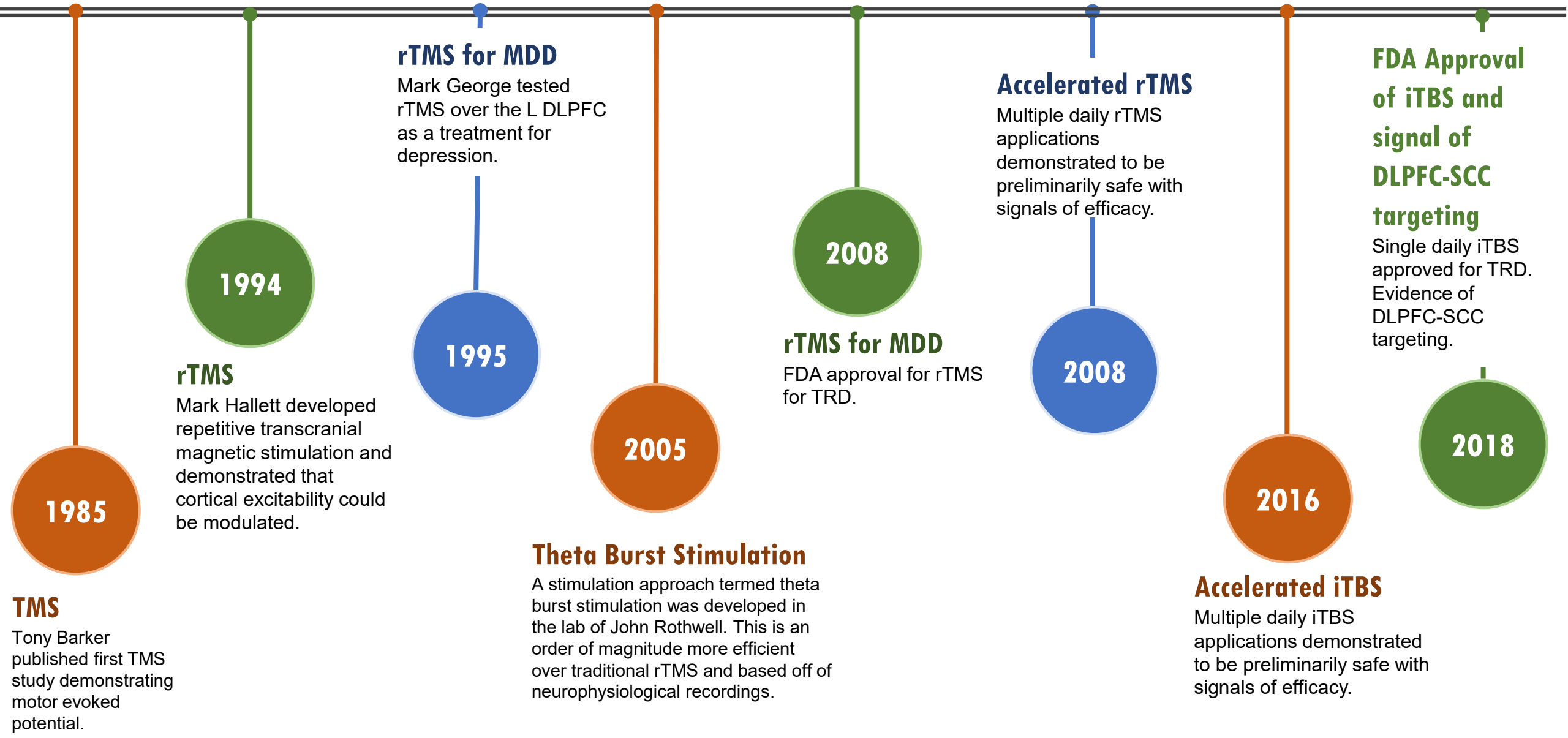
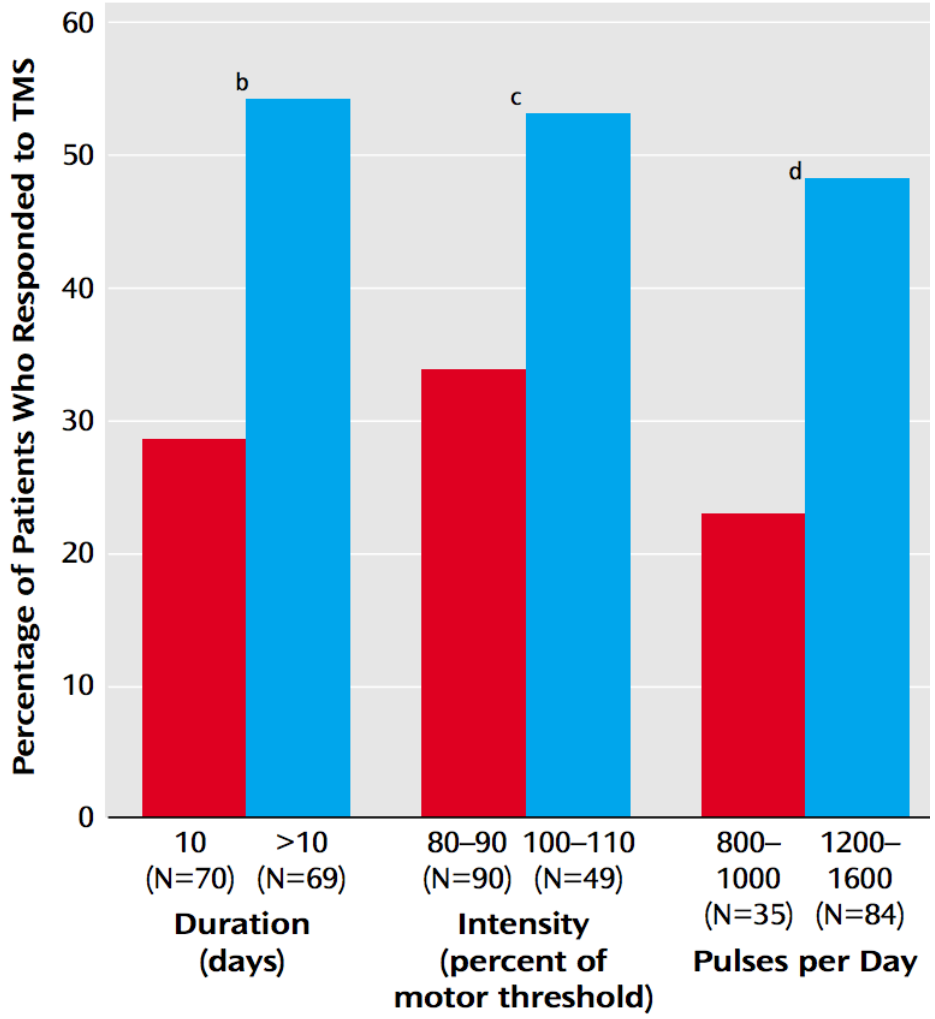


First Generation Stimulation Parameters

- The first reported patient received excitatory left dorsolateral prefrontal cortex in 1995 (L DLPFC) stimulation (George 1995).
- L DLPFC target selected based off of converging clinical and neuroimaging evidence (George 1994).
- Parameters derived from motor physiology findings (Pascual-Leon, 1994).
- The parameters evolved over time with longer duration, higher intensities, and more pulses per day producing greater efficacy.



Original FDA Approved rTMS Parameters

- Frequency: 10Hz
- Pulse Potency: 1X
- Train Duration: 4 seconds
- Inter-train Interval: 26 seconds
- Pulse Dose/session: 3000 pulses/session
- %MT: 120% rMT
- Sessions/day: 1
- Sessions/week: 5
- Sessions/course: 30
- Pulses/course: 90,000 pulses
- Target: L DLPFC
- Targeting: skull-based measurements

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Mon	Mon	Mon	Mon	Mon	Mon
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Tues	Tues	Tues	Tues	Tues	Tues
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Wed	Wed	Wed	Wed	Wed	Wed
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Fri	Fri	Fri	Fri	Fri	Fri

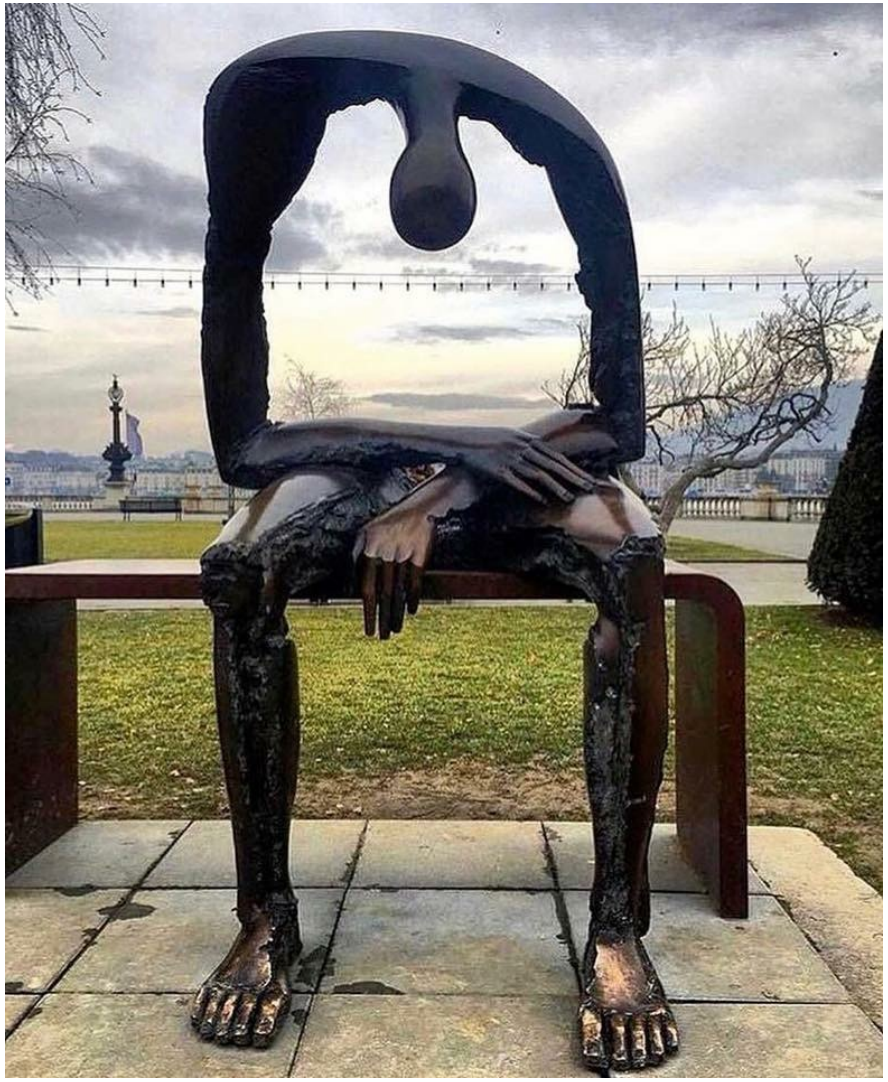
First Generation Stimulation Parameters

- In open label settings, ~30% remit and ~50% respond after this course.
- 62% of patient maintain response/remission at 6 mo and that increases to 84% if mTMS added in.
- Recent data suggests more pulses may increase efficacy (Yip 2017).

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Mon	Mon	Mon	Mon	Mon	Mon
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Tues	Tues	Tues	Tues	Tues	Tues
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Wed	Wed	Wed	Wed	Wed	Wed
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Fri	Fri	Fri	Fri	Fri	Fri

rTMS for SI

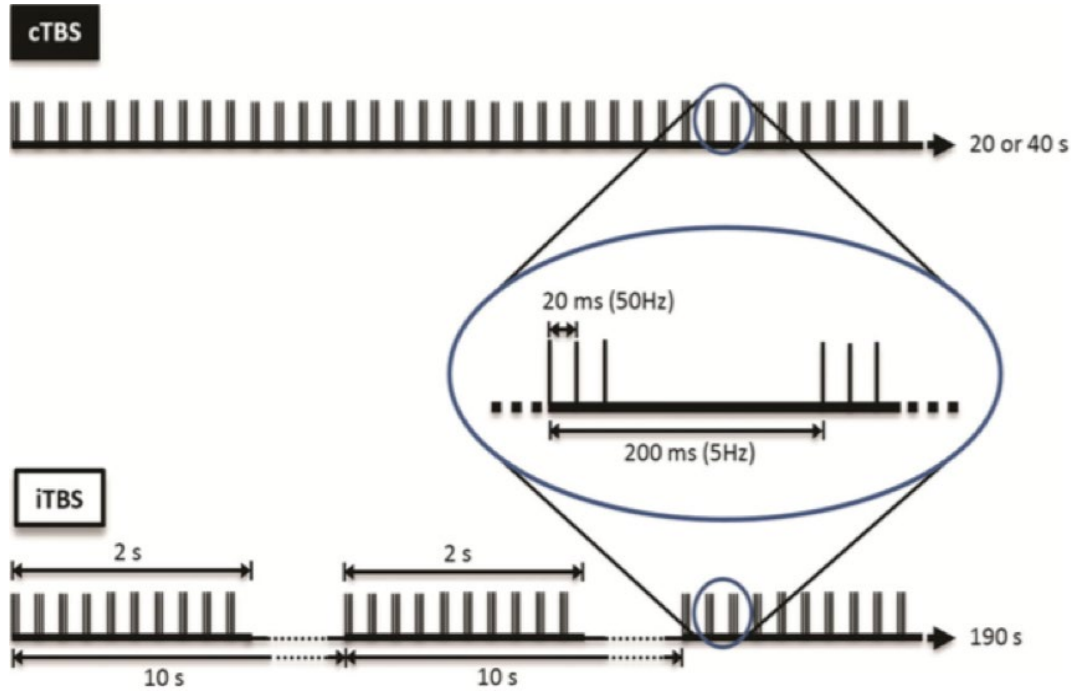
- Single daily rTMS has been explored for the treatment of symptoms of suicidal ideation.
- A recent RCT demonstrated efficacy of bil DLPFC rTMS for SI in adults (Weissman 2018).
- Early evidence for L-DLPFC rTMS for SI in adolescents (Pan 2018, Croarkin 2018).



Melancholy by Albert György

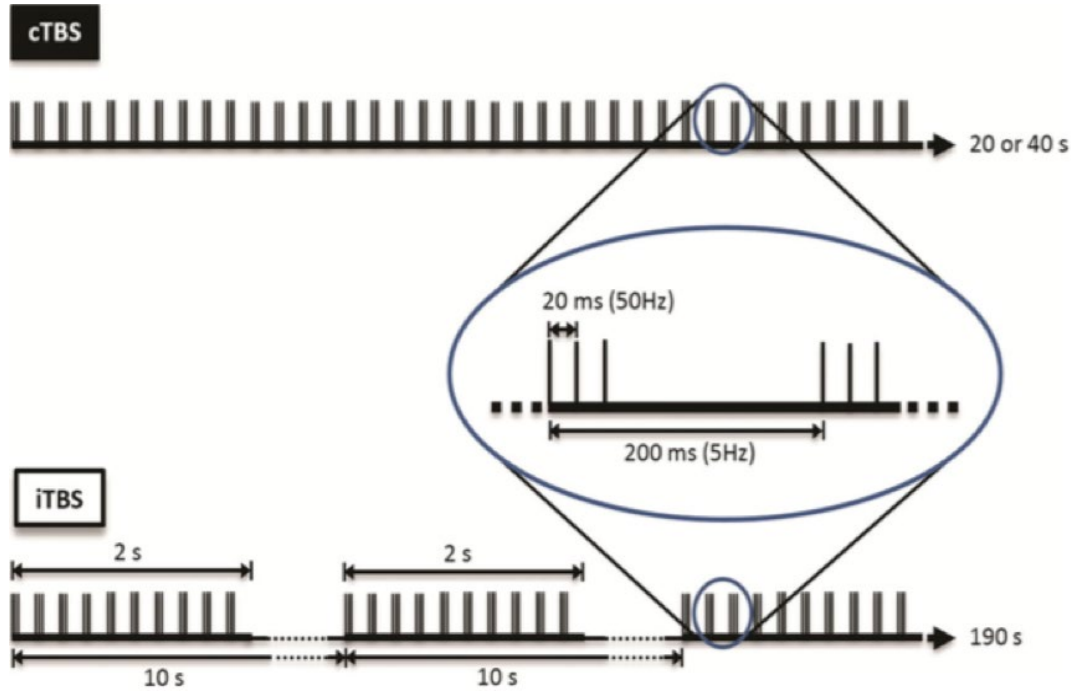
Second Generation Stimulation Parameters

- Human motor physiology studies have demonstrated that Theta-Burst Stimulation (TBS) when applied intermittently (iTBS), produces excitation in cortex (Huang 2005).
- 600 pulses of iTBS can be applied in 3 min and this application is equivalent to 3000 pulses of 10Hz (37 min) as far as motor cortical excitability.
- Allows for much more efficient application of pulses /session.

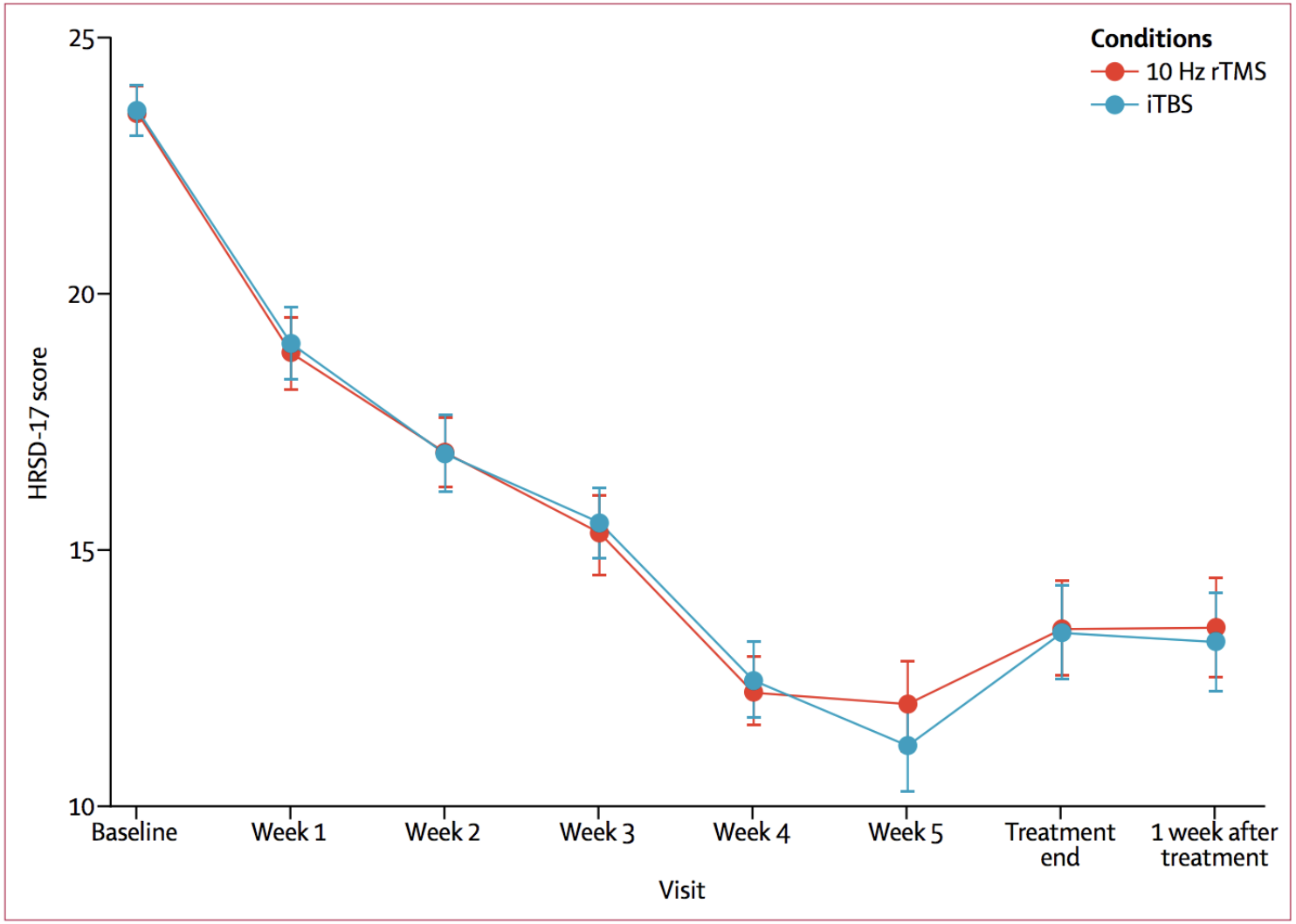


Second Generation Stimulation Parameters

- A recently completed non-inferiority trial demonstrated that 600 pulses of iTBS (3 min protocol) is non-inferior to 3,0000 pulses of 10hz rTMS (37 min protocol) in ~400 subjects (Blumberger 2018).
- 1,800 pulses of iTBS over L DLPFC has been demonstrated to be effective in treating moderate TRD (Li 2012).
- iTBS when applied at least 50 min apart produces robust LTP induction (Kramar 2012, Lynch 2013).



iTBS versus Traditional rTMS: Non-inferiority



Blumberger 2018

FDA-Approved Single Daily iTBS Parameters

- Frequency: 5Hz/50Hz (iTBS)
- Pulse Potency: 5X
- Train Duration: 2 seconds
- Inter-train Interval: 8 seconds
- Pulse Dose/session: 600 pulses/session
- %MT: 120% rMT
- Sessions/day: 1
- Sessions/week: 5
- Sessions/course: 30
- Pulses/course: 18,000 pulses
- Target: L DLPFC
- Targeting: Average MNI Coordinate

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Mon	Mon	Mon	Mon	Mon	Mon
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Tues	Tues	Tues	Tues	Tues	Tues
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Wed	Wed	Wed	Wed	Wed	Wed
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Fri	Fri	Fri	Fri	Fri	Fri

iTBS is Biologically Active for TRD

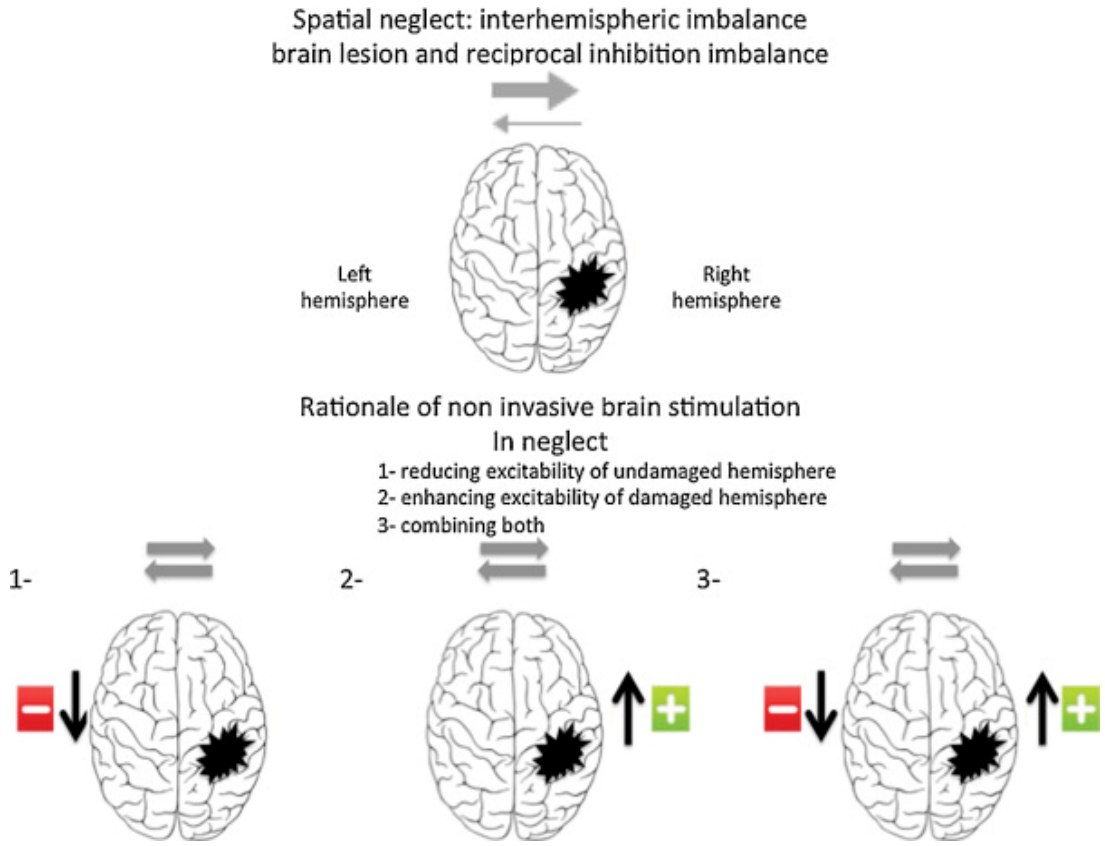
Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Mon	Mon	Mon	Mon	Mon	Mon
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Tues	Tues	Tues	Tues	Tues	Tues
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Wed	Wed	Wed	Wed	Wed	Wed
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
iTBS600	iTBS600	iTBS600	iTBS600	iTBS600	iTBS600
Fri	Fri	Fri	Fri	Fri	Fri

=

Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Mon	Mon	Mon	Mon	Mon	Mon
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Tues	Tues	Tues	Tues	Tues	Tues
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Wed	Wed	Wed	Wed	Wed	Wed
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Thurs	Thurs	Thurs	Thurs	Thurs	Thurs
rTMS	rTMS	rTMS	rTMS	rTMS	rTMS
Fri	Fri	Fri	Fri	Fri	Fri

Why Accelerate Stimulation?

- Multiple applications of stimulation appear to produce non-linear effects.
- One application of cTBS lasts 30-40 min, two spaced applications lasts 3-8 hours, 4 lasts 32 hours, and 8 lasts 3 weeks.
- Pragmatically, improvement in symptoms may produce more rapid responses and even more effects and/or longer lasting effects.



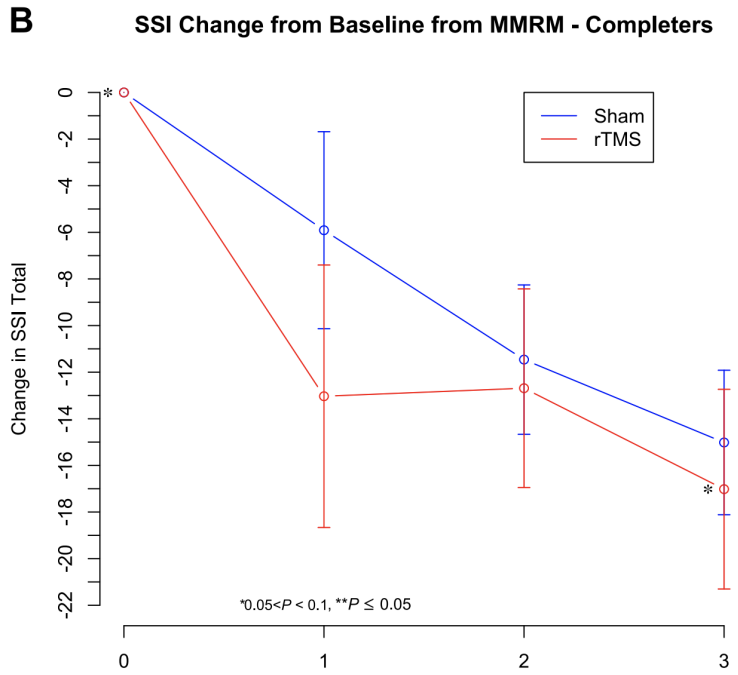
Cazzoli 2012

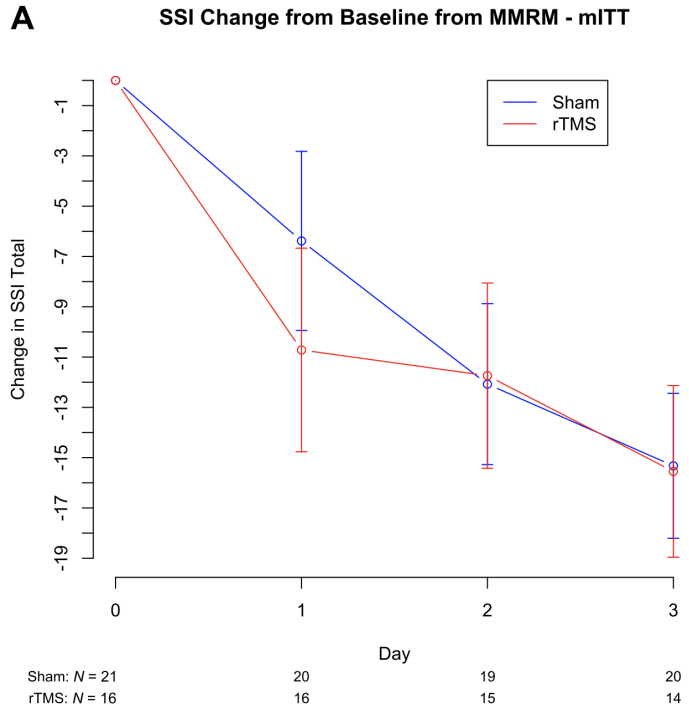
Previous Attempts

Beck scale of suicide ideation (BSI) scores.

	BSI							
	T1		T2		T3		T4	
	Mean	(95%CI)	Mean	(95%CI)	Mean	(95%CI)	Mean	(95%CI)
Total group	13.31	(10.52–16.13)	8.22	(5.08–11.61)	7.53	(4.57–10.50)	5.26	(2.47–8.24)
iTBS—sham	13.43	(9.21–17.64)	9.36	(4.46–14.26)	7.57	(3.12–12.02)	5.00	(0.90–9.62)
sham—iTBS	13.22	(9.51–16.94)	7.33	(3.02–11.65)	7.50	(3.57–11.43)	5.44	(1.67–9.22)

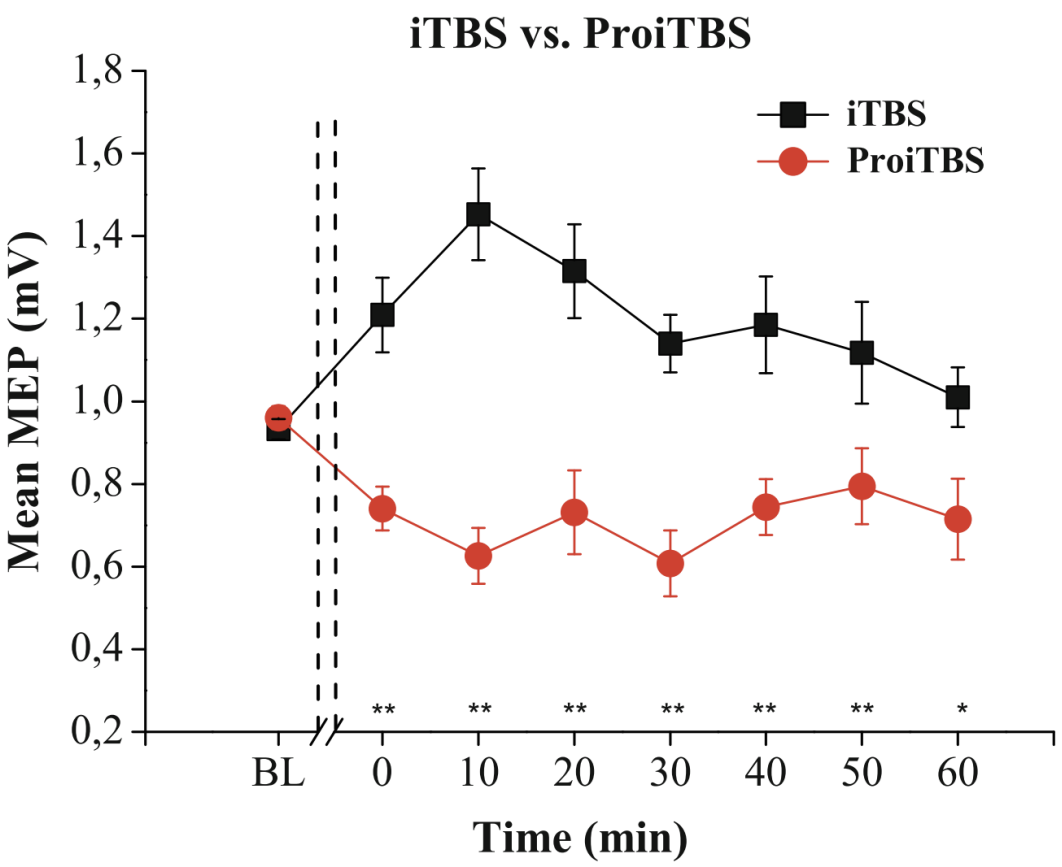
Mean BSI scores and 95% CI on time-point T1, T2, T3 and T4 for the suicidal subgroup (n = 32).

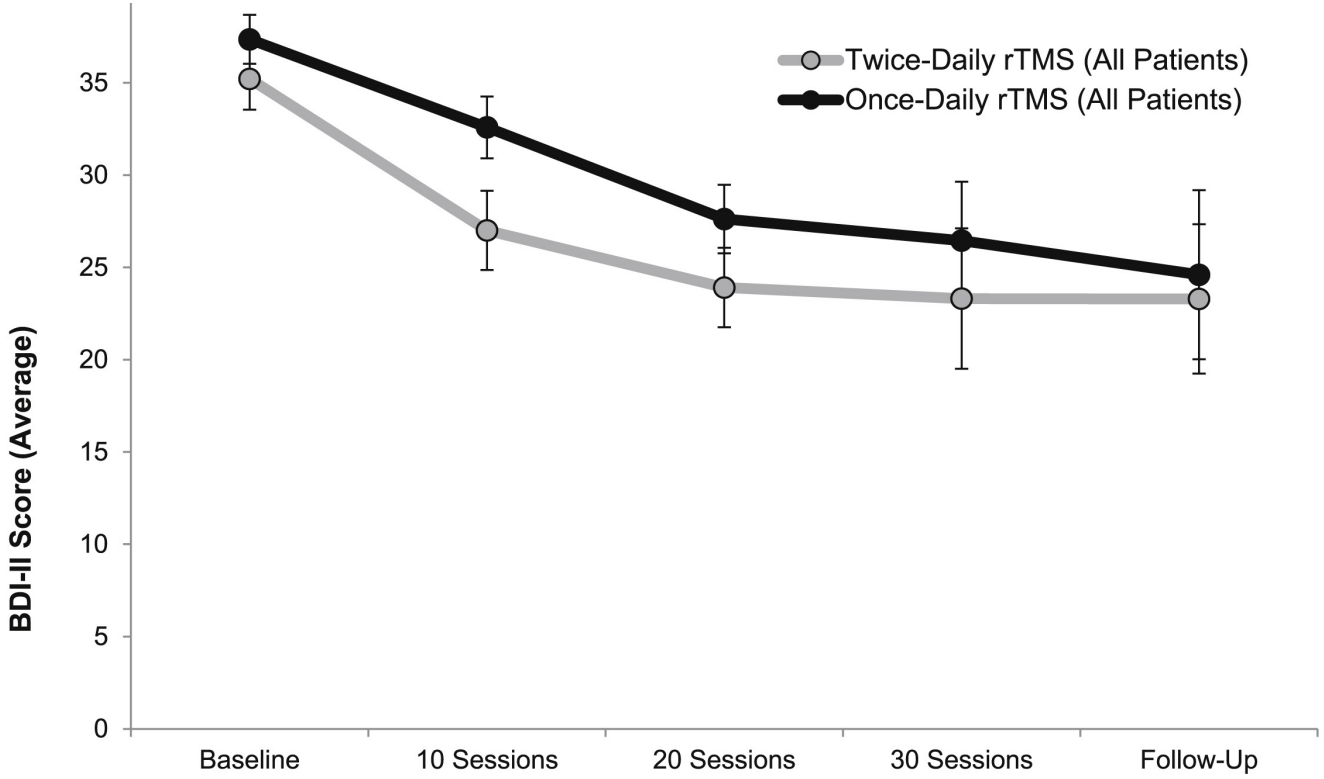




Desmyter 2016
George 2014

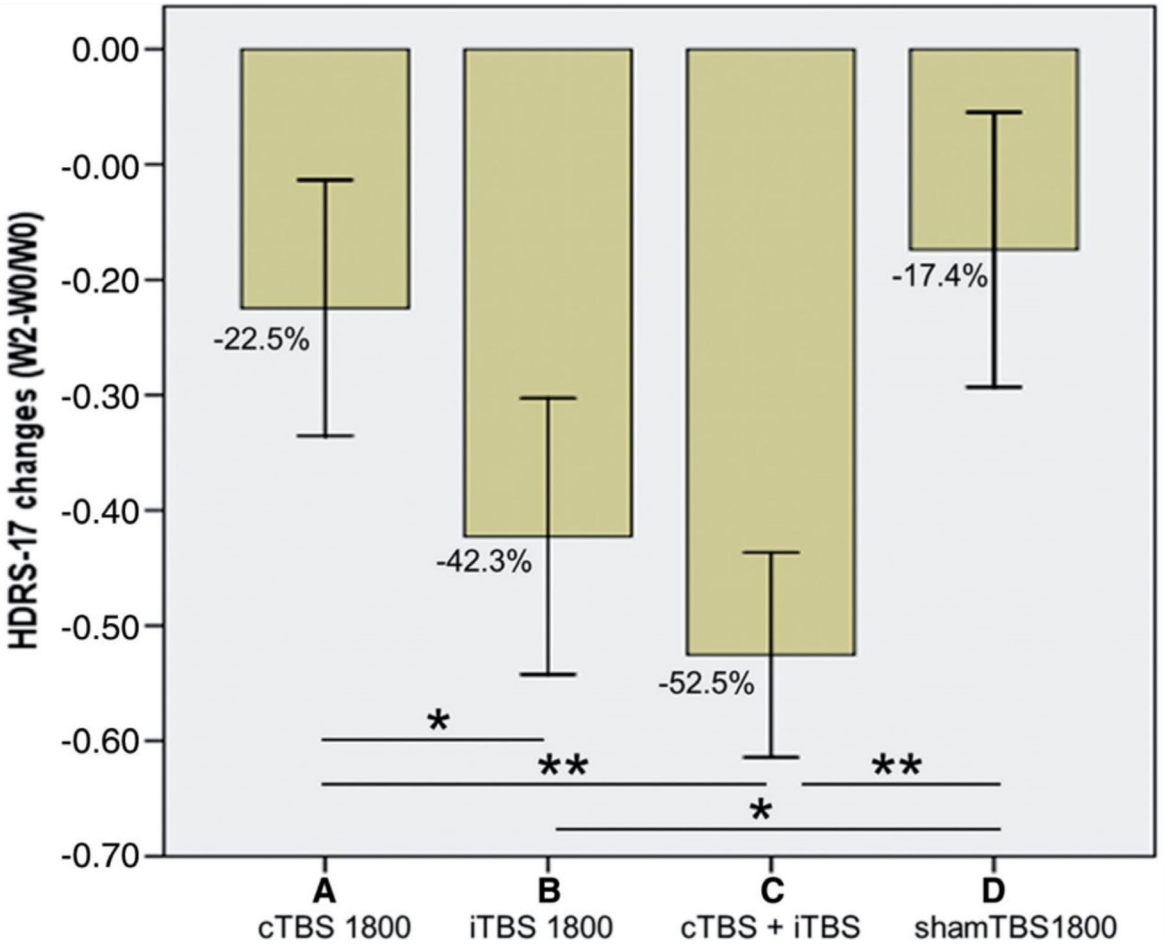
Optimal Pulse Dose/Session





Gamboa 2010
Schulze 2018

$iTBS_{1800}$ for 2 weeks

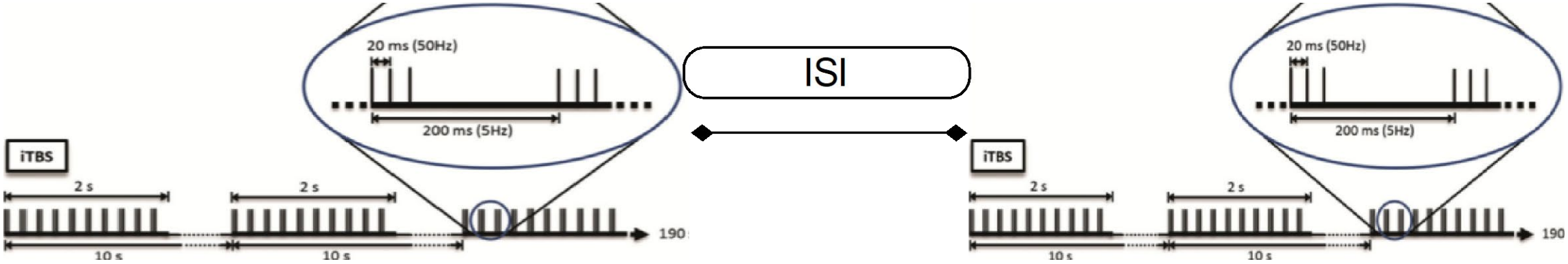


Li 2014

Third Generation Stimulation Parameters

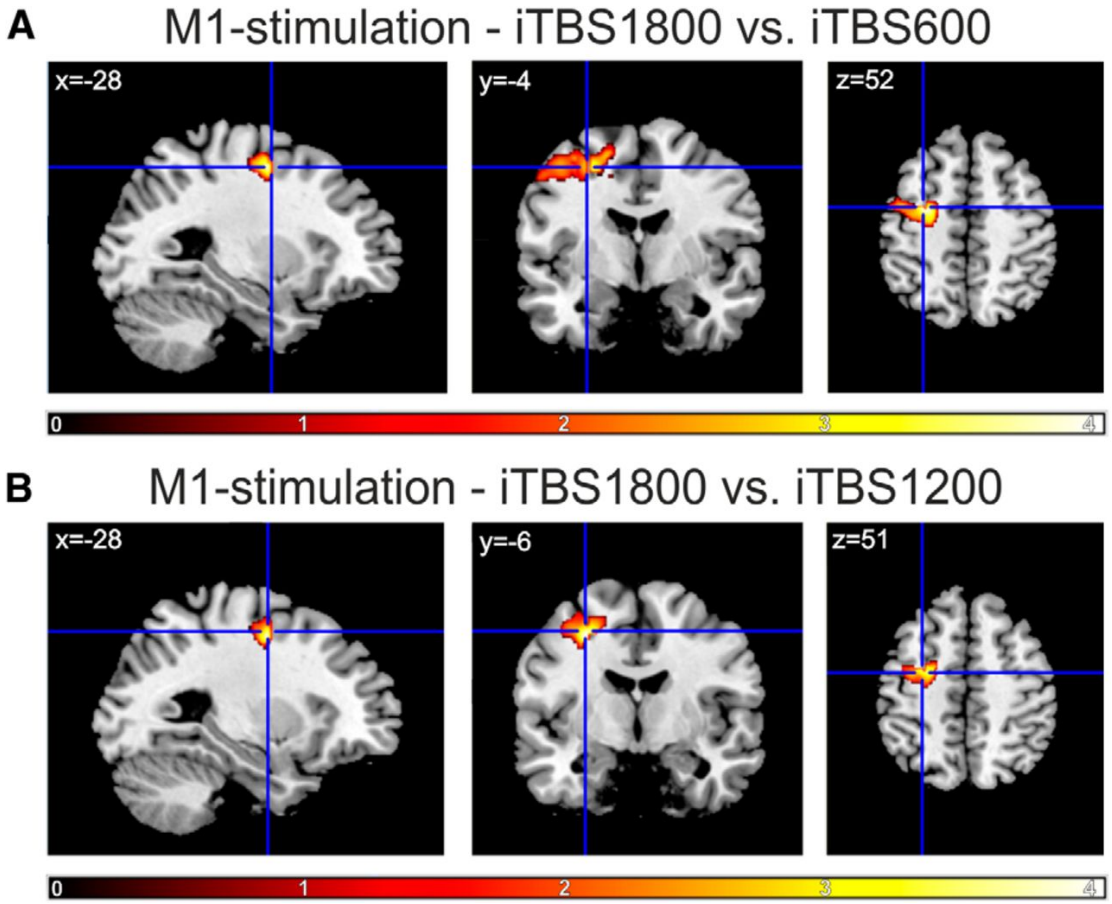
- Frequency: 5Hz/50Hz (iTBS)
- Train Duration: 2 seconds
- Inter-train Interval: 8 seconds
- Pulse Dose/session: 1800
- Intersession Interval:
- Pulse Dose/day:
- %MT:
- Sessions/day:
- Sessions/week:
- Pulses/course:
- Target:
- Targeting:

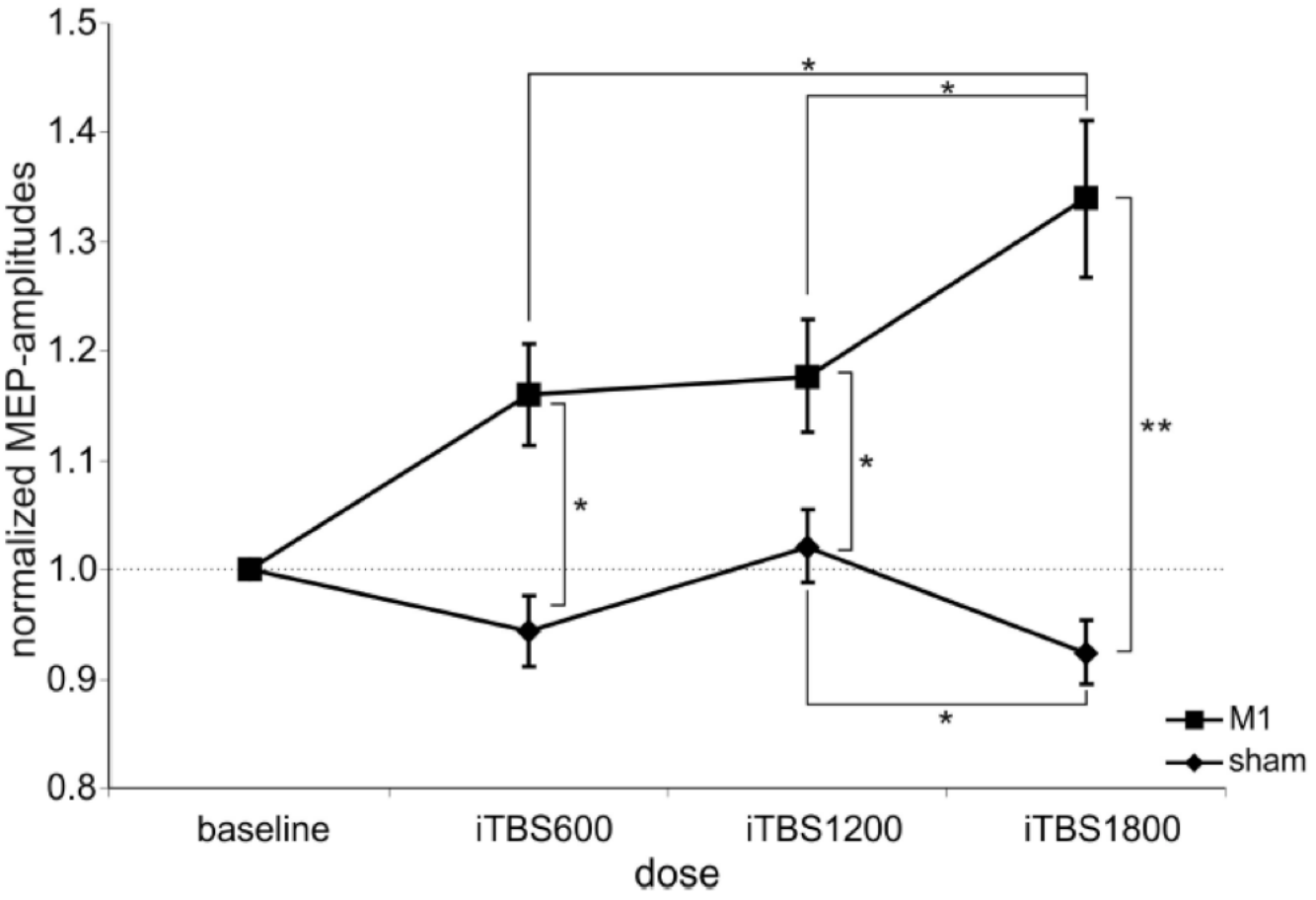
What is the Optimal Inter-session Interval?



Depends on the type of stimulation (iTBS vs cTBS)

Inter-session Interval Based off of Motor Physiology Experiments

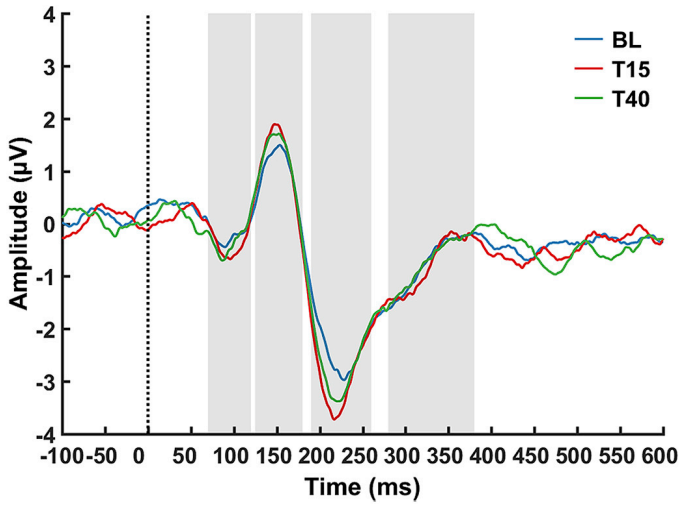


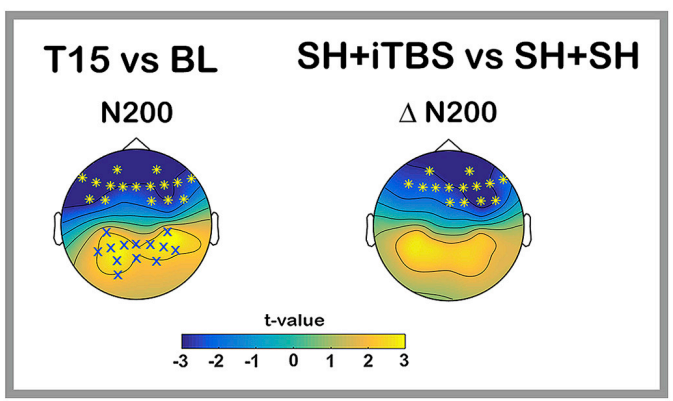


Nettekoven, 2014

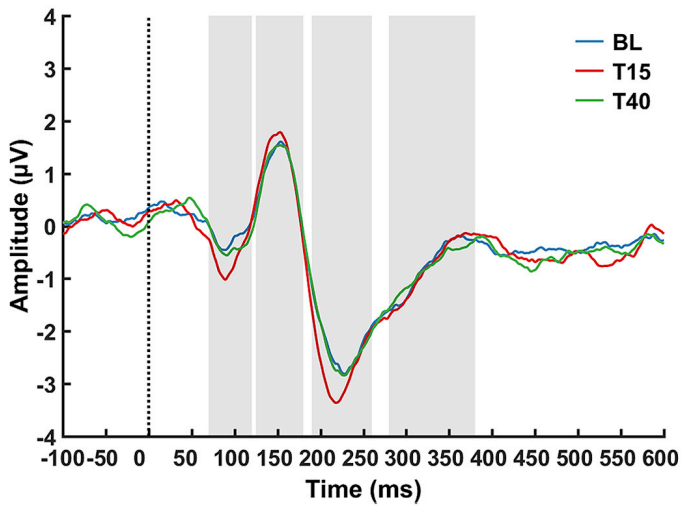
Inter-session Interval Based off of DLPFC TMS Physiology Experiments

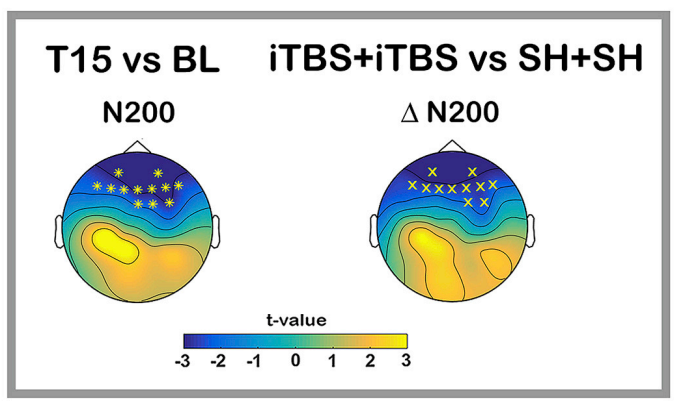
A) SH+iTBS



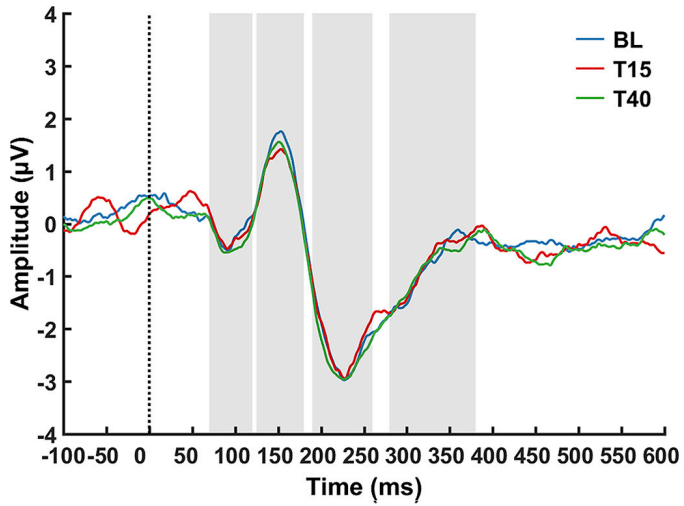


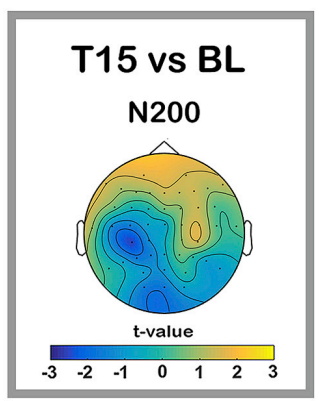
B) iTBS+iTBS





C) SH+SH

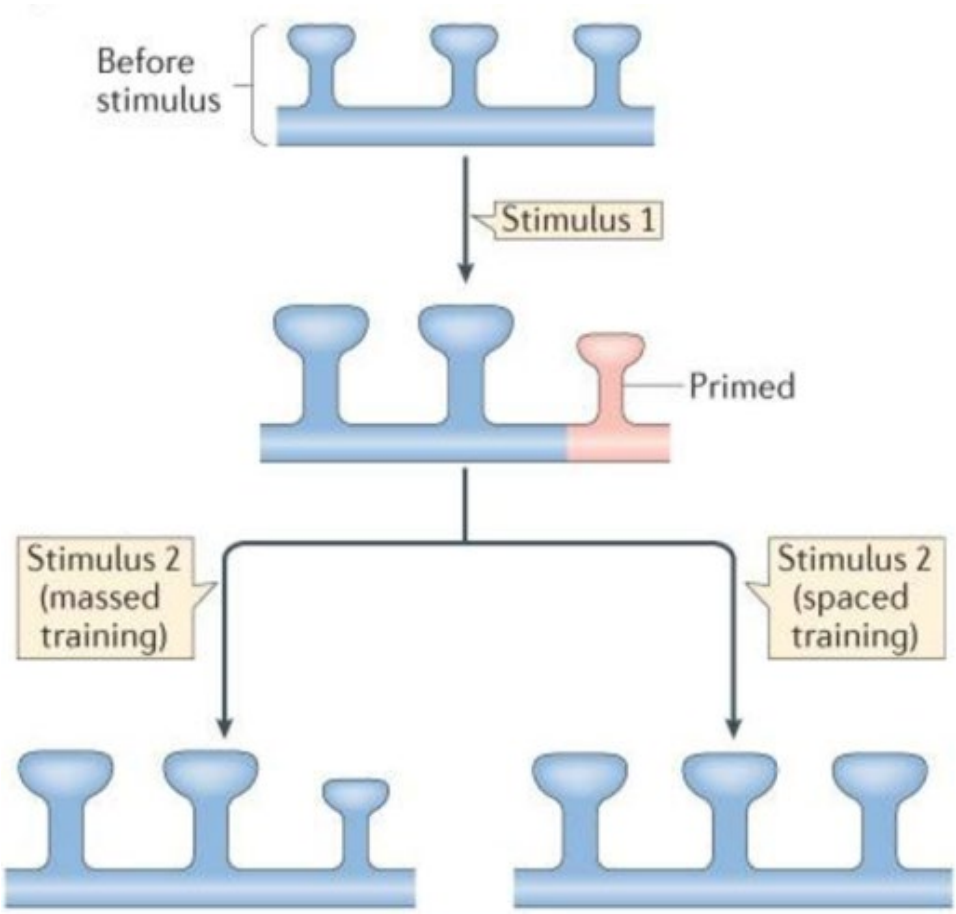




Chung, 2018

Inter-session Interval Based off of Spaced Learning Theory

- Experiments involving TBS applications to hippocampal slice preparations have demonstrated that ≥50 minutes is necessary for subsequent dendritic spine enlargement.
- Enhancement of LTP results from successive rounds of strengthening of new synaptic contacts.
  - Stimulus 1 only enlarges a subset of affected spines, but primes additional spines.
  - If stimulus 2 follows shortly after stimulus 1 (as in massed training), it has no effect.
  - If stimulus 2 comes later (as in spaced training), it does not further enlarge the first subset of spines. Instead, stimulus 2 enlarges those spines that were primed, but not enlarged, by stimulus 1.

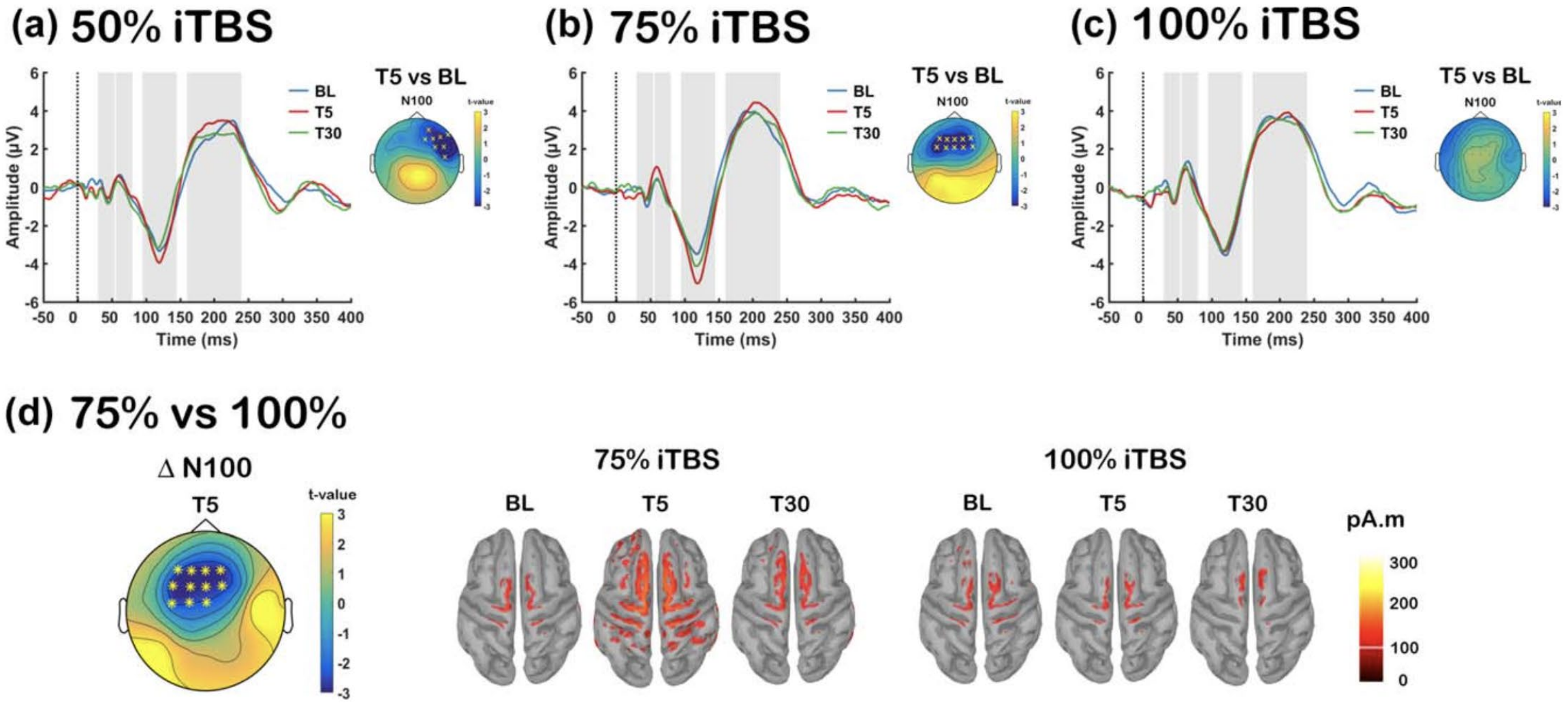


Smolen 2016

Third Generation Stimulation Parameters

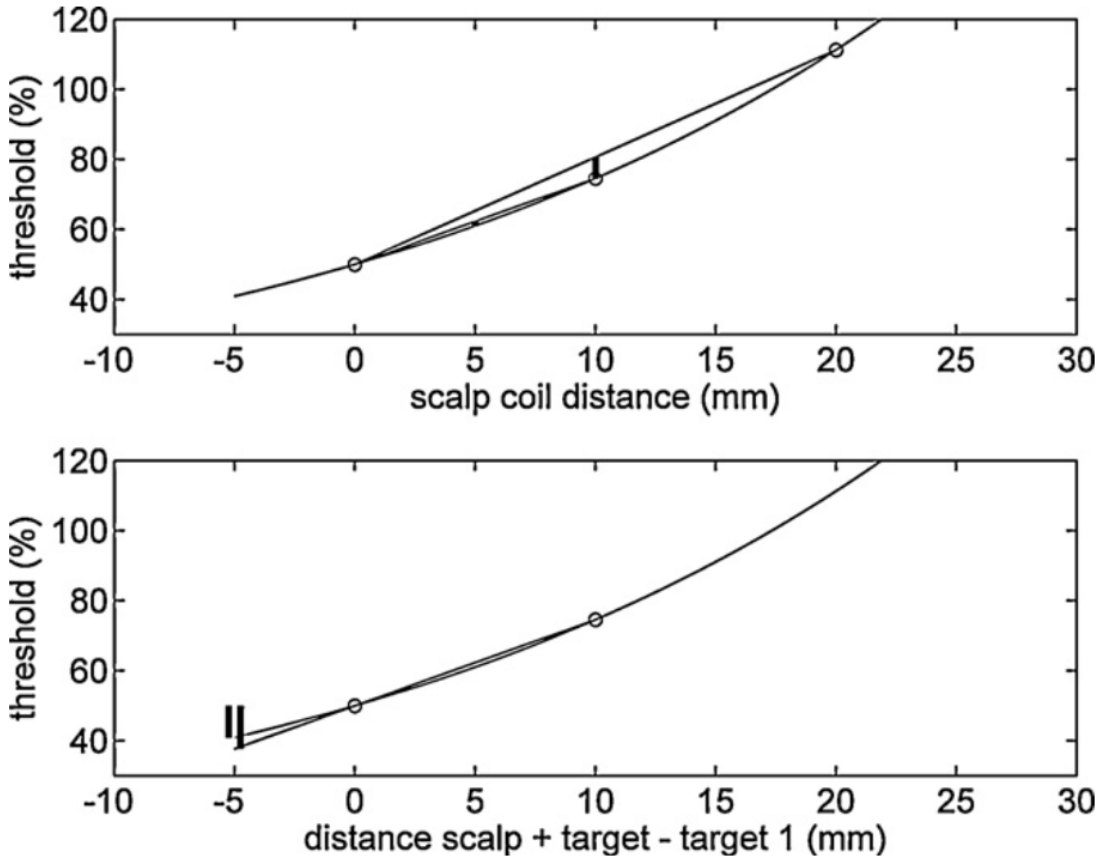
- Frequency: 5Hz/50Hz (iTBS)
- Train Duration: 2 seconds
- Inter-train Interval: 8 seconds
- Pulse Dose/session: 1800
- Intersession Interval: 50 min
- Pulse Dose/day: 18,000= 6 weeks of iTBS at 600 pulses/session for 30 sessions
- %MT:
- Sessions/day:
- Sessions/week:
- Pulses/course:
- Target:
- Targeting:

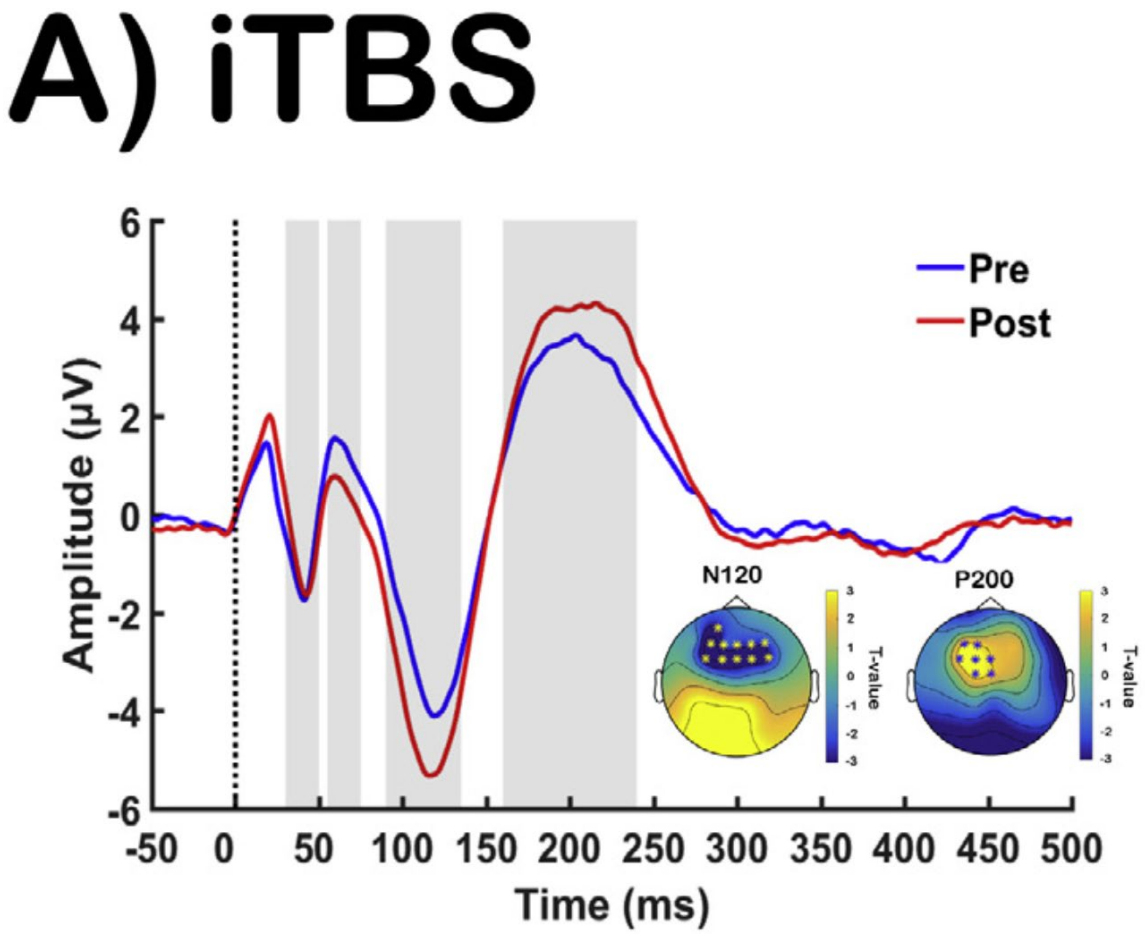
Percent MT Based off of TEPs



Chung 2017

Optimal Percent MT





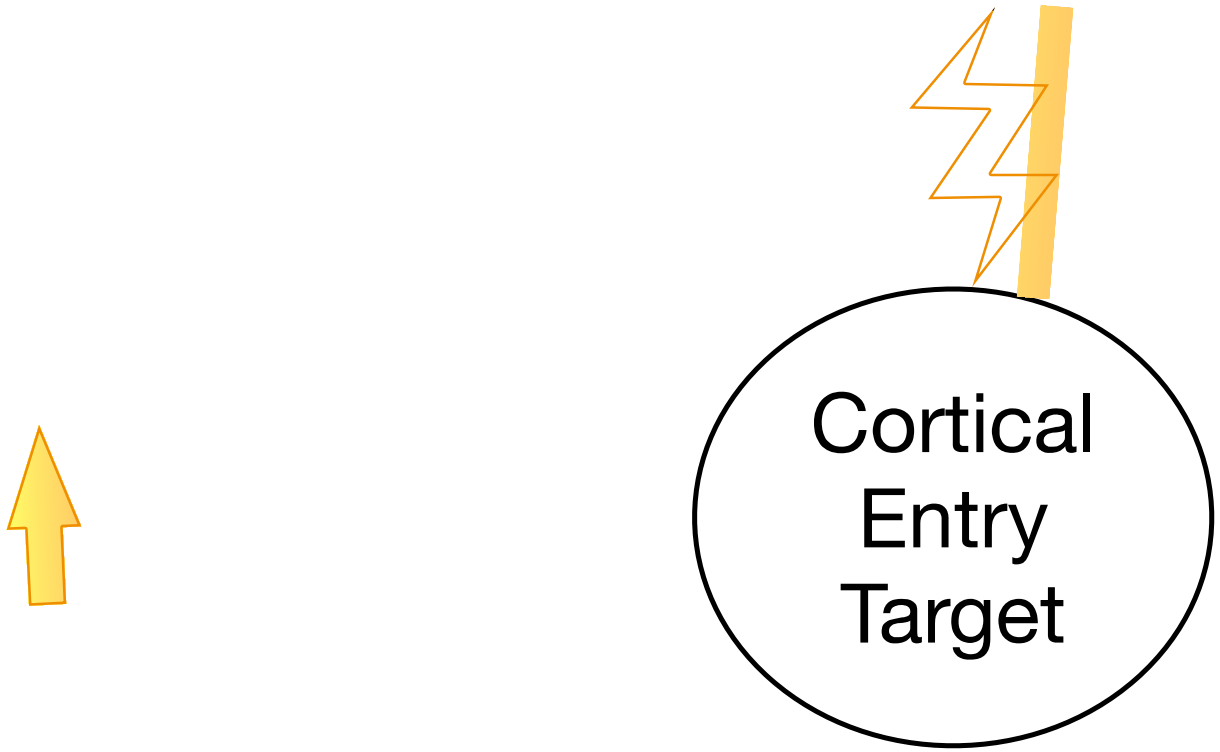
Chung 2017
Trillenberg 2012

Third Generation Stimulation Parameters

- Frequency: 5Hz/50Hz (iTBS)
- Train Duration: 2 seconds
- Inter-train Interval: 8 seconds
- Pulse Dose/session: 1800
- Intersession Interval: 50 min
- Pulse Dose/day: 18,000
- %MT: 90% rMT with depth adjustment
- Sessions/day: 10
- Sessions/week: 50
- Pulses/course: 90,000
- Target:
- Targeting:

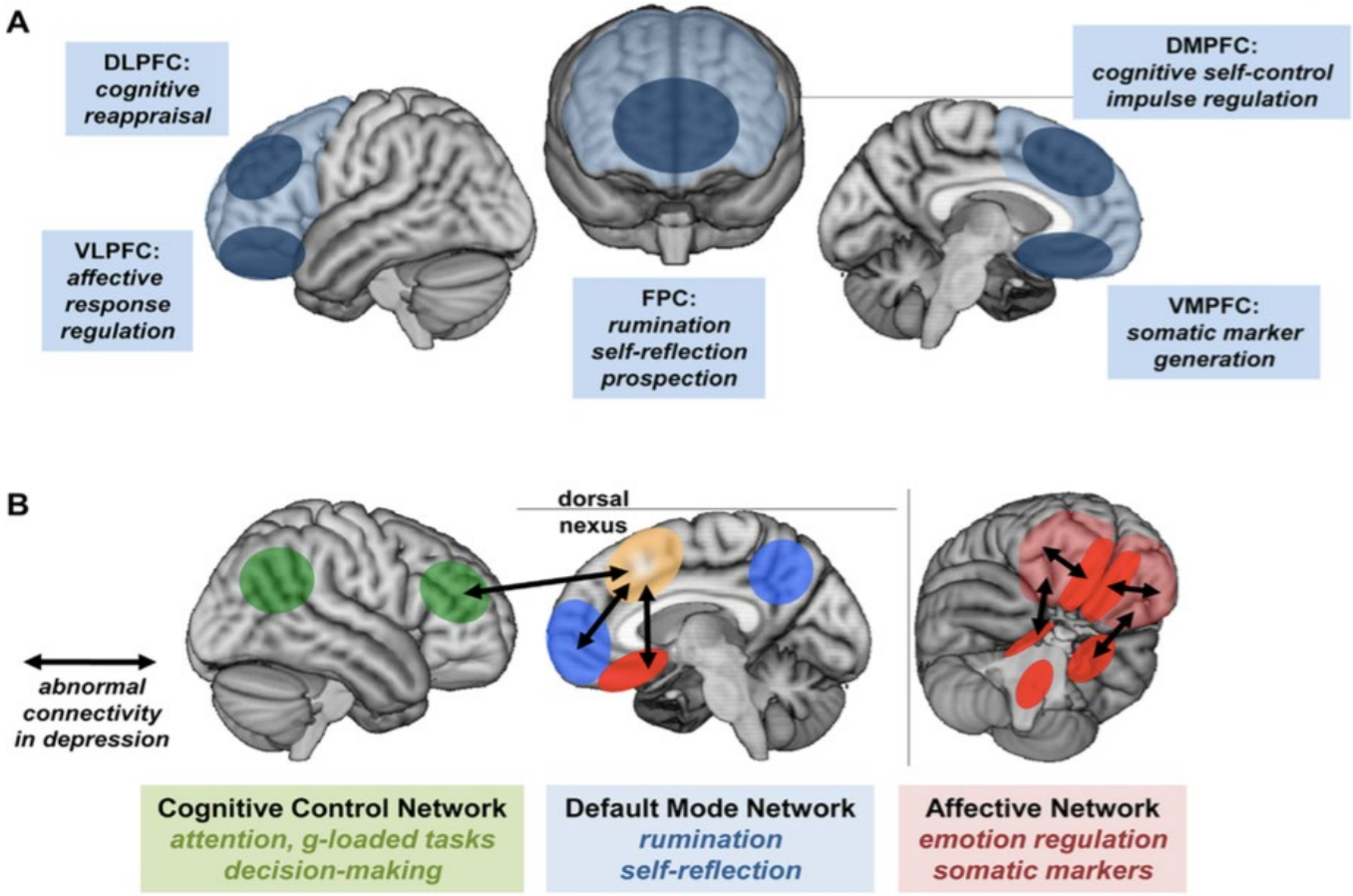
Day 1	Day 2	Day 3	Day 4	Day 5
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800

Cortical Entry Node: Site of Stimulation



Cortical Entry Node: Based off of Lesion Studies

- There is one established target for depression, the L DLPFC.
- Inhibitory stimulation of the R DLPFC has strong data.
- DMPFC has + OL data.
- FPC has some emerging data.
- L DLPFC is the only target to do parameter development because it is an established target.



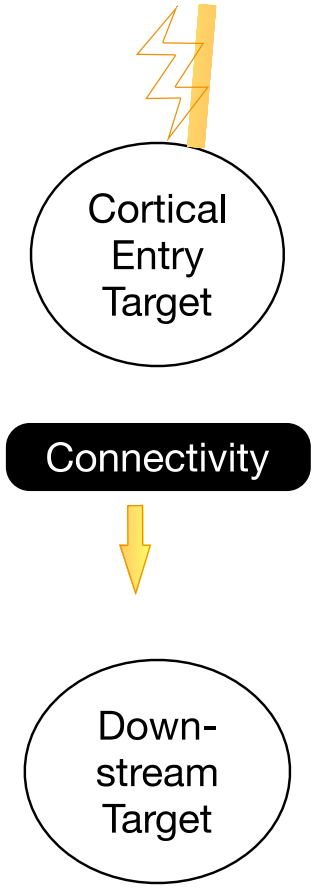
Downar, 2014

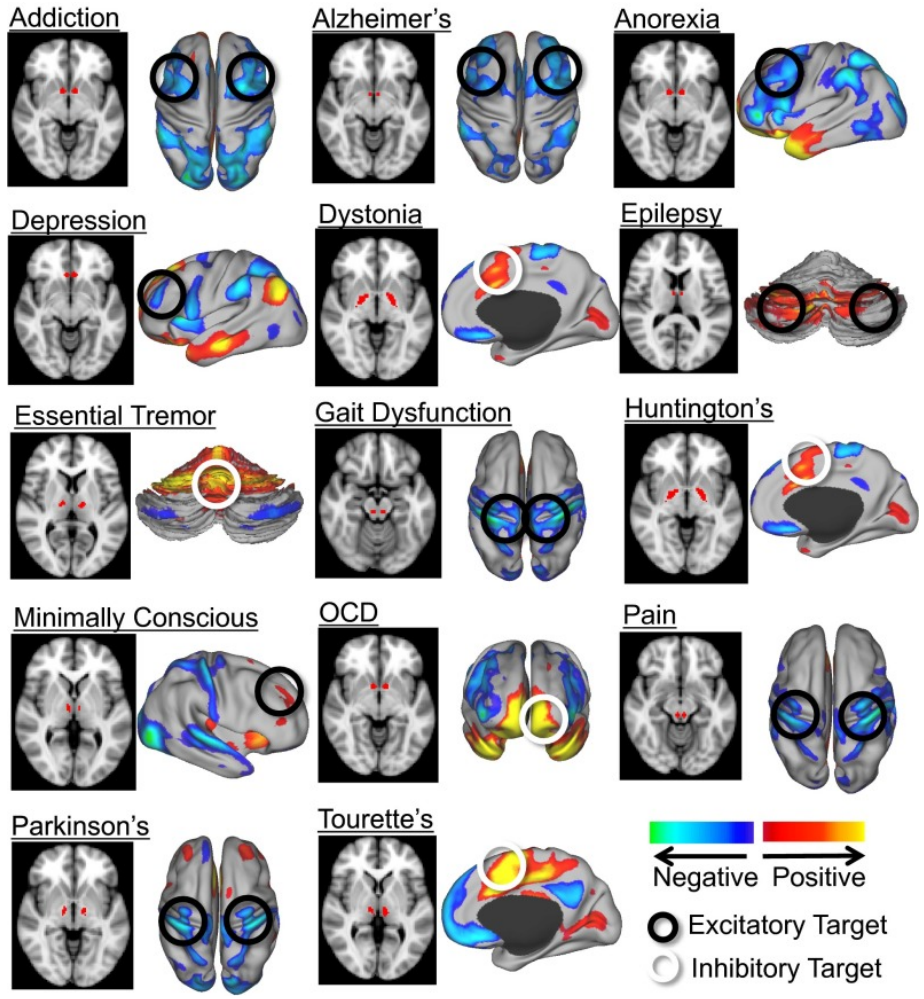
Third Generation Stimulation Parameters

- Frequency: 5Hz/50Hz (iTBS)
- Train Duration: 2 seconds
- Inter-train Interval: 8 seconds
- Pulse Dose/session: 1800
- Intersession Interval: 50 min
- Pulse Dose/day: 18,000
- %MT: 90% rMT with depth adjustment
- Sessions/day: 10
- Sessions/week: 50
- Pulses/course: 90,000
- Target: Left Dorsolateral Prefrontal Cortex
- Targeting:

Day 1	Day 2	Day 3	Day 4	Day 5
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800

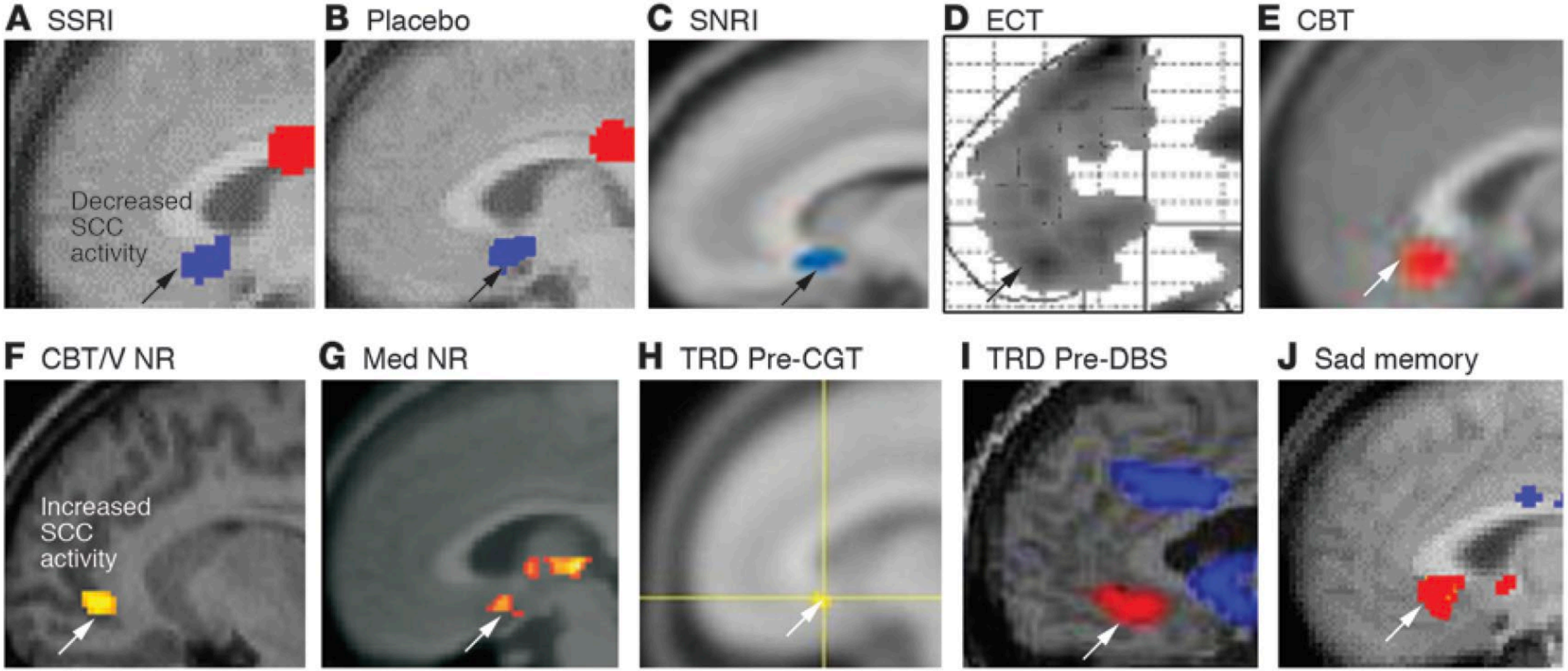
Downstream Network Target





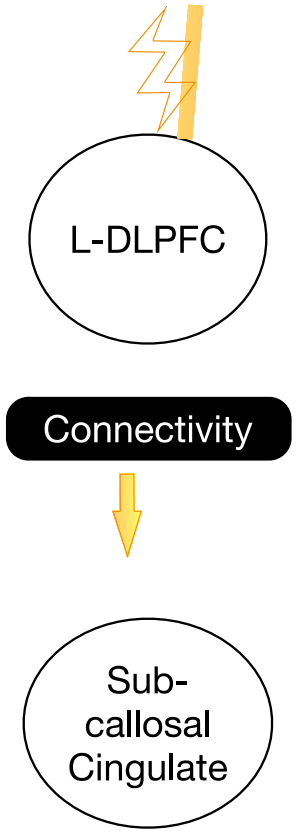
Fox, PNAS, 2014

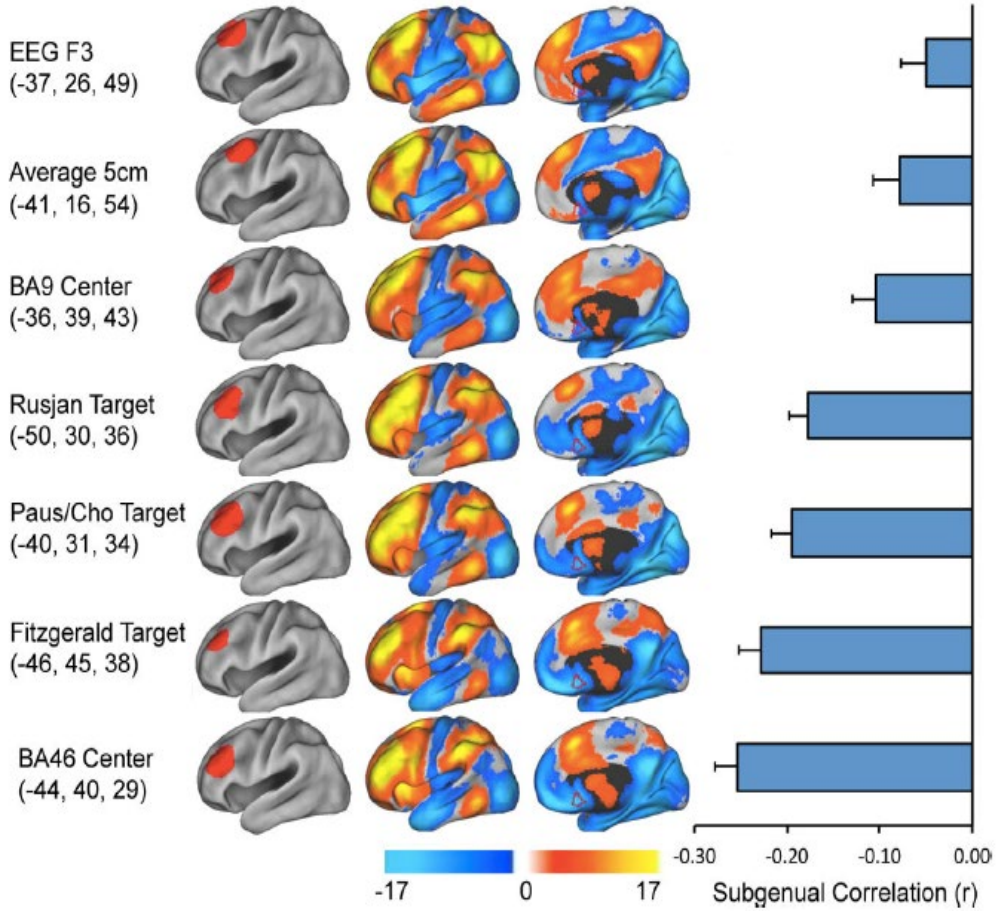
Subcallosal Cingulate Cortex: Downstream Target for Depression



Mayberg, 2009

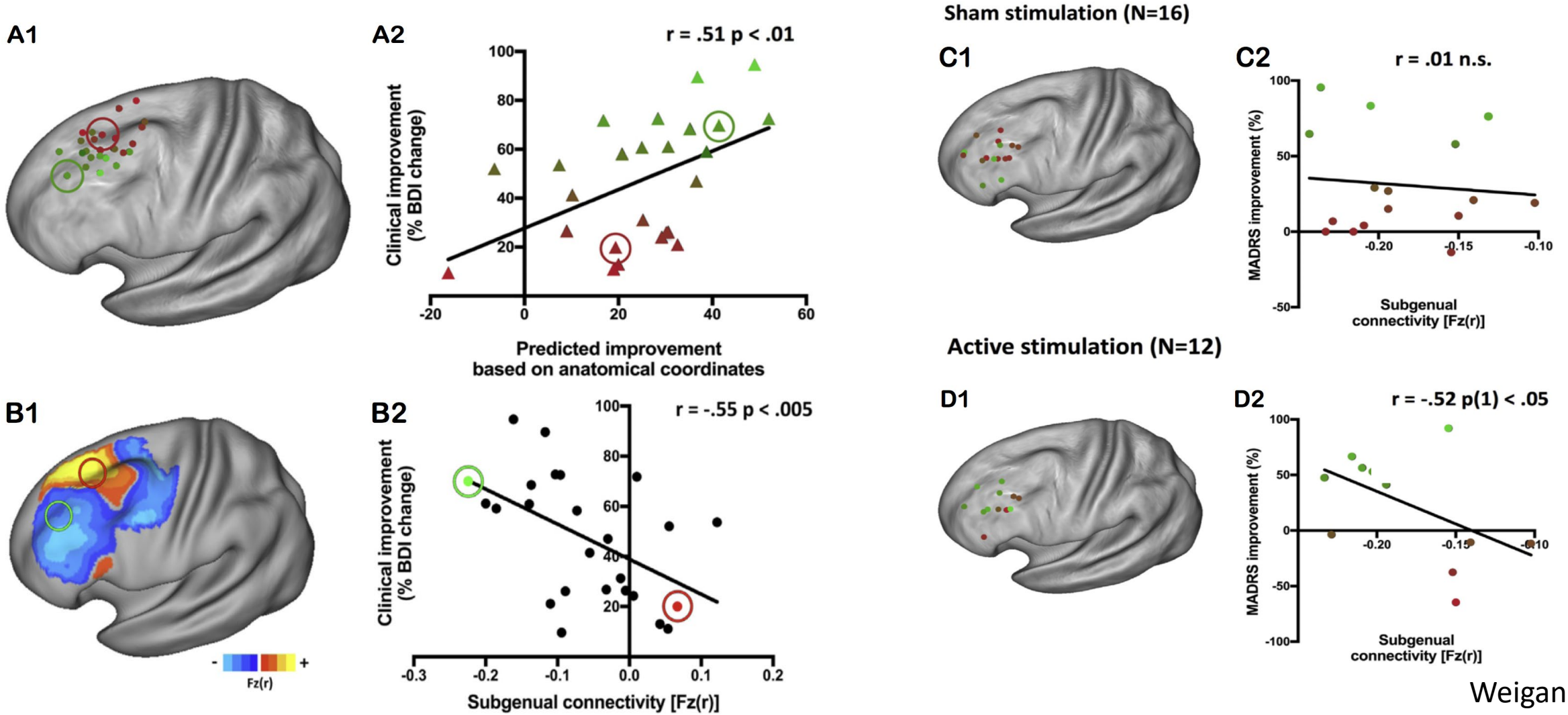
Connectivity Properties Between Cortical Entry and Downstream Target: L DLPFC-SCC





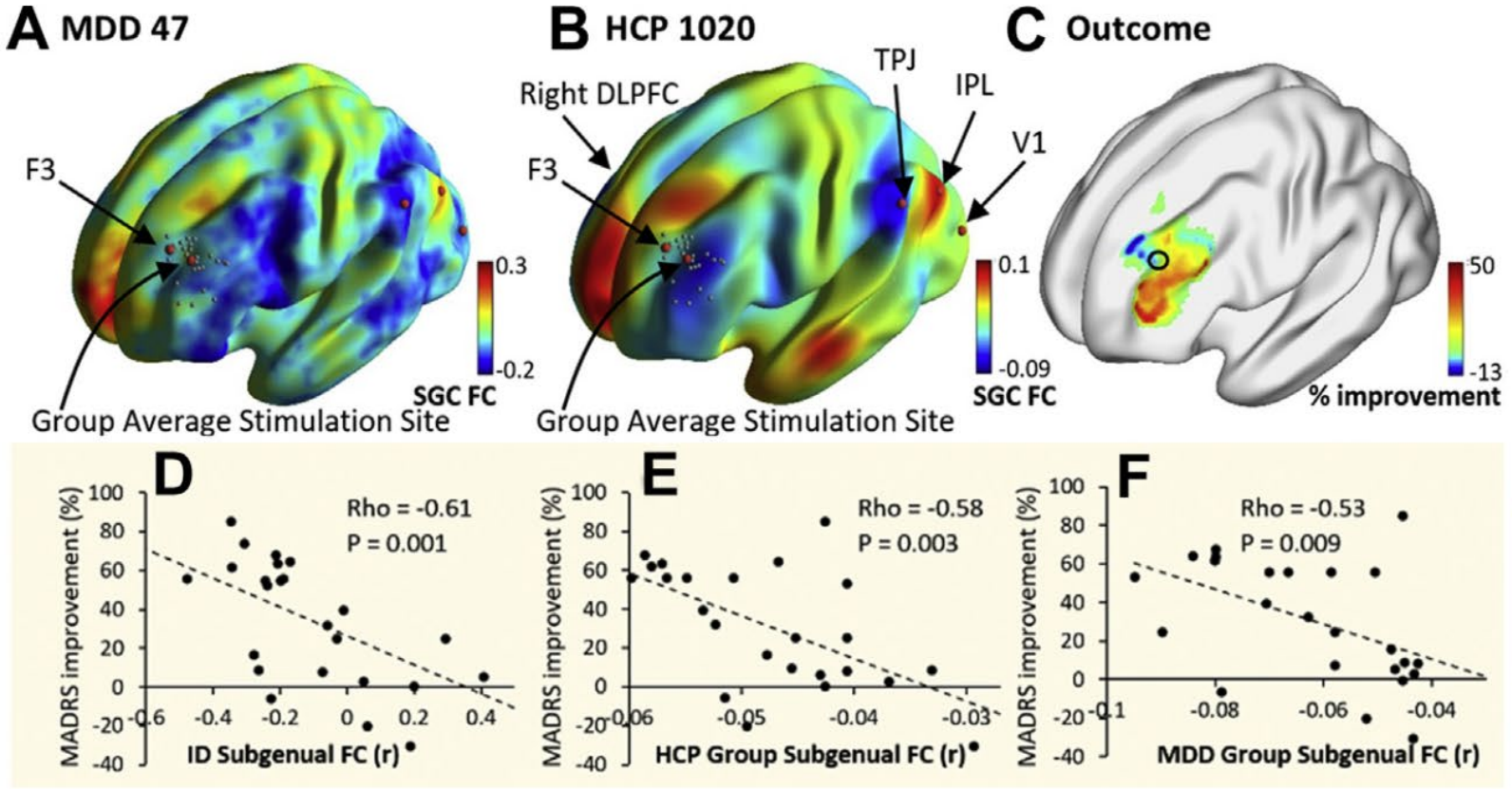
Fox, Biol Psych, 2014

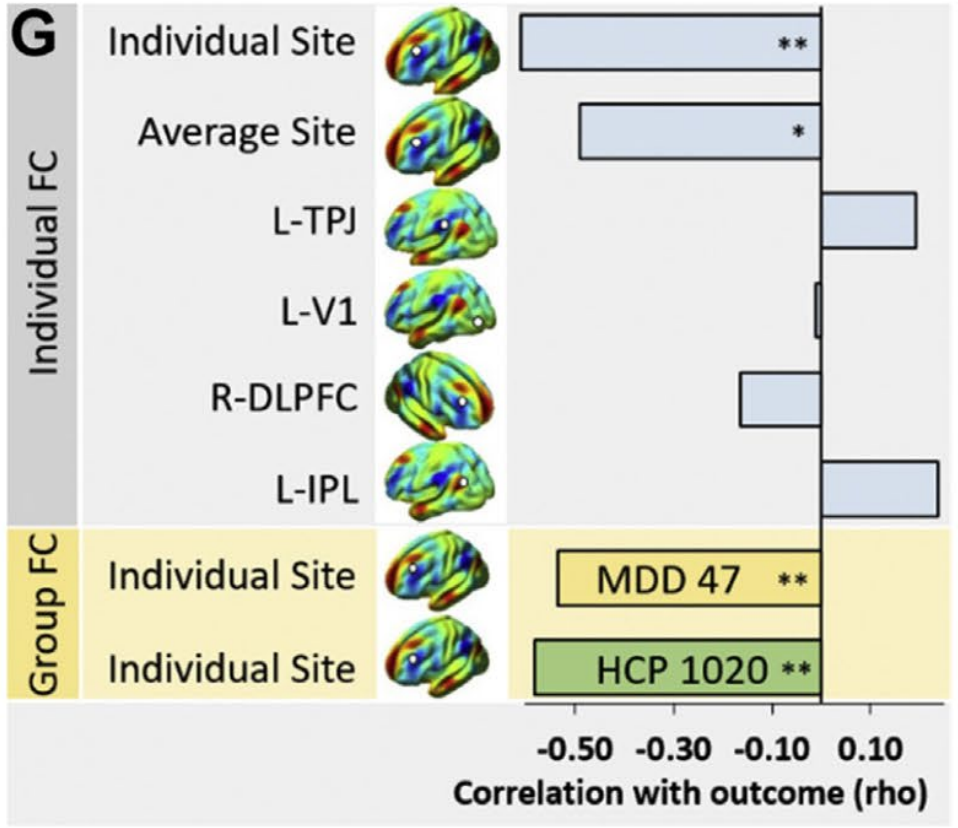
Cortical Entry Node:
Based off of Functional Connectivity



Weigand, 2017

Cortical Entry Node:
Based off of Functional Connectivity





Cash, 2019

Third Generation Stimulation Parameters

- Frequency: 5Hz/50Hz (iTBS)
- Train Duration: 2 seconds
- Inter-train Interval: 8 seconds
- Pulse Dose/session: 1800
- Intersession Interval: 50 min
- Pulse Dose/day: 18,000
- %MT: 90% rMT with depth adjustment
- Sessions/day: 10
- Sessions/week: 50
- Pulses/course: 90,000
- Target: Left Dorsolateral Prefrontal Cortex
- Targeting: Greatest RSFC MRI DLPFC AC to sgACC
- Brain Condition:

Day 1	Day 2	Day 3	Day 4	Day 5
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
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iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
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50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
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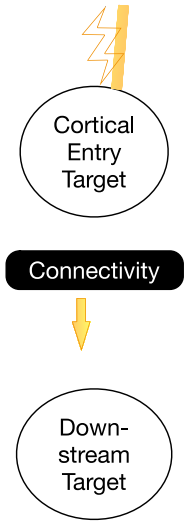
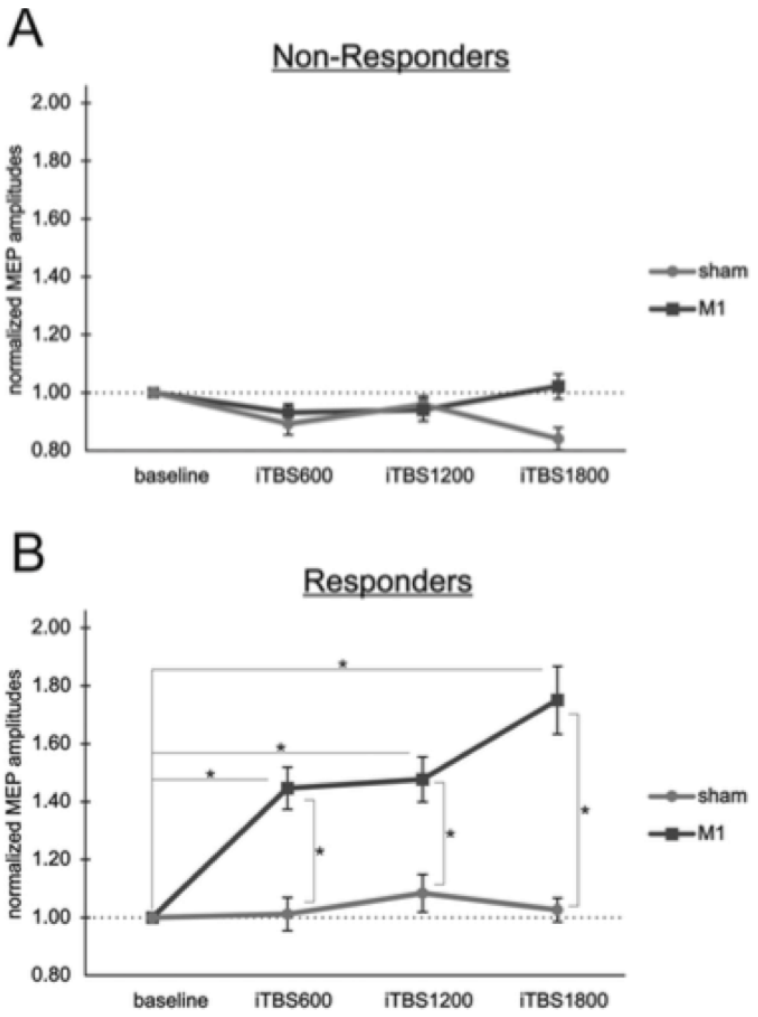
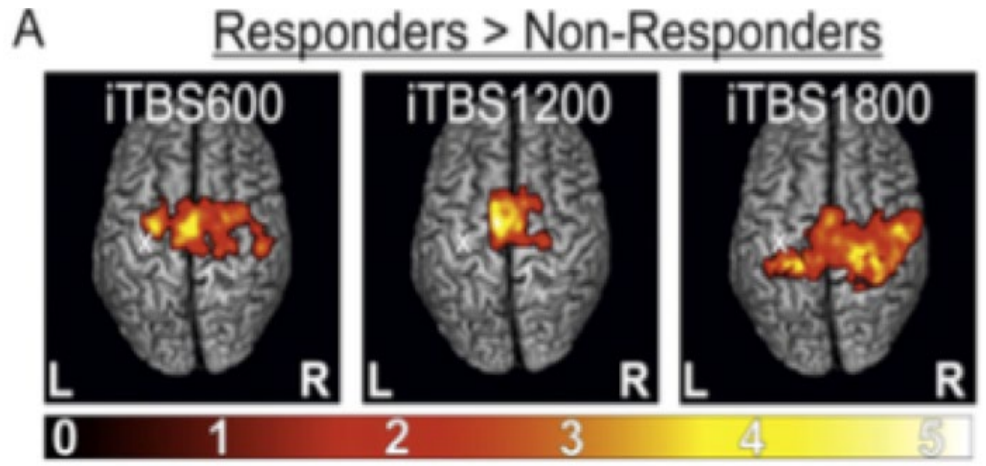
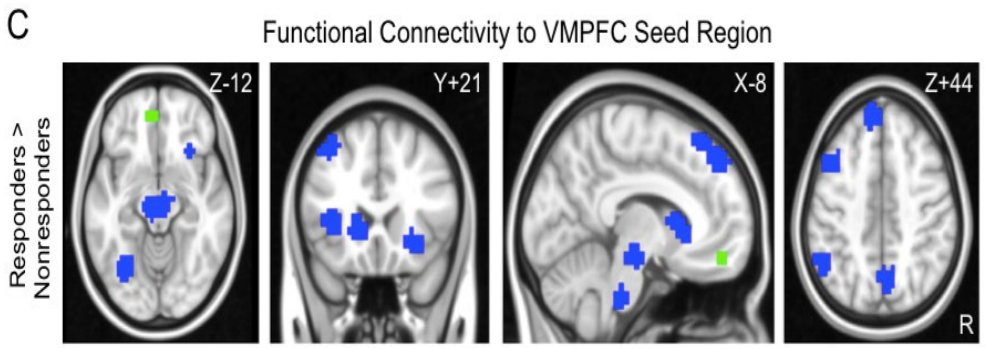
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800

Individual Connectivity Properties of Targeted Network May Predict Change in Excitability





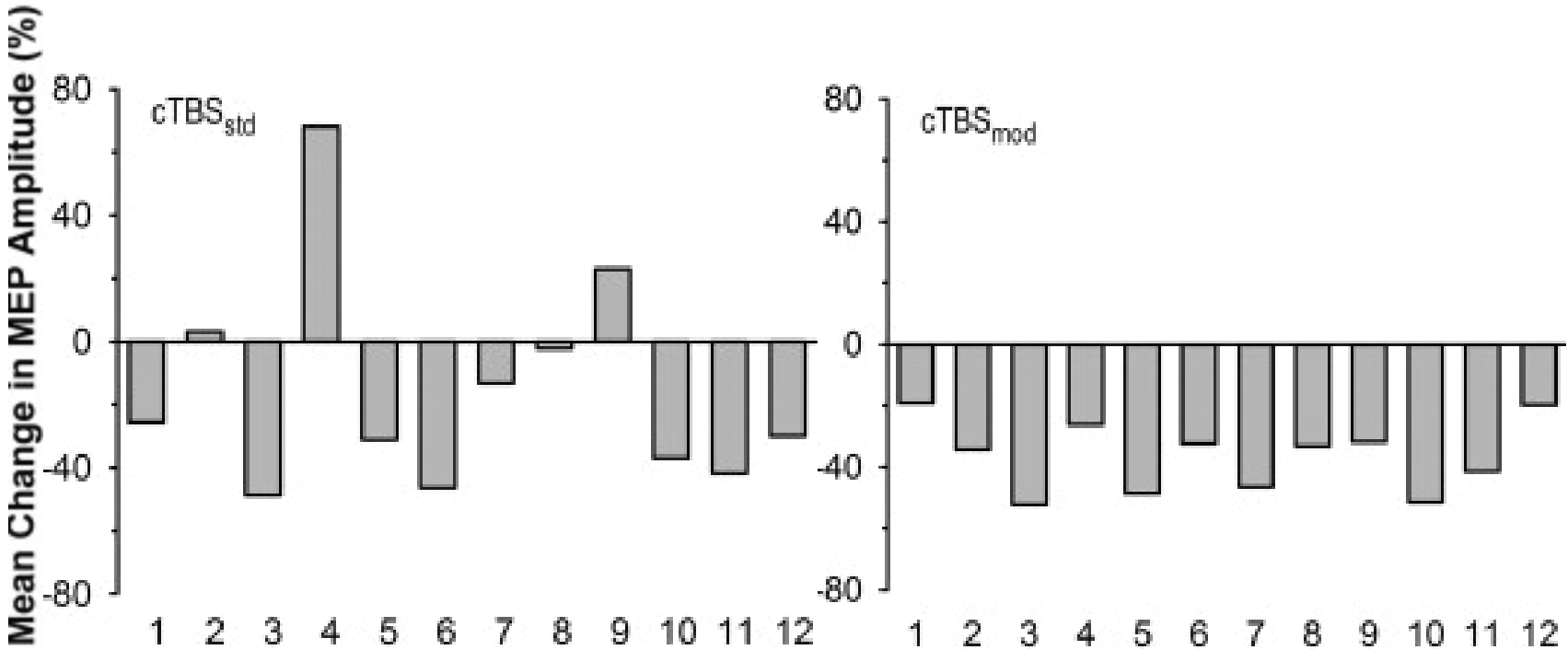




Nettekoven, J Neuro, 2014
Downar, 2014

Picking a consistently inhibitory cTBS approach

- $cTBS_{std}$ is 50Hz bursts at 5Hz and $cTBS_{mod}$ is 30Hz bursts at 6Hz.
- $cTBS_{std}$ produces inhibition 60% of the time.
- $cTBS_{mod}$ produces inhibition in 100% of participants.



Goldsworthy, Clin Neurophys, 2012

Third Generation Stimulation Parameters

- Frequency: 5Hz/50Hz (iTBS)
- Train Duration: 2 seconds
- Inter-train Interval: 8 seconds
- Pulse Dose/session: 1800
- Intersession Interval: 50 min
- Pulse Dose/day: 18,000
- %MT: 90% rMT with depth adjustment
- Sessions/day: 10
- Sessions/week: 50
- Pulses/course: 90,000
- Target: Left Dorsolateral Prefrontal Cortex
- Targeting: Greatest RSFC MRI DLPFC AC to sgACC
- Brain Condition: Depressed

Day 1	Day 2	Day 3	Day 4	Day 5
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
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50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
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50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
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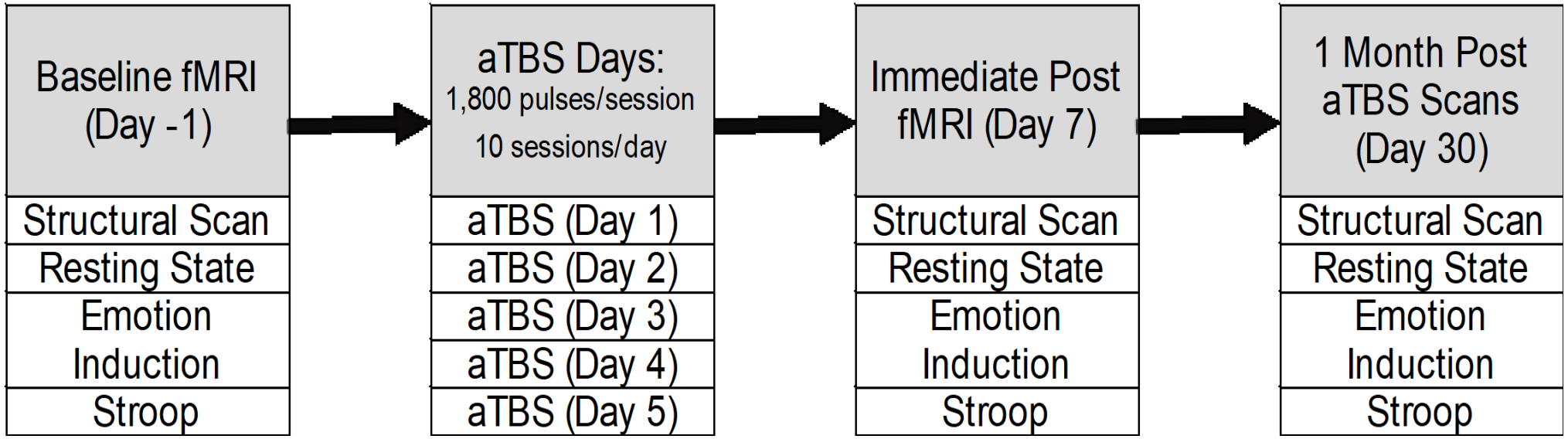
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800
50 min ISI	50 min ISI	50 min ISI	50 min ISI	50 min ISI
iTBS1800	iTBS1800	iTBS1800	iTBS1800	iTBS1800

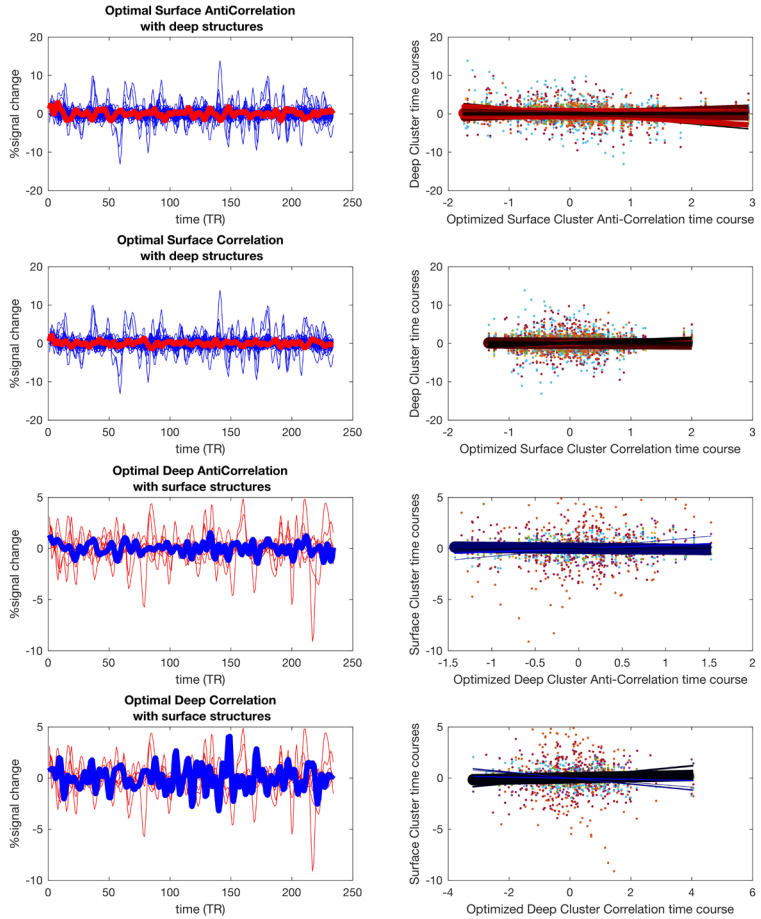
Study Design



Self-Imposed Requirements for Technique

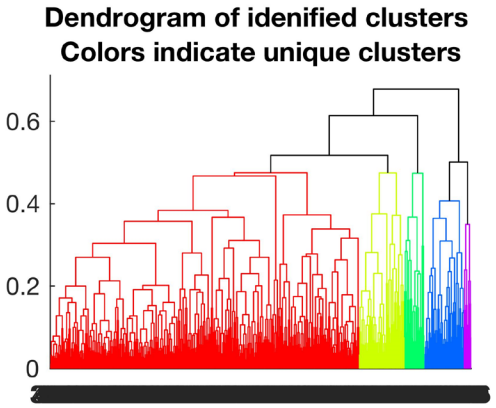
- Better than ~50% remission rate for TRD (48% for ECT, 23.8% ketamine, 30% for traditional rTMS).
- Better than 55-63% resolution of suicidal ideation (ECT, ketamine respectively).
- Less than 25% loss of responders at 1 week.
- Better than 8 weeks durability in TRD (8.6 weeks for ECT, <7 days for ketamine).
- Finish in 5 days (<10% response rate for ECT at one week (3 ECT treatments), ketamine takes ½ day).
- No more than 2 hours per day required for stimulation (ECT about 100 minutes/session).
- No SAEs and no cognitive SE.

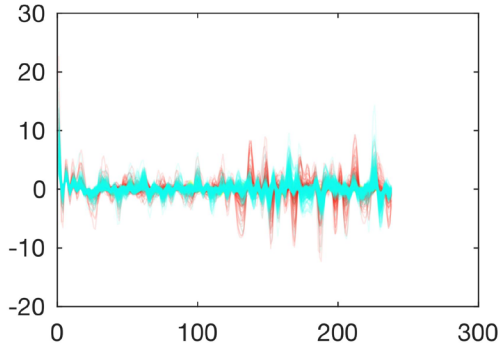
Relationship Between Cluster (Median) Timecourses

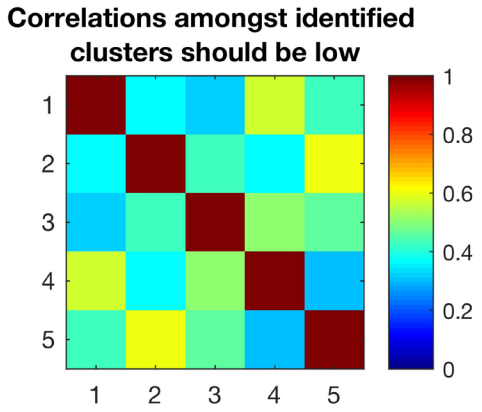


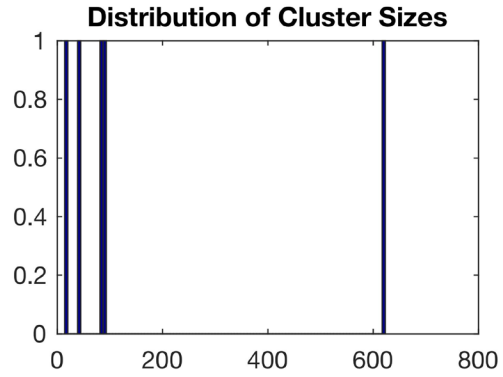
Hierarchical Clustering To Identify Functional Subregions

DLPFC

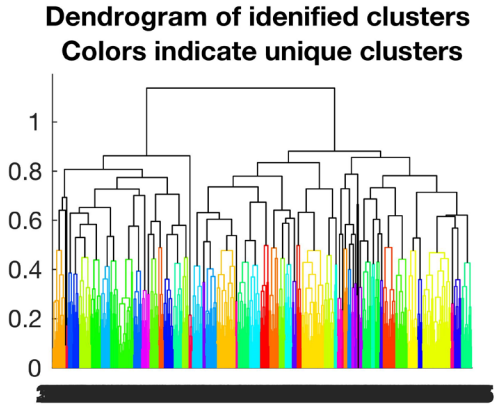


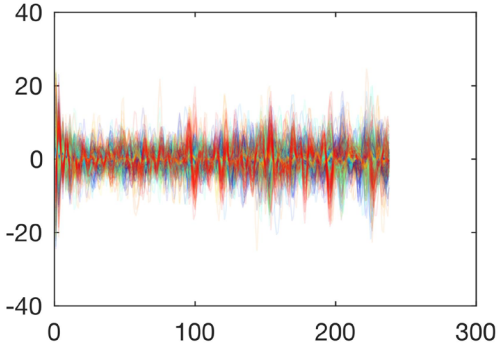


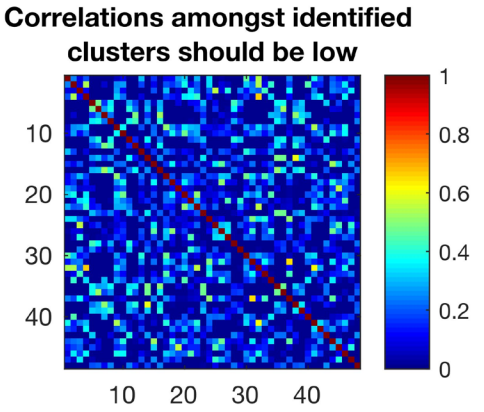


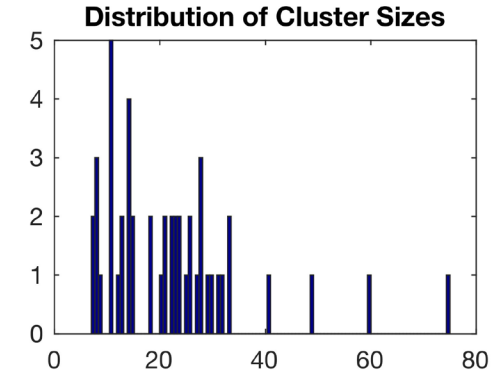


SUBGENUAL

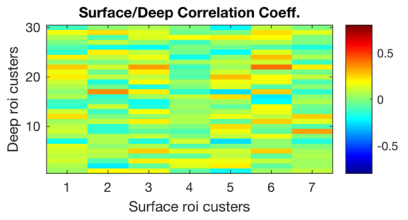


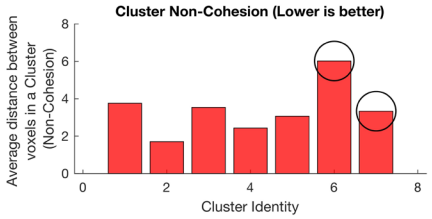


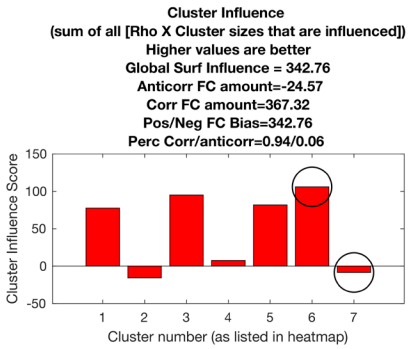


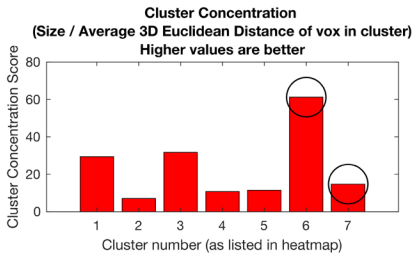


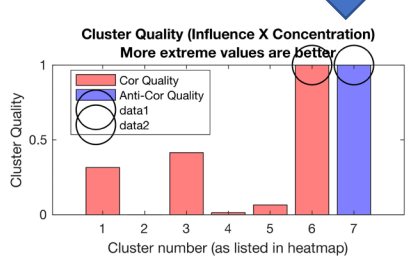
Algorithms for Converting Complex relationships into targets

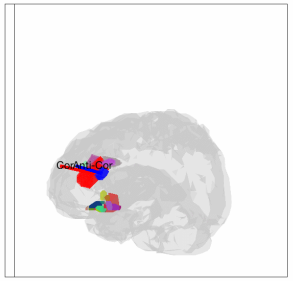


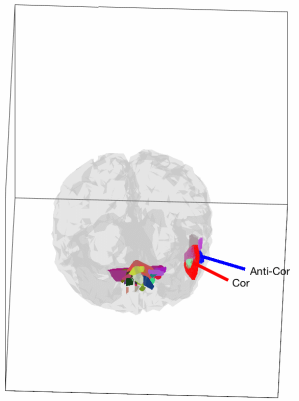


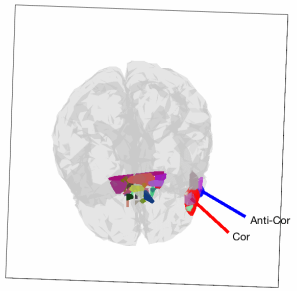




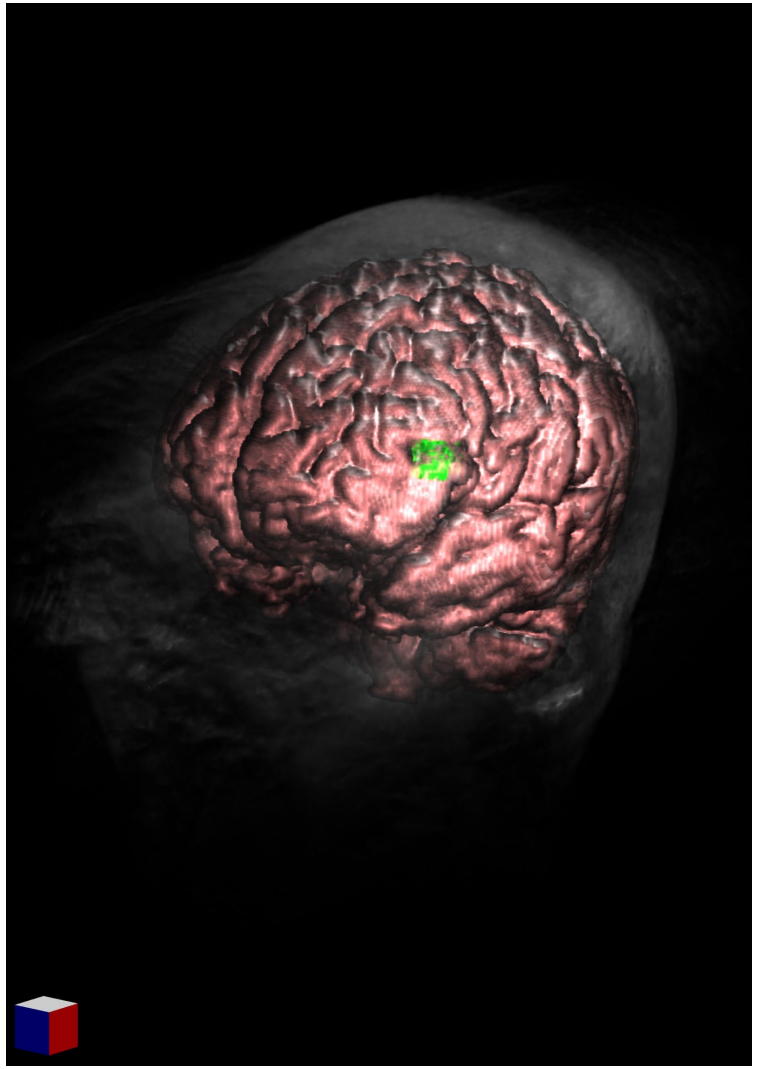


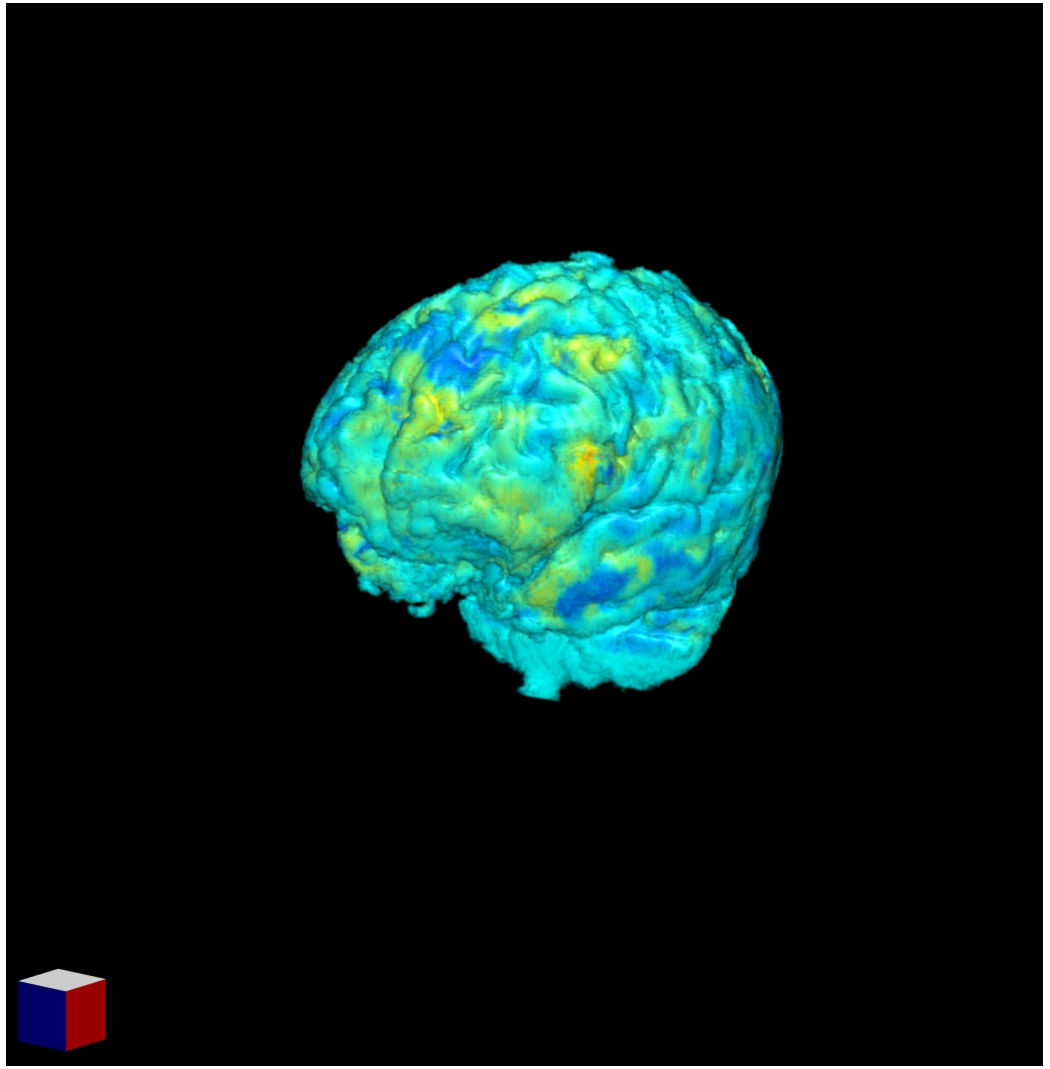






Outputting Targets to Neuronavigation





Our participant sample

Participant info	Mean (SD)
N	31
Gender (male:female)	12:19
Age	48.12 (17.05)
Age of onset of depression	22.45 (9.88)
Duration of depression	25.56 (15.86)
Number of antidepressant failures (lifetime)[1]	8.84 (6.03)
Number of adjunctive medications (lifetime)[2]	1.48 (1.39)
Number of participants attempted rTMS	12*
Number of participants attempted ECT	6**
Maudsley Staging Method Score	11.19 (2.04)

Table 1: Demographic information and treatment history for all participants
[1]adequate antidepressant trials defined as a minimum of 6 weeks at an appropriate dose according to the Anti-depressant Treatment History Form (ATHF).
[2]medications defined as adequate augmentation strategies according to the ATHF
*1 remitter, all other participants did not respond.
**1 remitted to bilateral but did not respond to unilateral, all other participants were non-responders.

Cole, in prep

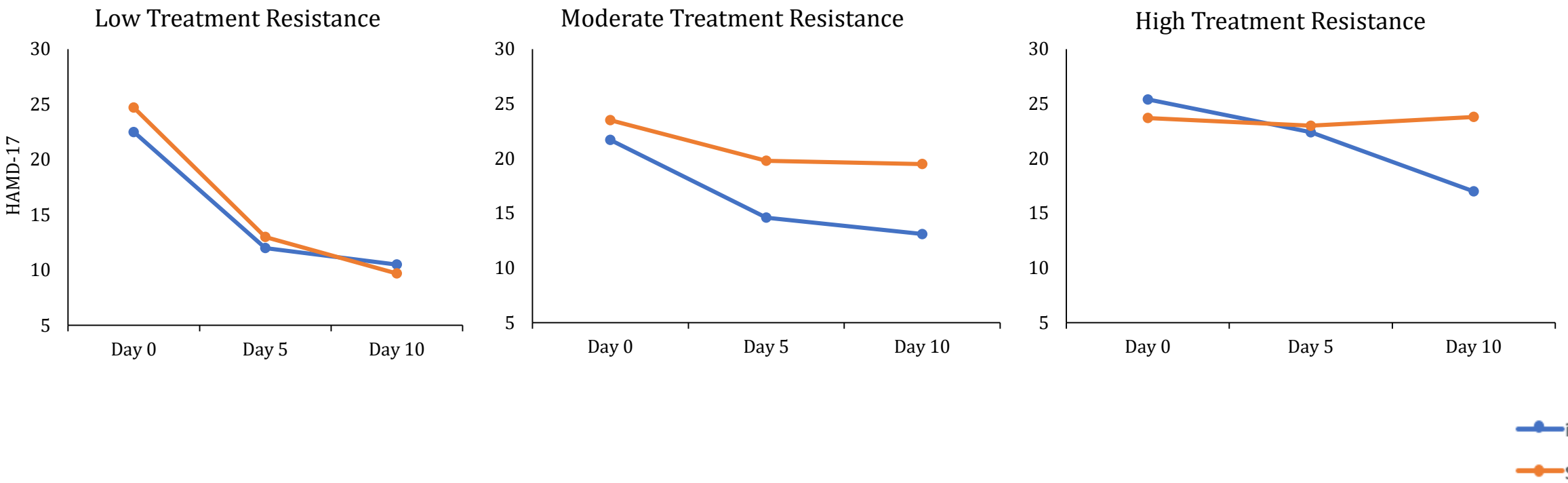
Our participant sample

Participant info	Mean (SD)
N	22
Gender (male:female)	10:12
Age	48.36 (15.98)
Age of MDD onset	21.95 (8.90)
Duration of MDD	26.41 (15.48)
Number of antidepressant failures (lifetime)[1]	8.77 (5.51)
Number of adjunctive medications (lifetime)[2]	1.36 (1.47)
Number of participants attempted rTMS	10*
Number of participants attempted ECT	4**
Maudsley Staging Method Score	11.32 (2.12)

Table 2: Demographic information and treatment history for the MDD subsample
[1]adequate antidepressant trials defined as a minimum of 6 weeks at an appropriate dose according to the Anti-depressant Treatment History Form (ATHF).
[2]medications defined as adequate augmentation strategies according to the ATHF
*1 remitter, all other participants did not respond.
**all participants were non-responders.

Cole, in prep

No placebo effect in high TR



Li 2014

Can you really treat depression in 5 days?

	Pre aiTBS	Post aiTBS	Responders (%)[1]	Remission (%)[2]
MADRS	37.71 (7.24)	4.81 (6.41)	90.32	90.32
HAMD-17	27.87 (5.23)	4.55 (5.07)	90.32	83.87
HAMD-6	15.23 (2.80)	2.39 (3.32)	87.10	83.87
BDI[3]	32.61 (12.37)	6.64 (7.07)	87.50	85.71
C-SSRS[4]	1.52 (1.29)	0.00 (.00)	100.00	100.00
HAMD-Q3	1.52 (.85)	0.03 (.18)	96.77	96.77
MADRS-Q10	2.39 (.99)	0.07 (.36)	96.77	96.77

Table 3: Clinical assessment scores for all participants n=31; mean (SD)
[1]Response defined as >50% reduction in score
[2]Remission defined <8 on HAMD-17 (Leucht et al., 2013), <5 on the HAMD-6 (Timmerby et al., 2017), ≤10 on MADRS (Zimmerman, Posternak, & Chelminski, 2004), BDI<13 (Schulte-van Maaren et al., 2013) and C-SSRS=0 (Price et al., 2009)
[3]n=24, 28 participants had a post-aiTBS BDI score so for remission % calculation n=28.
[4]Current suicidal ideation subscale, n=25

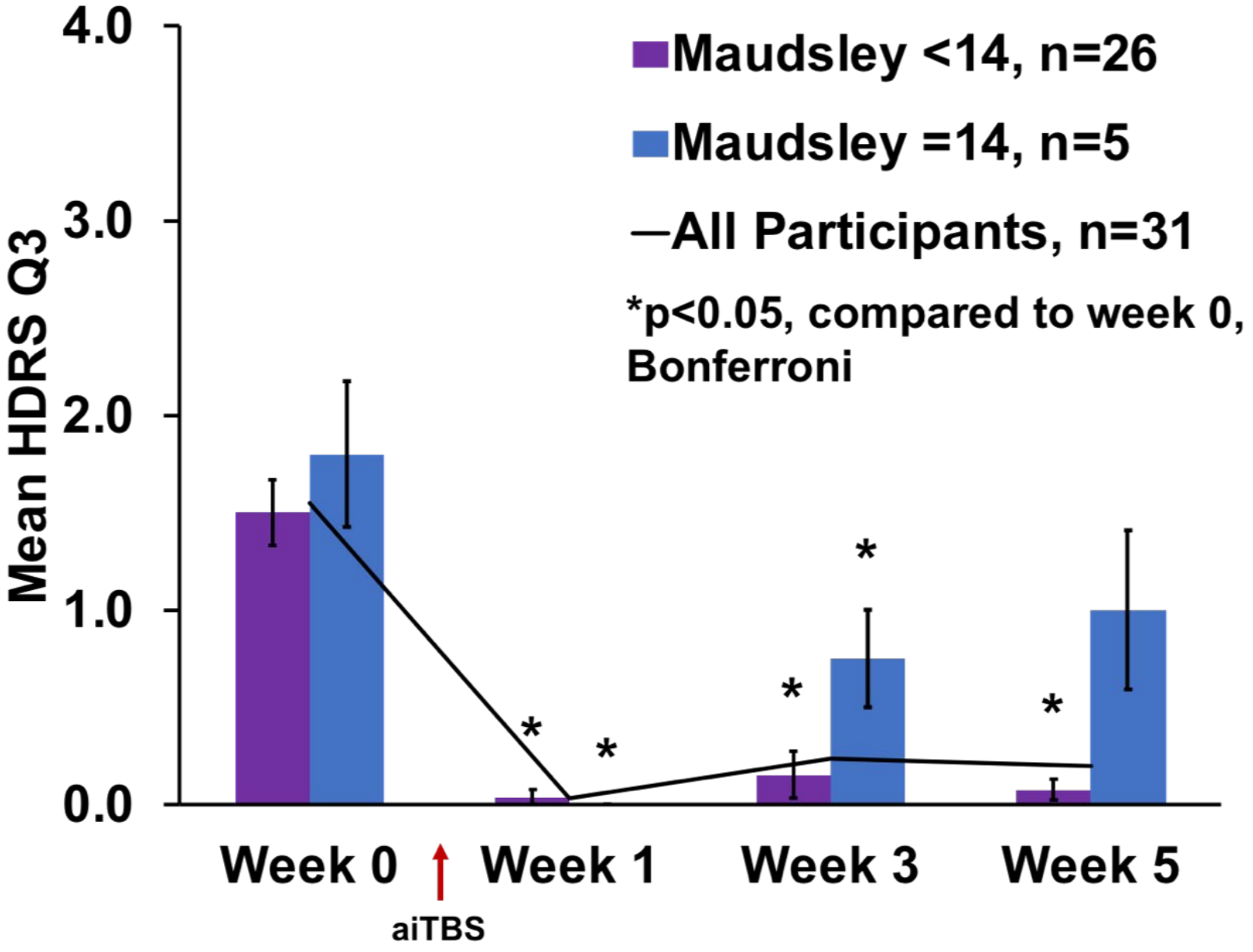
Cole, in prep

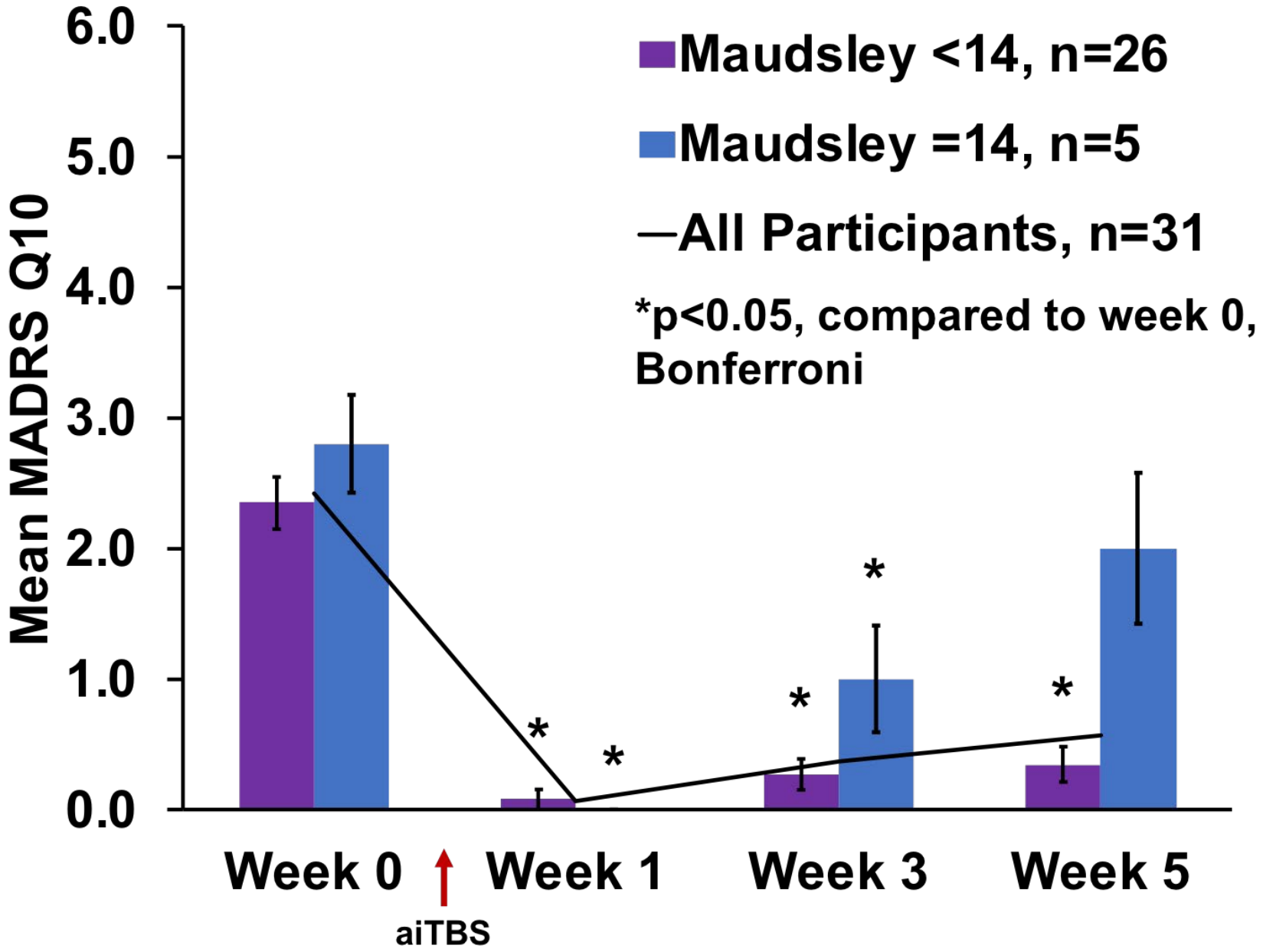
Can you really treat depression in 5 days?

	Pre aiTBS	Post aiTBS	Responders (%)[1]	Remission (%)[2]
MADRS	36.36 (6.82)	4.82 (5.45)	90.91	90.91
HAMD-17	27.14 (5.61)	4.36 (4.22)	90.91	81.82
HAMD-6	14.77 (2.96)	2.50 (3.04)	86.36	81.82
BDI	32.59 (11.21)	6.90 (7.08)	88.24	82.35
C-SSRS*	1.632 (1.34)	.00 (.00)	100.00	100.00
HAMD-Q3	1.50 (.96)	.00 (.00)	100.00	100.00
MADRS-Q10	2.32 (.99)	.00 (.00)	100.00	100.00

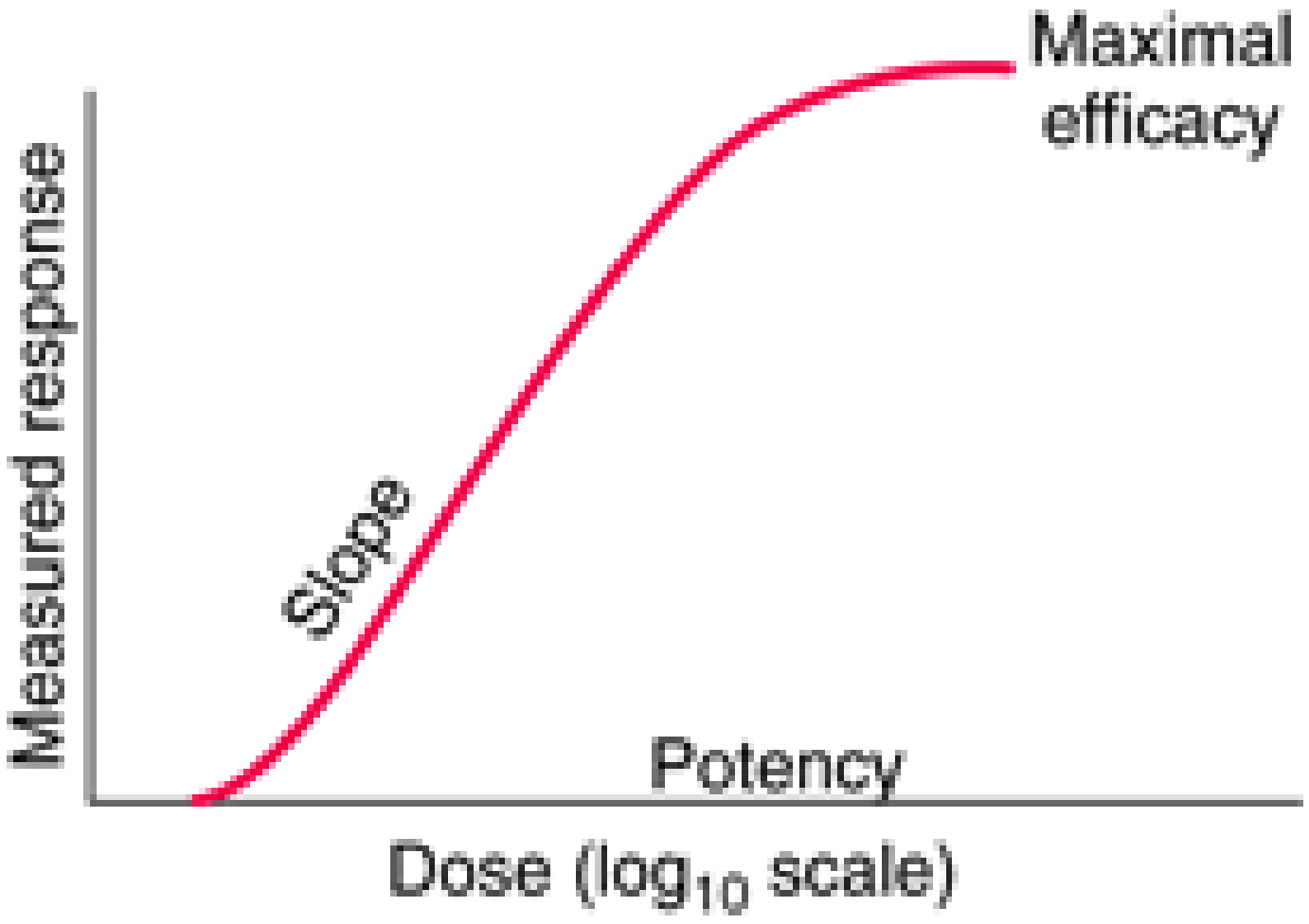
Table 4: Clinical assessment scores for MDD participants n=22; mean (SD)
[1]Response defined as >50% reduction in score
[2]Remission defined <8 on HAMD-17 (Leucht et al., 2013), <5 on the HAMD-6 (Timmerby et al., 2017), ≤10 on MADRS (Zimmerman, Posternak, & Chelminski, 2004), BDI<13 (Schulte-van Maaren et al., 2013) and C-SSRS=0 (Price et al., 2009)
[3]n=16
[4]Current suicidal ideation subscale, n=18

Cole, in prep

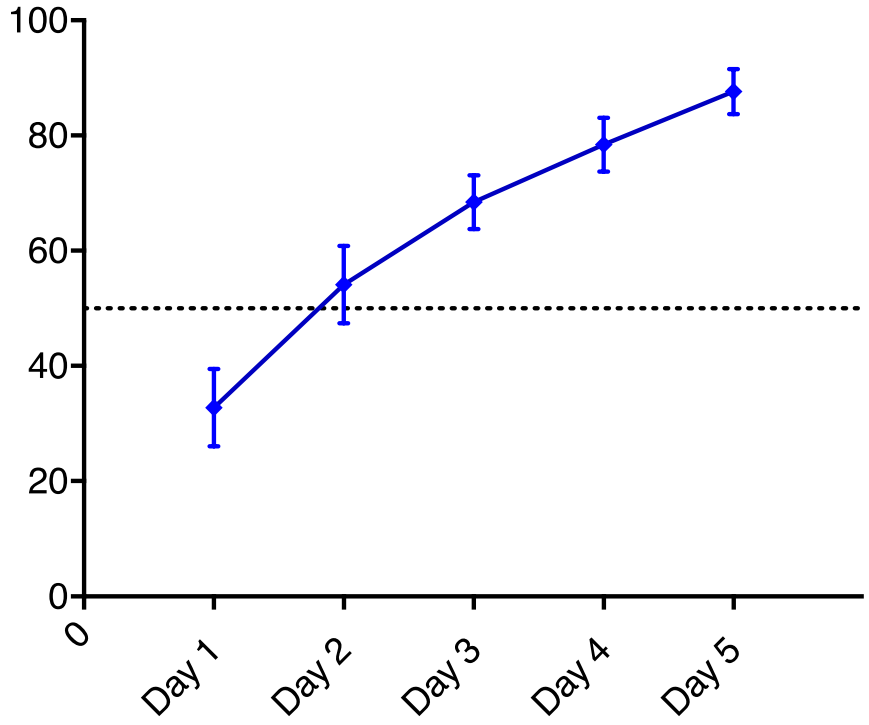

Maudsley <14, n=26
Maudsley =14, n=5
—All Participants, n=31
*p<0.05, compared to week 0, Bonferroni
Mean HDRS Q3
4.0
3.0
2.0
1.0
0.0
Week 0
aiTBS
Week 1
Week 3
Week 5
*
*
*
*
*


Mean MADRS Q10
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Maudsley <14, n=26
Maudsley =14, n=5
—All Participants, n=31
*p<0.05, compared to week 0, Bonferroni
*
*
*
*
*
Week 0
aiTBS
Week 1
Week 3
Week 5

Dose-response Curve



Can you really treat depression in 5 days?



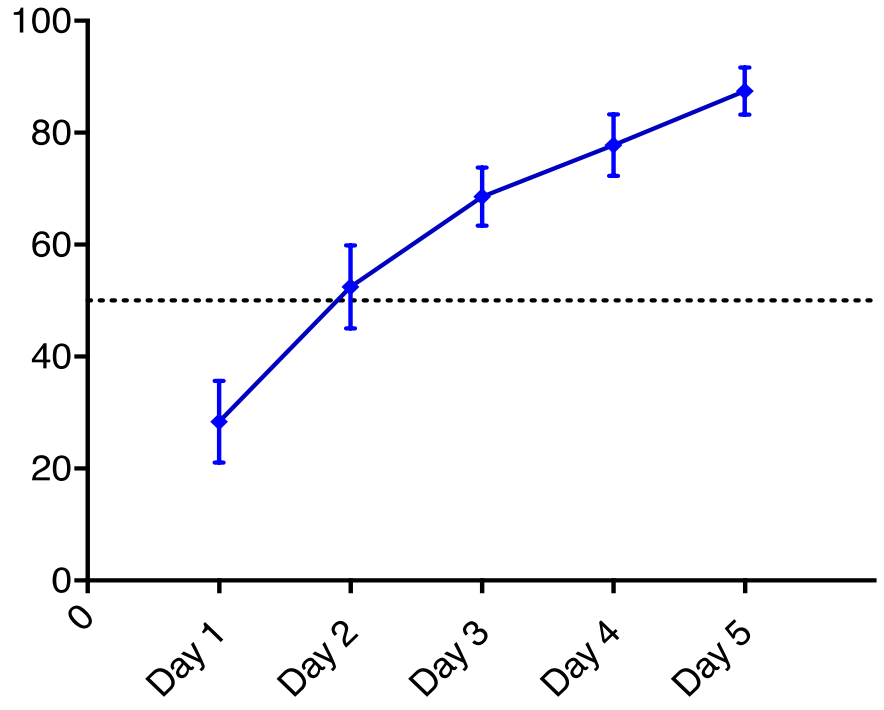


Figure 1: Average percentage change in Hamilton Depression Rating Scale score (6-item version) with each day of stimulation for A) All participants (n=29, daily HAMD-6 scores missing for two participants), diagnoses of MDD, bipolar and Parkinson's depression. B) MDD participants (n=21, daily HAMD-6 scores missing for one participant). Dotted lines indicate responder criteria.

Cole, in prep

Piloting on Inpatient Unit

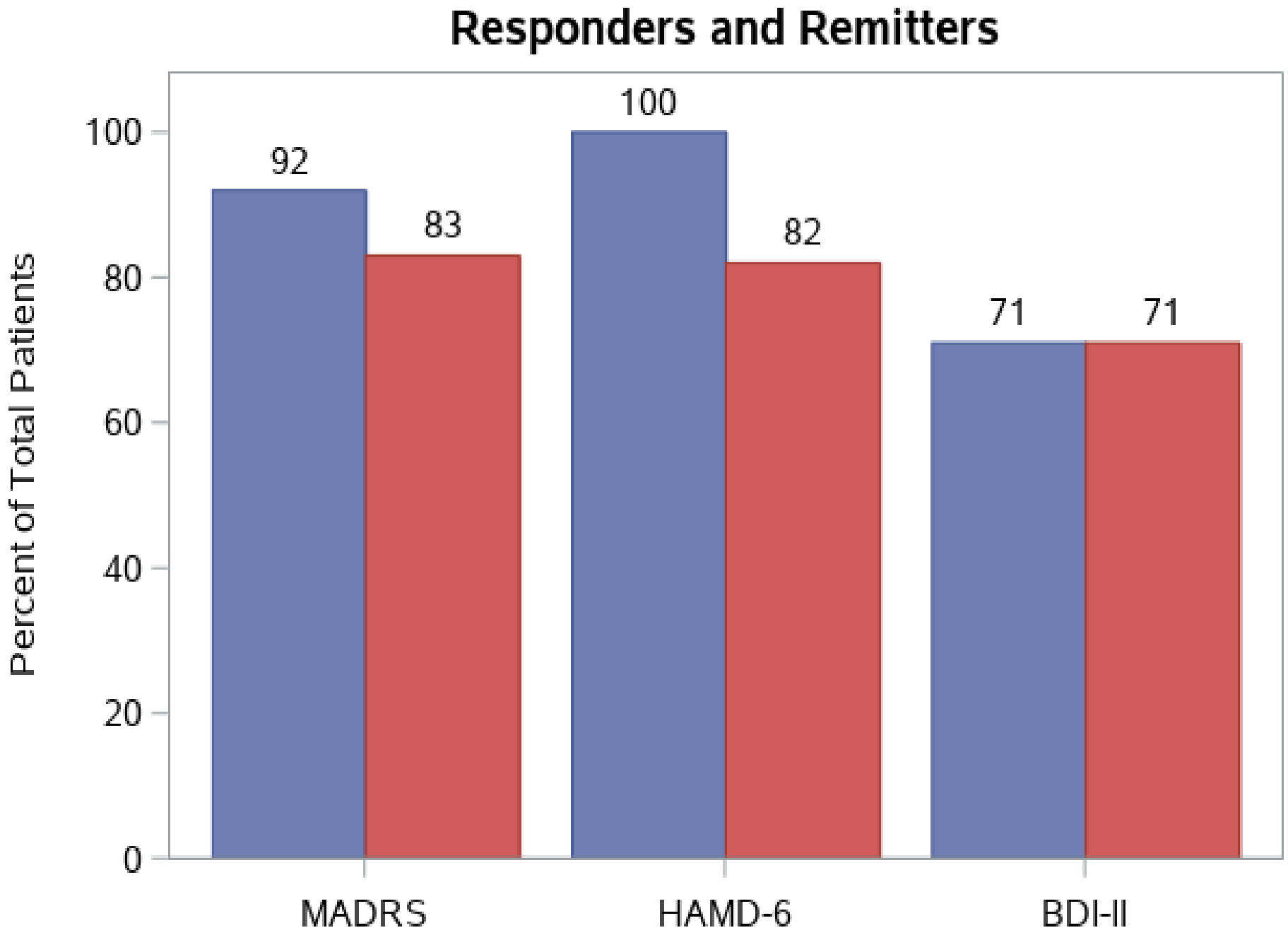
First 12 completers

3 previously had ECT

8 had previous suicide attempt

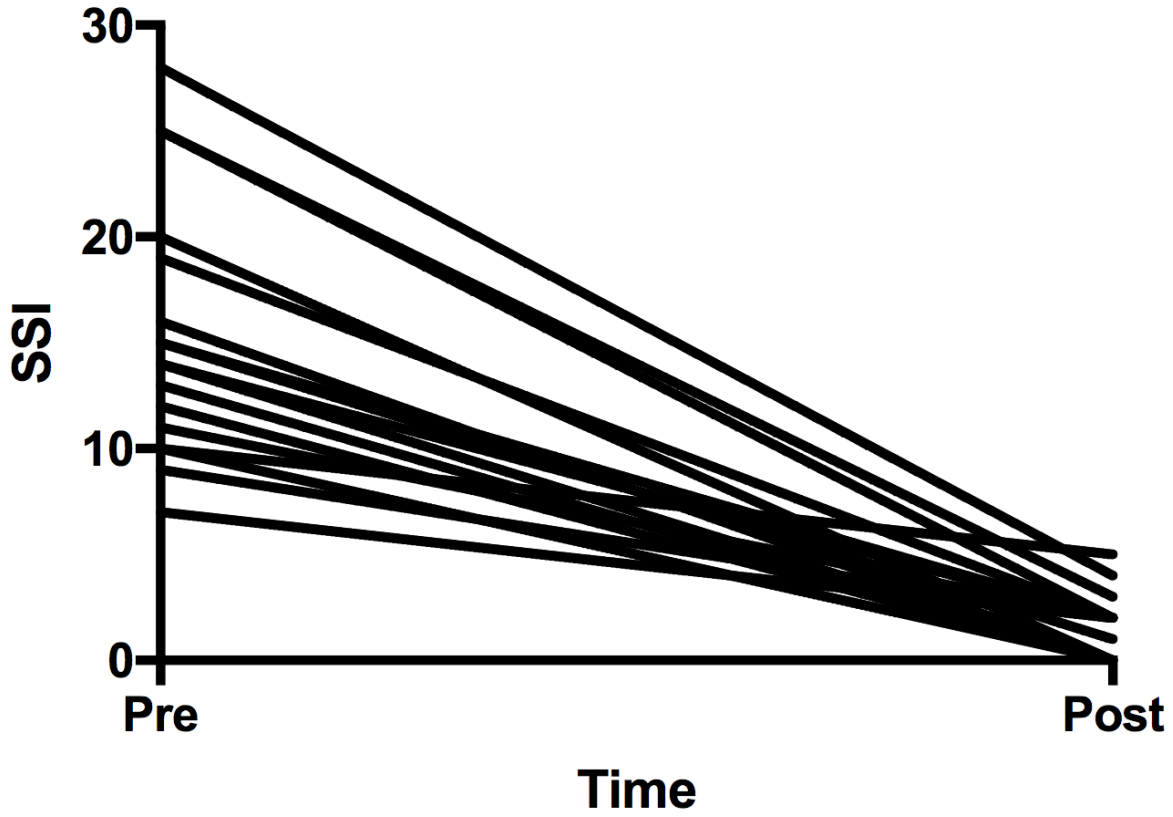
100% of suicidal patients experienced clinically significant reduction in SI immediate post

	Baseline Score	Post-Treatment Score	Percent Responder	Percent Remitter
MADRS (n = 12)	39 ± 8	8 ± 10	92%	83%
HAMD-6 (n = 11)	15 ± 2	2 ± 3	100	82%
BDI-II (n = 11)	33 ± 7	12 ± 13	71%	71%


Responders and Remitters
Percent of Total Patients
100
80
60
40
20
0
92
83
100
82
71
71
MADRS
HAMD-6
BDI-II

Suicidal Ideation after aiTBS (Inpt + Outpt SSI)

- 17 Subjects with SSI ≥6.
- Average entry SSI score of 15.5 (±6).
- Average Immediate post score of 1.6 (±1.5).
- Average %reduction was 88%.
- No pts worsened.
- In 100% pts, SSI reduced below 6.



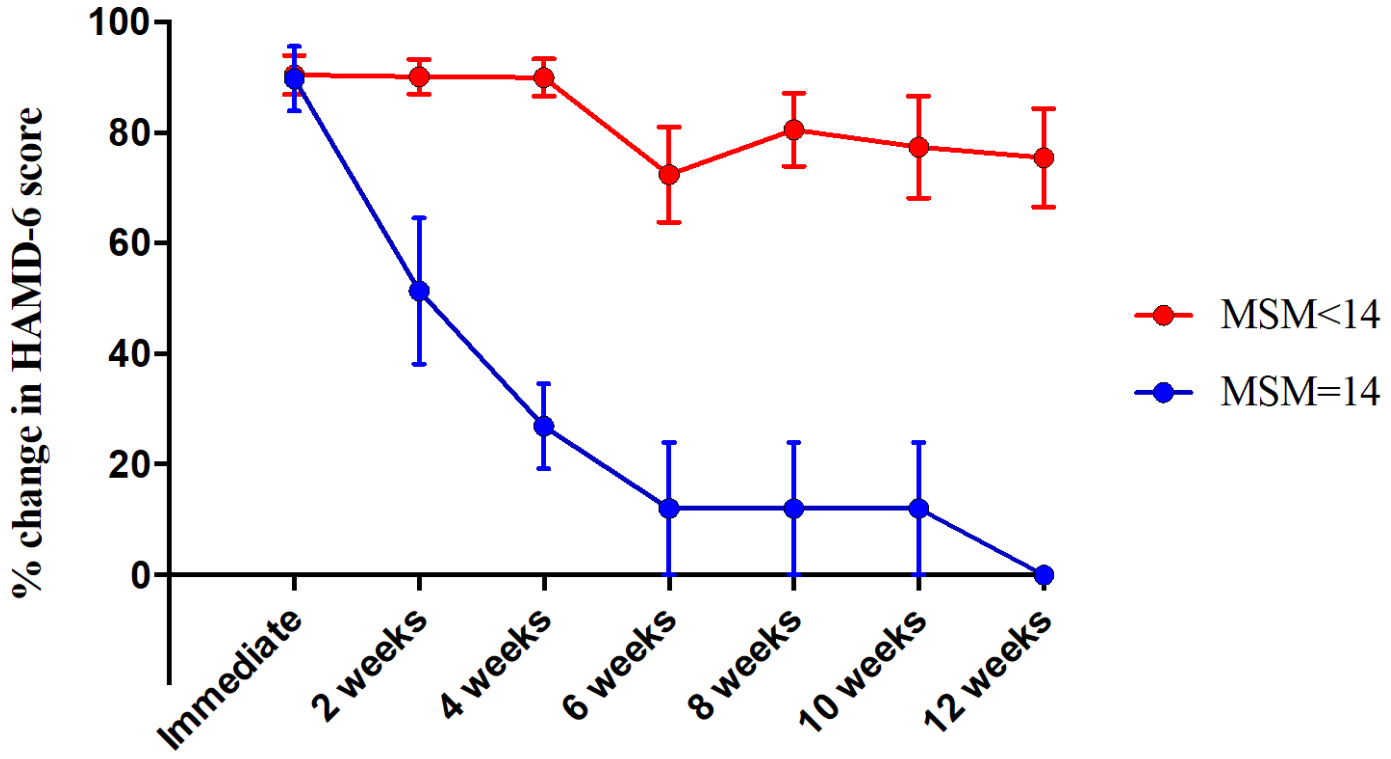
Cole, in prep

Neuropsychological Data

- Preliminary data analysis comparing baseline testing to post-treatment testing shows no significant change with the exception of **improvements** in:

- Cognitive Inhibition
- Cognitive Switching
- Speed of number & letter sequencing
- Stroop Color-Word

Durability



Average DOR= 15 weeks
(not inc. 1 still remitted and 1 responder)

Average DOR= 4.4 weeks

Cole in prep

Brain Stimulation Lab

<u>Instructors</u>
Flint Espil
Danielle DeSouza

<u>Post-Docs</u>
James Bishop
Xiaoqian Xiao
John Coetzee
Eleanor Cole

<u>CRCs</u>
Romina Nejad
Heather Pankow
Claudia Tischler
Pooya Toosi

<u>Lab Manager</u>
Merve Gulster

<u>Residents/Fellows</u>
Jessica Bentzley
Brandon Bentzley

<u>Students</u>
Jassi Pannu
Sham Singh
Kirsten Cherian
Christina Chung
Katy Stimpson
Will Tate
Liz Choi

Funding Sources