UTHSC PSYCHIATRY

PJ Sparer, MD Memorial Visiting Professorship Endowment Fund

This fund was established by Mrs. PJ Sparer, being deeply interested in continuing her late husband's good works and commemorating his interest in Psychiatry and Medicine, and his dedication as a College of Medicine Faculty Professor from 1951 until retirement in 1969.

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Strategic Director for Behavioral Health Services Florida Medical Practice Plan

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Combining Neuromodulatory Therapeutics & Psychosocial Treatment for Unipolar Depression

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Director, FSU Mood & Anxiety Disorder Center of Excellence

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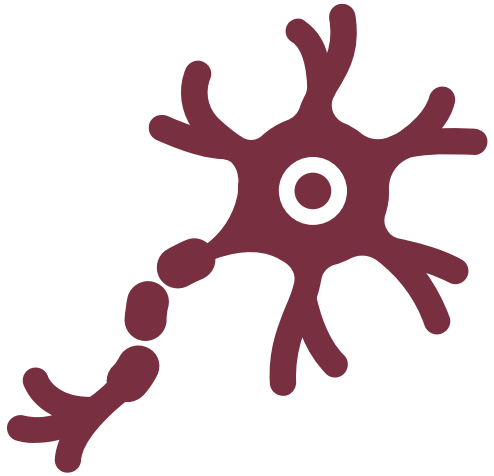
Disclosures

- Financial Support
  - NIMH, National Science Foundation, Blue Gator Foundation, Watzinger Foundation, Myocarditis Foundation, Mayo Foundation
- Off-label/Investigational Uses
  - This presentation will mention FDA-approved therapeutics for TRD but will focus on investigational medications
- Patents
  - U.S. Patent No. 11869633 ("Analytics and machine learning framework for actionable intelligence from clinical and omics data")



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Starting from the basic premise that the health department encompasses all the health needs and problems of the community, the author presents a general sketch of a plan for mental hygiene in a modern health department. A discussion by Dr. Lemkau follows.

MENTAL HYGIENE IN A MODERN HEALTH DEPARTMENT PROGRAM

GENERAL PERSPECTIVE AND PROGRAM PLANNING

P. J. Sparer, M.D.

Phineas J. Sparer, MD
Professor Emeritus of Preventive Medicine & Psychiatry

Dr. Sparer is professor of psychiatry and preventive medicine, Department of Psychiatry, University of Tennessee College of Medicine, Memphis, Tenn.

This paper was originally presented before the annual meeting of the Southern Branch of the American Public Health Association, Little Rock, Ark., 1958, and then later presented before the American Psychiatric Association, Philadelphia, Pa., April 25-30, 1959.

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How This Discussion is Organized

Part 1	Mechanistic Convergence	How do NIBS, RAADs, and psychotherapy converge around plasticity and new learning mechanisms ?
Part 2	Study Design, Inter-action, & Mediation	What study designs are needed to show true clinical synergy and mechanistic specificity?
Part 3	Review of Current Studies	What are the major efficacy and safety signals from the current literature?
Part 4	Limitations of Current Evidence, Future Directions	How well do existing studies show true clinical synergy and mechanistic specificity? What are the next steps?

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The Clinical Problem[1-3]

Depression affects over 350 million people worldwide…

- ☑ Almost **unparalleled burden** owing to high prevalence, adverse effects on functioning, direct/indirect costs, and early mortality
- ☑ Effective treatments exist, but are often slow in onset, with **variable** and **incomplete responses** (especially durable remission)
- ☑ These limitations have opened the door to newer neuromodulatory therapeutics, including **NIBS** and **RAADs**

Can biological interventions create neurobiological windows enabling more rapid, complete, or durable effects of psychotherapy in depression?

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[1] Zhou J et al. Sci Rep. 2025;15:9529. [2] GBD 2019. Lancet Psychiatry. 2022;9:137-50. [3] Friedrich MJ. JAMA. 2017;317:1517.

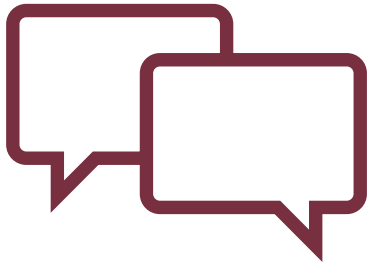
Key Definitions for This Lecture

Non-Invasive Brain Stimulation (NIBS)[1-3]

- **Specific interventions:** rTMS, deep TMS, theta-burst stimulation, tDCS, tACS

Rapidly-Acting Antidepressants (RAADs)[4,5]

- **Ketaminoids:** Racemic IV ketamine, intranasal esketamine, other psychoactive ketamine metabolites
- **Psychedelics:** psilocybin, DMT/ayahuasca, others



Psychosocial Treatments[6,7]

- **Manualized Psychotherapy:** BA, CBT, mbCBT, BCBT-SP, ACT, IPT, Unified Protocol, etc.
- **Other Psychotherapy or Psychosocial Treatment(s):** digital/computer-assisted CBT, Cognitive Control Training, Mental Health Coaching, Automated Self-Association Training, etc.

[1] Nejati V et al. J Neural Transm. 2025;132:369-385.
[3] Chung SW et al. Depress Anxiety. 2015;32:182-192.
[4] Duman RS et al. Nat Med. 2016;22:238-249.
[5] Ko K et al. J Affect Disord. 2023;322:194-204.
[6] Clough BA, Casey LM. Clin Psychol Rev. 2011;31:279-292.
[7] Cuijpers P et al. J Consult Clin Psychol. 2008;76:909-922.

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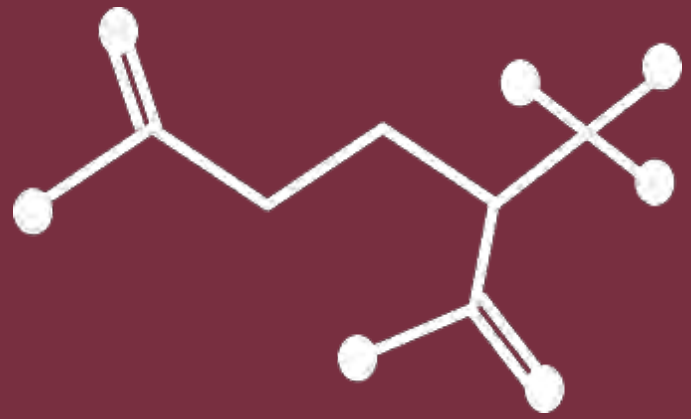
Part 1.
Mechanistic Convergence



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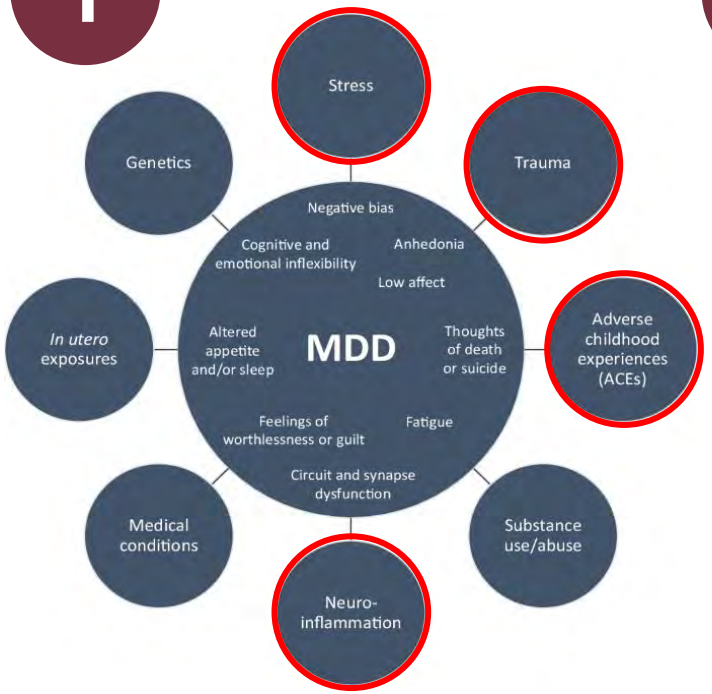
Neuroplasticity and Depression (Pt. 1)[1-3]

1



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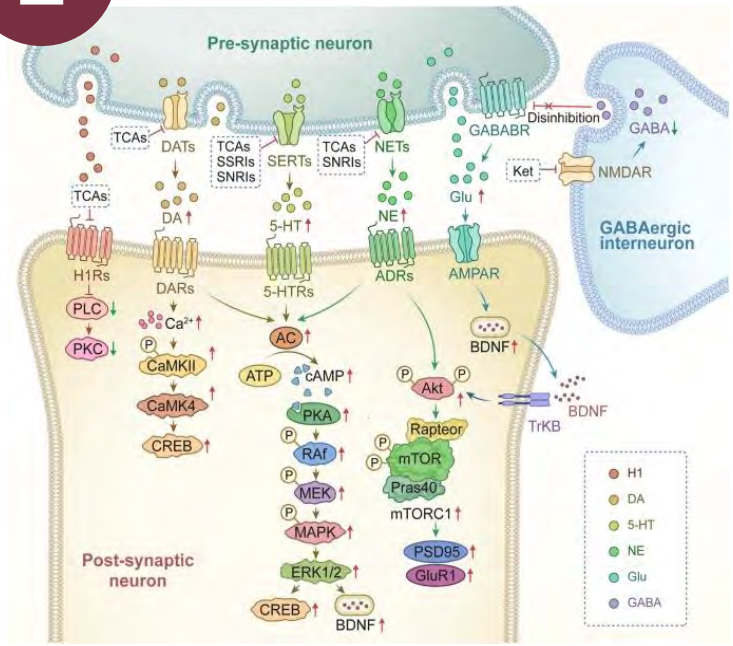

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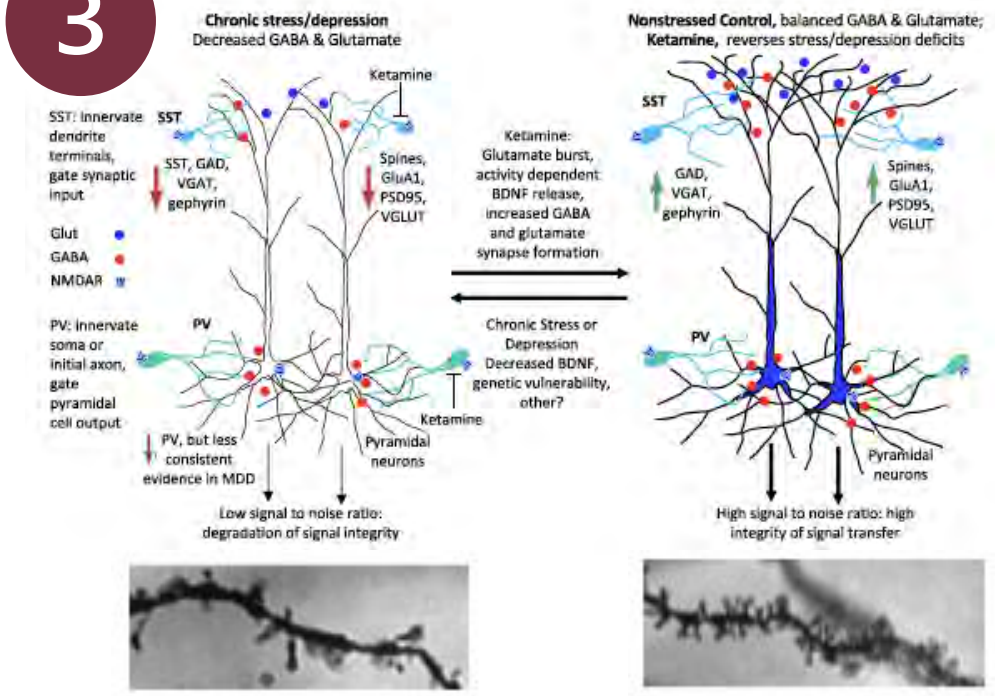

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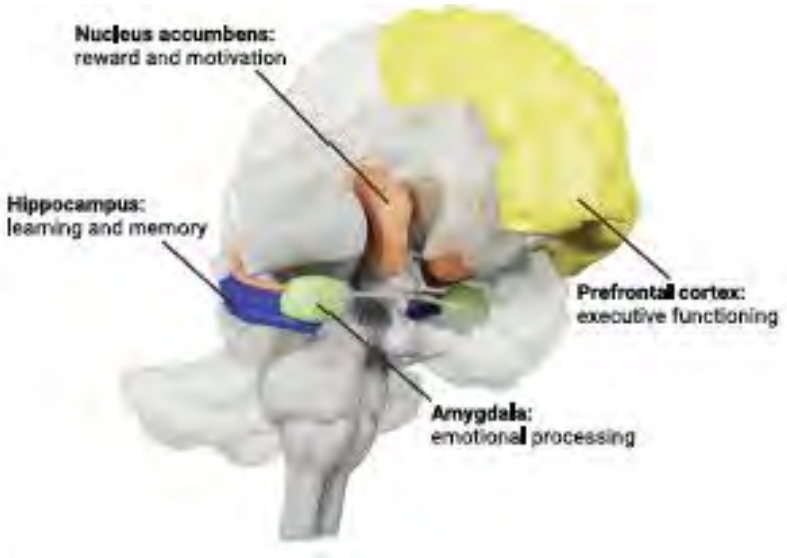
[1] Pittenger C, Duman RS. Neuropsychopharmacol Rev. 2008;33:88-109.
[2] Page CE et al. Mol Psychiatry. 2024;29:3802-3813.
[3] Cui L et al. Signal Transduction & Targeted Ther. 2024;9:30.

Neuroplasticity and Depression (Pt. 2)[1,2]

4



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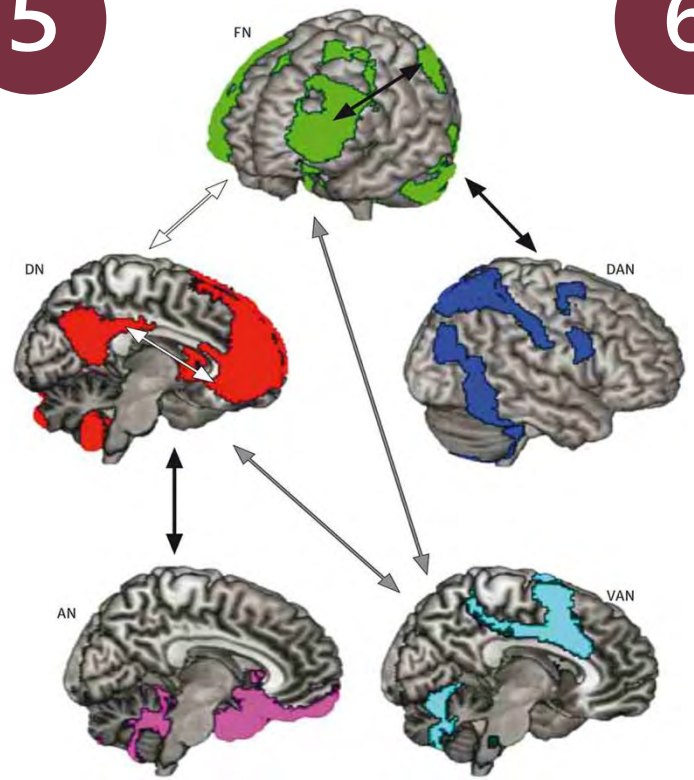

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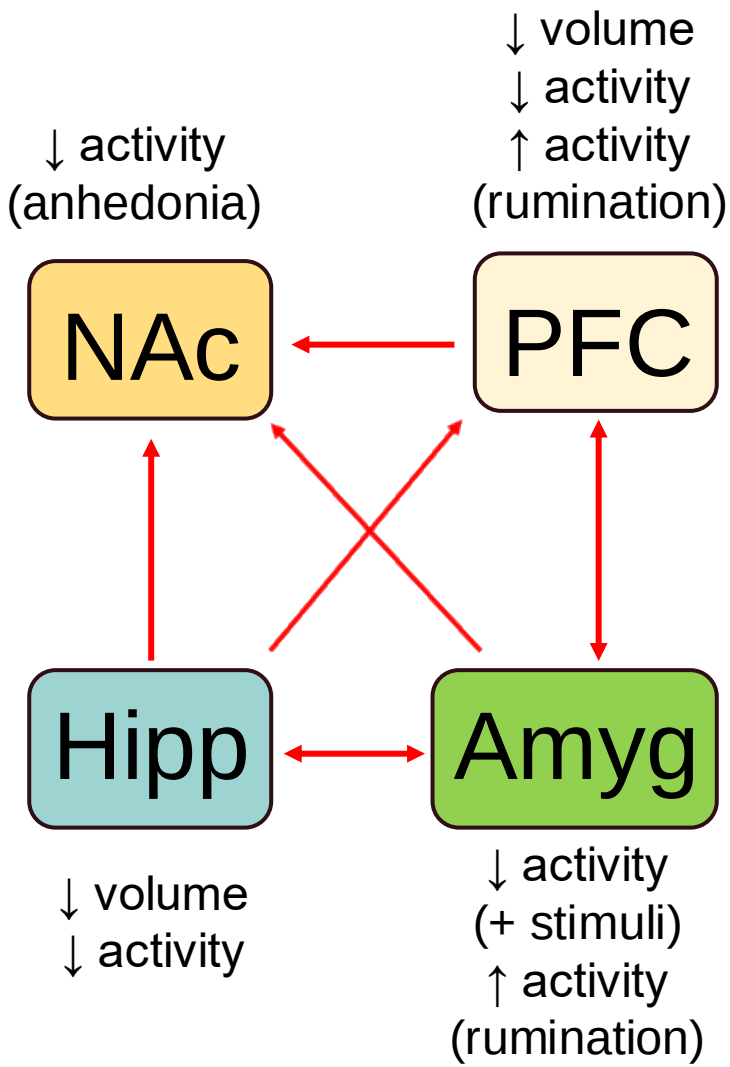

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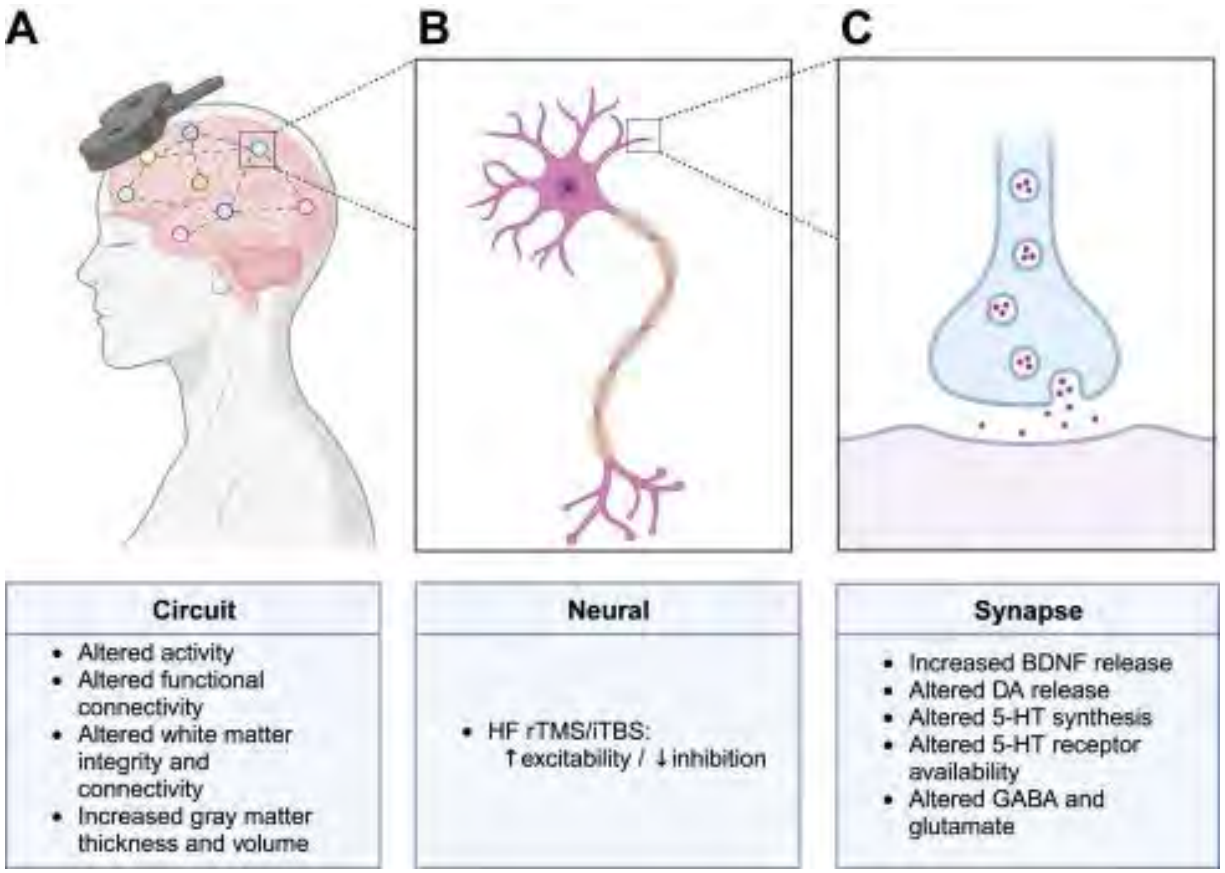
[1] Page CE et al. Mol Psychiatry. 2024;29:3802-3813.
[2] Kaiser RH et al. JAMA Psychiatry. 2015;72:603-611.

Non-Invasive Brain Stimulation (NIBS), Circuit Excitability, & Plasticity



rTMS and Related NIBS Techniques

↓

Altered Cortical Excitability
(e.g., ↑ PFC cognitive control and emotional regulation circuitry)

↓

Activated Neuroplasticity Mechanisms
(e.g., LTP/LTD-like effects, imaging biomarkers, blood biomarkers)

↓

Modified Network Connectivity

Fitzsimmons SMDD et al. Biol Psychiatry. 2024;95:592-600.

Rapid-Acting Antidepressants: Rapid Plasticity Activators

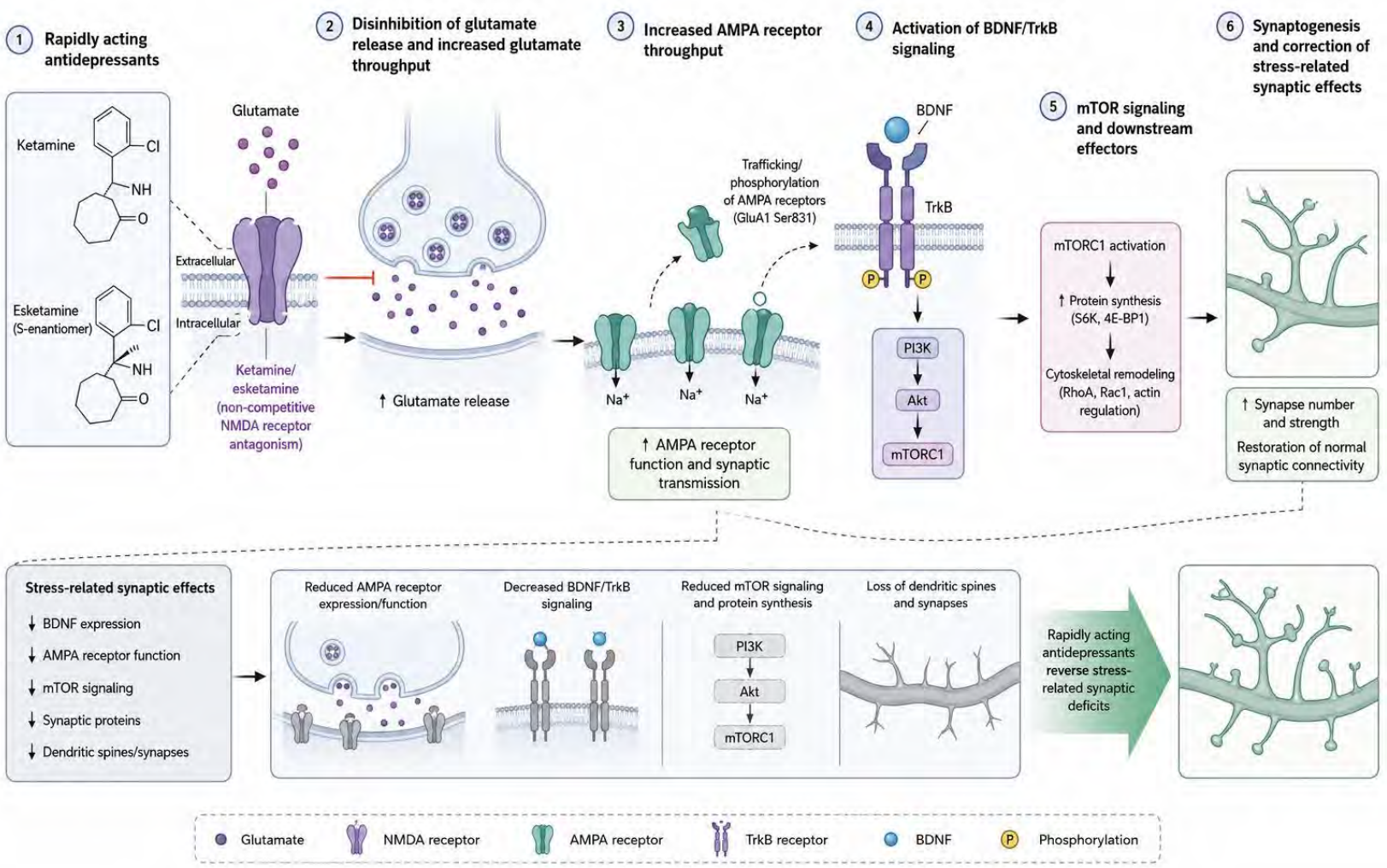
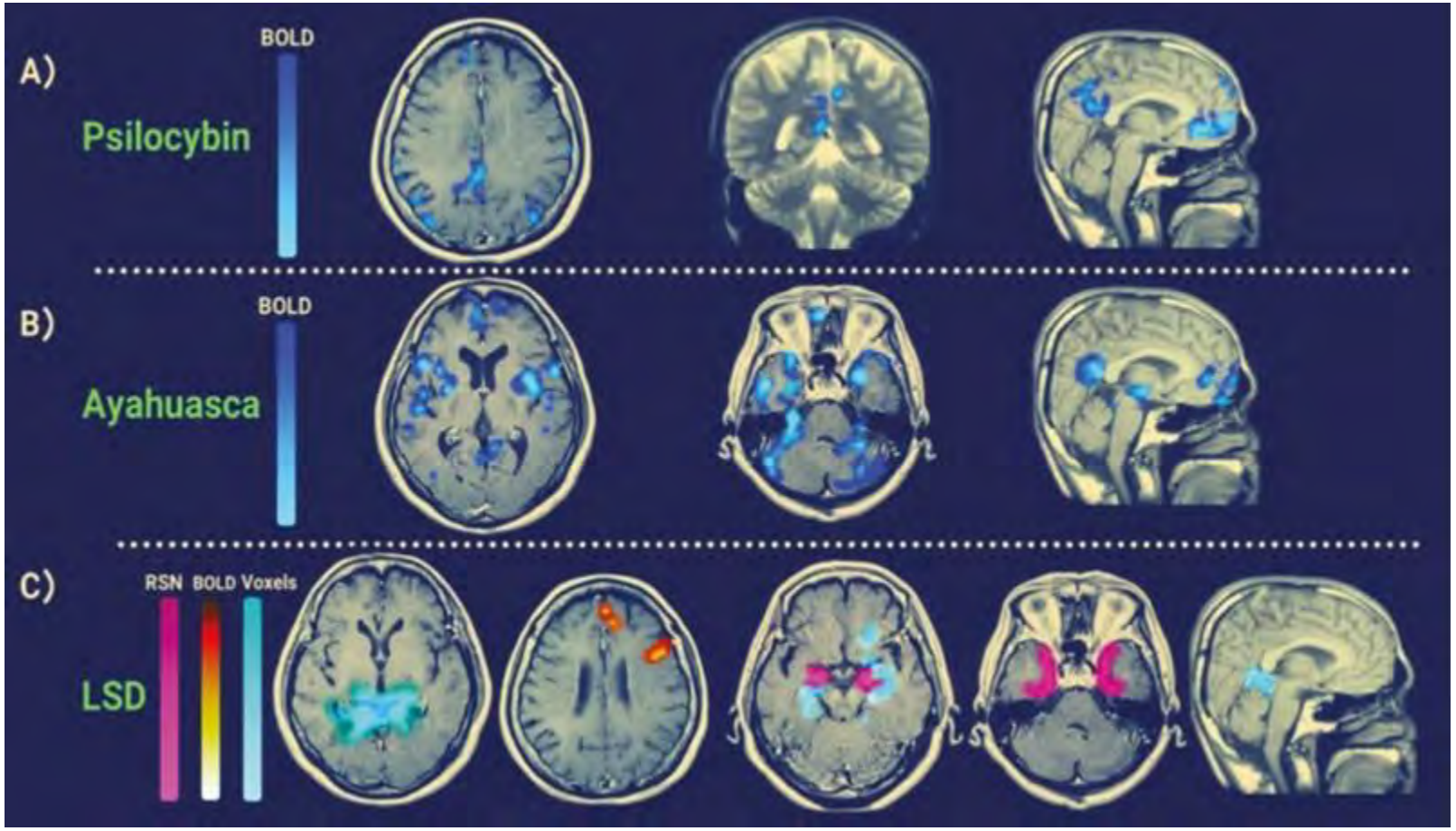


Figure illustration generated with ChatGPT (OpenAI) from author-developed scientific content/prompt; reviewed and edited by the author for accuracy.

McIntyre RS, Jain R. CNS Drugs. 2024;38:869-90; Kang MJY et al. Front Psychiatry. 2022;13:860882.

Rapid-Acting Antidepressants: Psychoplastogens

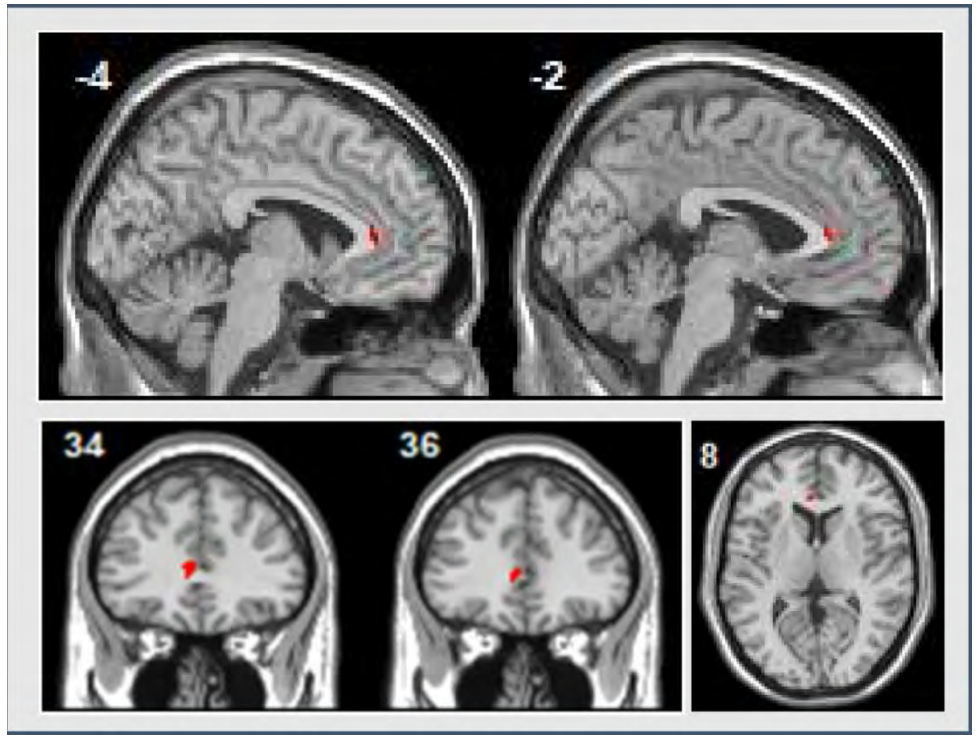
Systematic review of **28 studies** investigating the effects of various serotonergic **psychedelics** (5-HT_{2A} full/partial agonists) on resting state connectivity within **Default Mode Network (DMN)** and functional connectivity between canonical resting-state networks



Gattuso JJ et al. Int J Neuropsychopharmacol. 2023;26:155-88.

Psychological Treatment, New Learning, & Plasticity[1-3]

Systematic review (17 studies pre-post studies, 4 subjected to meta-analysis)
Imaging biomarkers for MDD patients who received CBT (9 studies), BA (2 studies), IPT (2 studies), or long-term psychodynamic psychotherapy (4 studies)



LEFT: Patients with MDD showed increased rACC activation, while healthy controls showed decreased activation (group x time interaction, $p<0.05$ FDR corrected).

ABOVE: Main effect of decreased left precentral gyrus activity following psychotherapy for MDD ($p<0.05$ FDR corrected).

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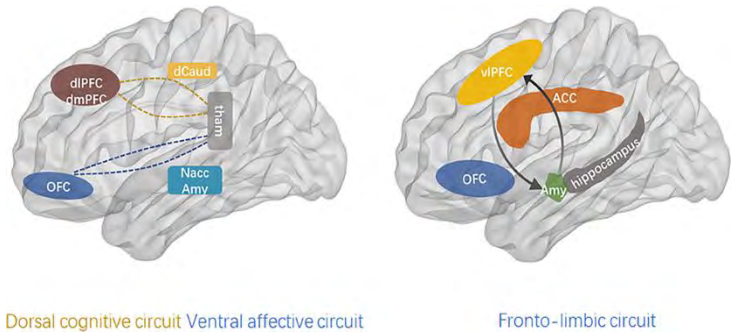
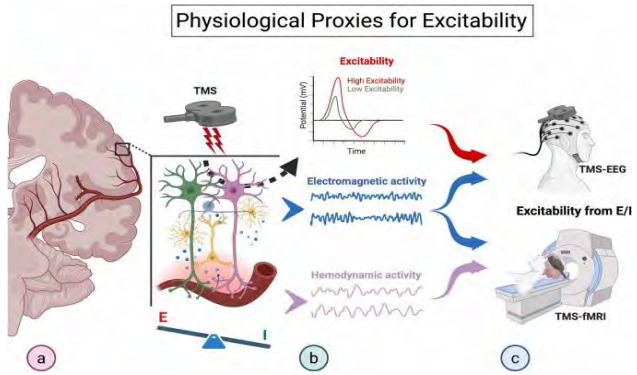
[1] Sankar A et al. Psychiatry Res Neuroimaging. 2018;279:31-39.
[2] Konig P et al. J Affect Disord. 2025;368:872-887.
[3] Piotrkowicz M et al. J Clin Med. 2021;4424.

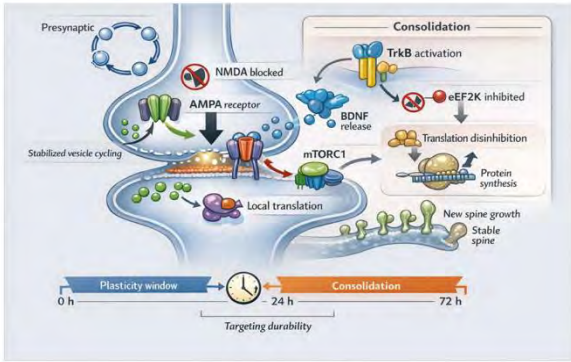
Plasticity Window Concept[1-6]



Dorsal cognitive circuit Ventral affective circuit

Fronto-limbic circuit





Altered Excitability & Network Connectivity (DLPFC-ACC-limbic)

Modulated Cortical Excitability to Prime Task-Dependent Learning

Engagement of Glu, AMPA, BDNF, mTOR-linked plasticity

TMS | iTBS | tDCS | tACS

Ketaminoids | Psychedelics

CBT | CCT | BA | Exp. | Mind.

NIBS

RAADs

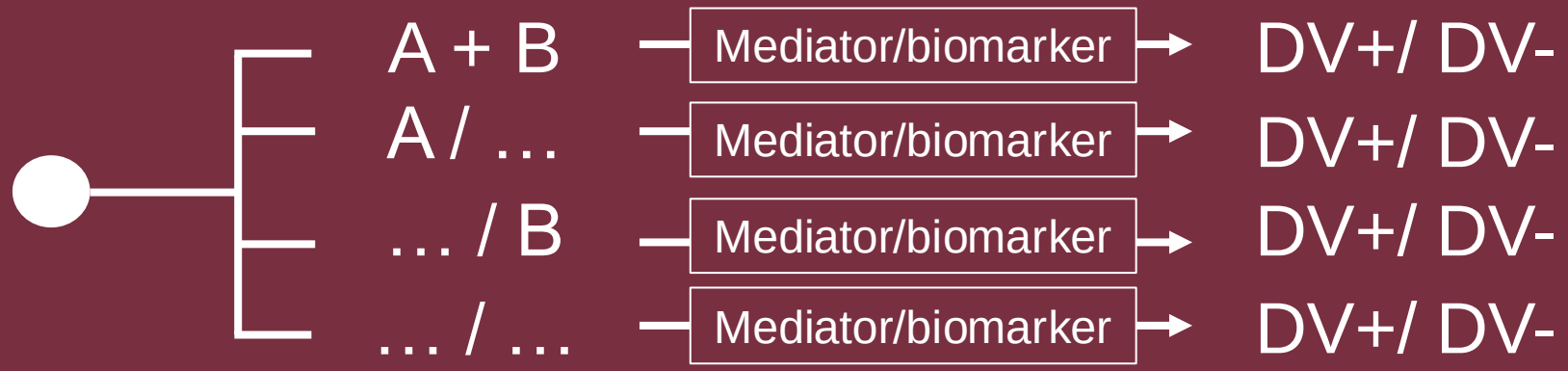
Psychosocial tx.

NIBS and RAADs → "plasticity windows"

PT → content, direction, repetition, consolidation

[1] Bi B et al. Transl Psychiatry. 2022;12:143. [2] Shuler A-L et al. Neurosci Biobehav Rev. 2025;177:106338. [3] Tanaka M. Preprints 2026;2026042155. [4] Lepow L et al. Front Neurosci. 2021;15:710004. [5] Tatti E et al. Neurosci Biobehav Rev. 2022;142:104867. [6] Saccenti D et al. Neural Plast. 2024;2024:7853199.

Part 2.
Study Designs Showing Synergy



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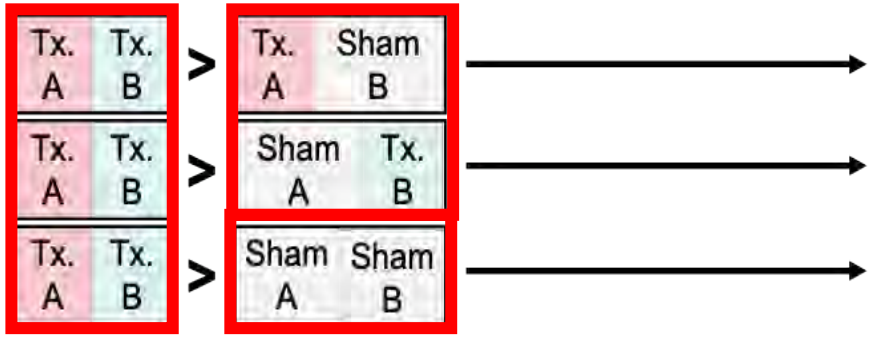
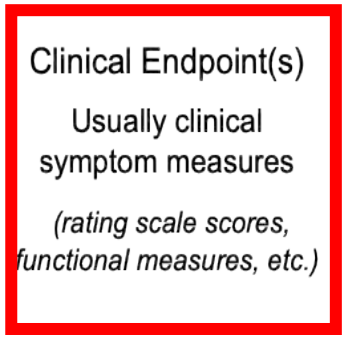
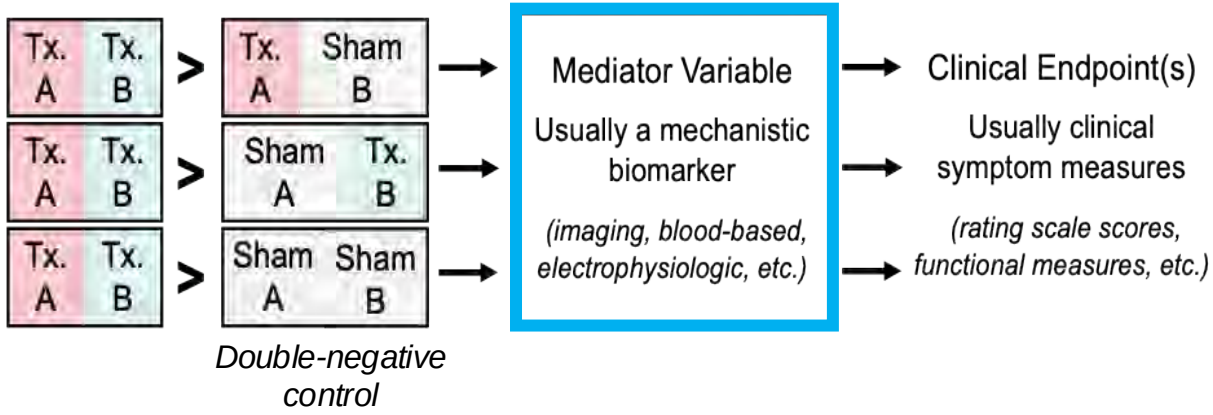
Synergy ≠ Co-Administration, Augmentation, Sequencing

"Clinical synergy"

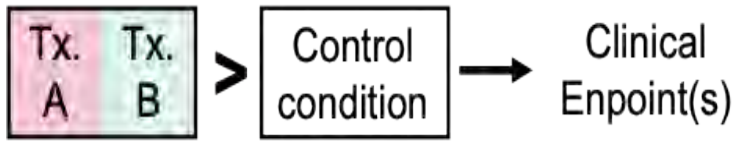




"Mechanistic synergy"



Co-administration



Augmentation

Sequencing

Tx. A is given before Tx. B

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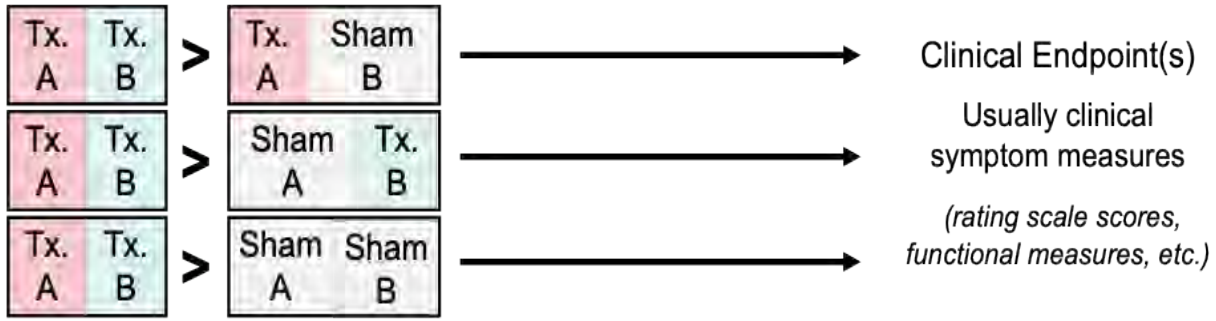
Tatti E et al. Neurosci Biobehav Rev. 2022;142:104867.
Kew BM et al. BJPsych Open. 2023;9:e79. DOI: 10.1192/bjo.2023.53.
Jonesborg I et al. J Affect Disord. 2022;315:105-112.

Designs That Show Synergy

Suppose that **Tx. A** is biological (NIBS, RAADs) and **Tx. B** is psychotherapy, that there is true randomization, and that blinding is adequate…

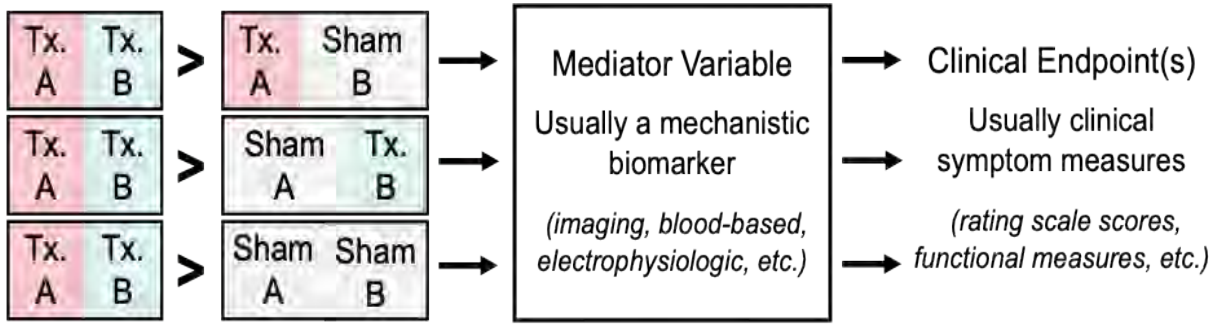
To show synergy, you must demonstrate that…

"Clinical synergy"



…The combined effect of Tx. A and Tx. B exceeds what is expected (observed) from the sum or additive effects of each treatment alone.

"Mechanistic synergy"



…The combination of Tx. A and Tx. B produces stronger activation of plasticity mechanisms—which mediate the outcomes of interest.

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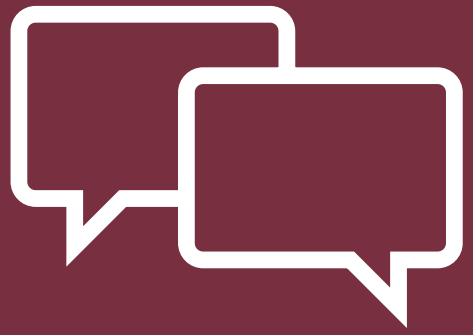
Watkins ER, Newbold A. Front Psychiatry. 2020;11:429.
Collins LM et al. Annu Rev Clin Psychol. 2024;9:10:21-47.
Zucker NL et al. Perspect Psychol Sci. 2023. DOI: 10.1177/17456916231197980.

Part 3A.
NIBS + Psychotherapy



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NIBS + Psychotherapy: Search Strategy

- NIBS:
  - Include: TMS, rTMS, TBS, iTBS/cTBS, tDCS
  - Exclude: ECT, VNS, DBS, MST

- Psychotherapy:
  - Include: Evidence-based psychotherapy, supportive therapy/ psychological support, coaching

MeSH Terms	TIAB terms
"Transcranial Magnetic Stimulation" "Transcranial Direct Current Stimulation"	TMS, rTMS, "repetitive transcranial magnetic stimulation", "transcranial magnetic stimulation", "theta burst stimulation", TBS, iTBS, cTBS, "intermittent theta burst stimulation", "continuous theta burst stimulation", "accelerated TMS", "accelerated rTMS", "Stanford neuromodulation therapy", SAINT, tDCS, "transcranial direct current stimulation", "direct current stimulation"

MeSH Terms	TIAB terms
"Psychotherapy" "Cognitive Behavioral Therapy" "Behavior Therapy" "Acceptance and Commitment Therapy" "Mindfulness-Based Cognitive Therapy" "Interpersonal Psychotherapy" "Psychotherapy, Brief" "Psychotherapy, Group" "Psychotherapy, Psychodynamic" "Psychosocial Intervention" "Counseling" "Motivational Interviewing" "Therapeutic Alliance"	psychotherap*, "psychological treatment*", "psychological therap*", "talk therap*", "evidence-based psychotherap*", "evidence based psychotherap*", CBT, "cognitive behavioral therap*", "cognitive behavioural therap*", "behavioral activation", BA, ACT, "acceptance and commitment therap*", MBCT, "mindfulness-based cognitive therap*", "mindfulness based cognitive therap*", IPT, "interpersonal psychotherap*", "psychodynamic therap*", "brief psychotherap*", "group psychotherap*", "supportive therap*", "supportive psychotherap*", "supportive counseling", "psychological support", ""non-directive support", coach*, "behavioral coaching", "health coaching", "wellness coaching", "recovery coaching", "therapeutic coaching"

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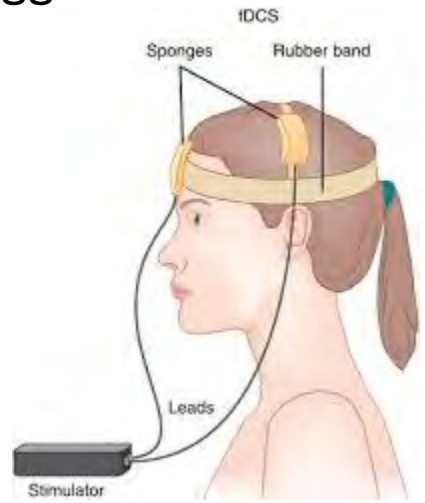
tDCS Augmentation of CBT for Major Depression

Multicenter randomized, 3-arm trial, 148 adults with MDD

Aust S et al. JAMA Psychiatry. 2022;79:528-537.

Transcranial Direct Current Stimulation:

- 1-2 mA current used to adjust resting state → more or less excitable
- Anode → (L) DLPFC



Study Design:

Randomized to 1 of 3 arms:

- tDCS + CBT
- Sham tDCS + CBT
- CBT alone

Does tDCS enhance CBT?

Main Results:

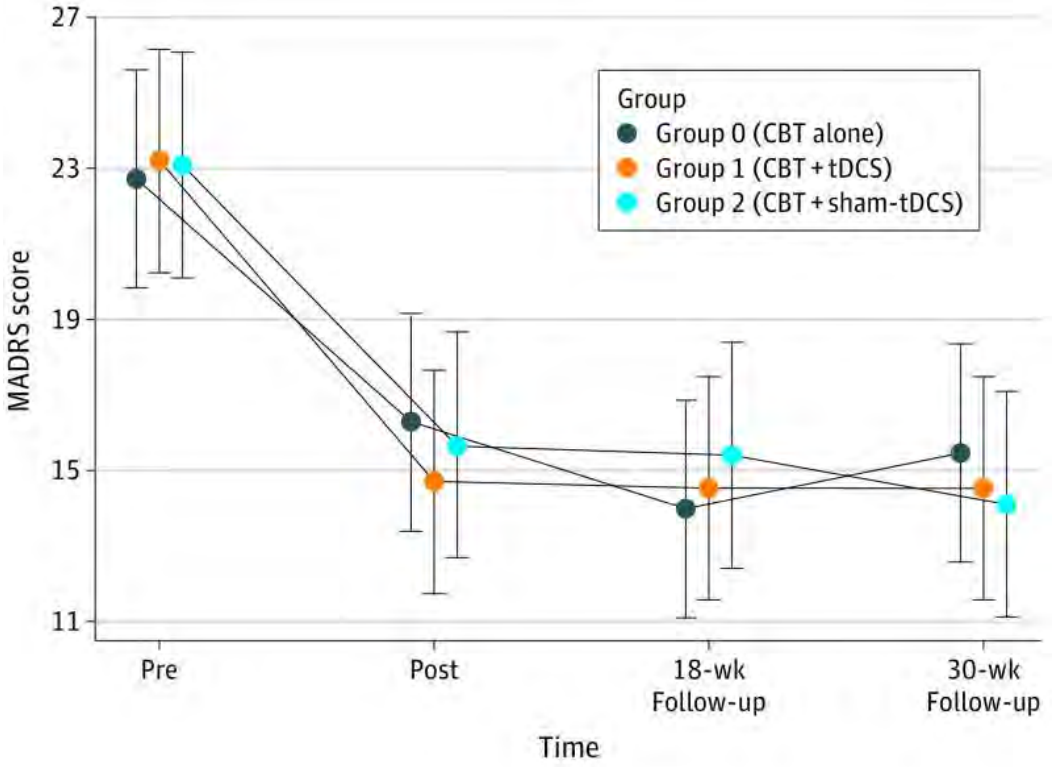


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Illustration: Rosa MA, Lisanby SA. Neuropsychopharmacol Rev. 2012;37:102-116.

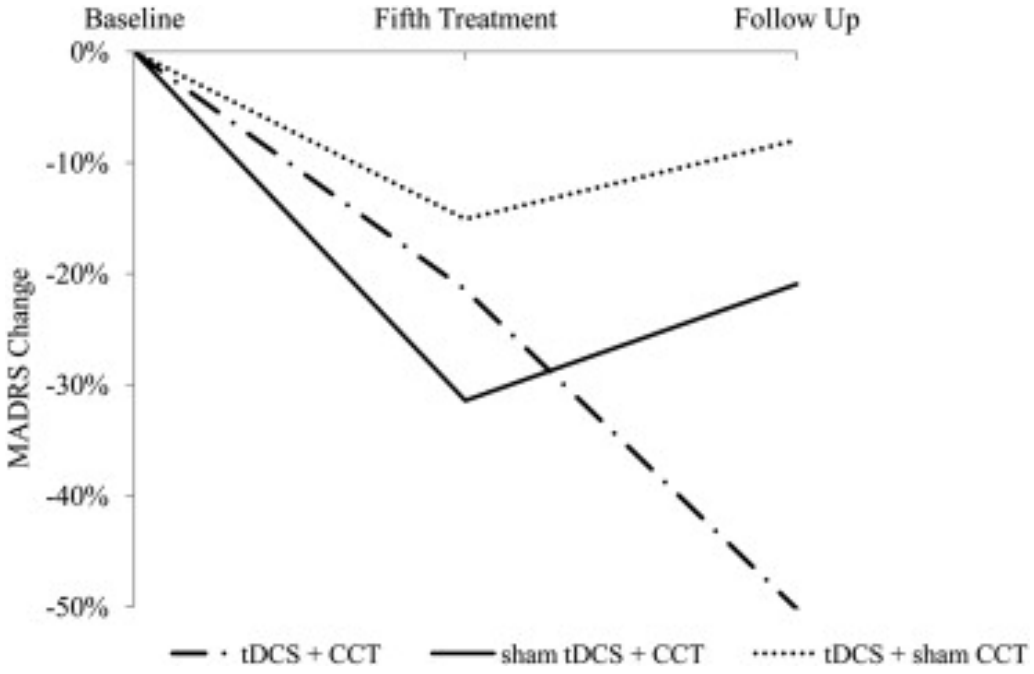
Concurrent tDCS & Cognitive Control Training for Depression

Randomized Three-Arm Mechanistic Pilot Trial

27 patients with MDD randomized to tDCS + CCT, sham tDCS + CCT, or tDCS + sham CCT

CCT and PFC stimulation are thought to converge on DLPFC-mediated cognitive system functioning

Change in MADRS total scores over time



Modulation of DLPFC-mediated cognitive control

Assessed using the two-back working memory task (matched affective and non-affective versions)

Summary of Results

All three groups showed reduction in MADRS scores through 5 treatments and at 3-week follow-up, but only tDCS + CCT showed sustained response at follow-up.

Five sessions of tDCS + CCT resulted in increased accuracy on the negative 2-back test at follow-up, which was associated with reduced MADRS scores

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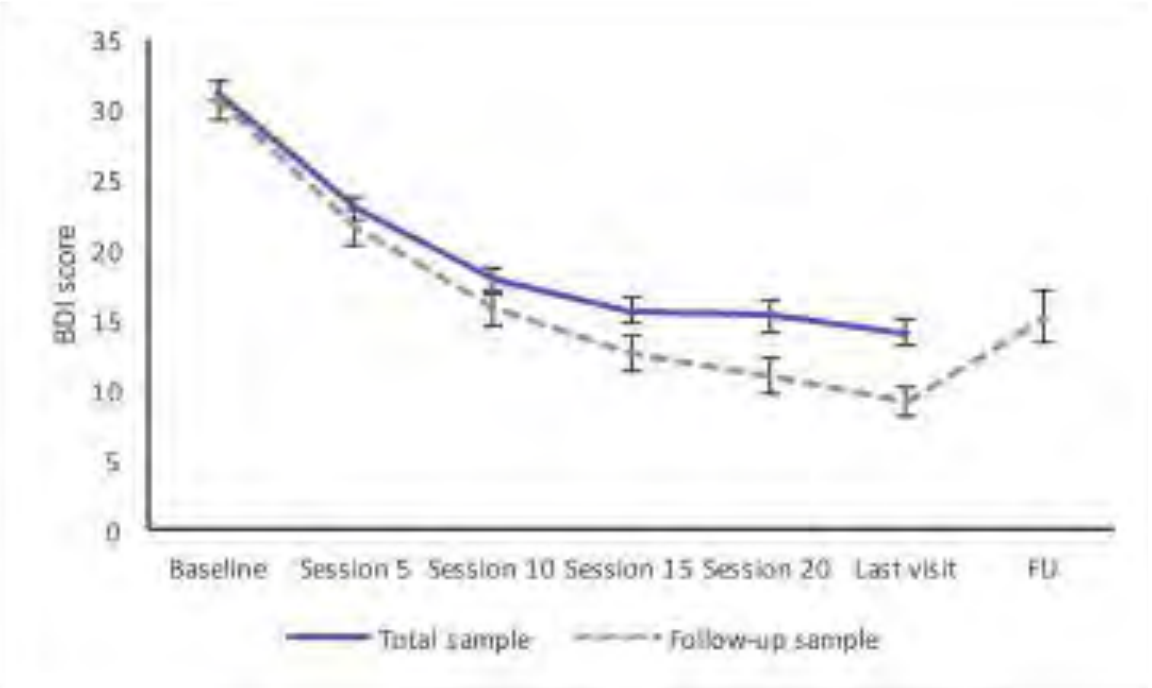
Seagrave RA et al. Brain Stim. 2014;7:325-331. ACTRN12613000050752.

Simultaneous TMS & Psychotherapy for MDD

Naturalistic Study – Is simultaneous TMS and PT feasible?

196 patients with MDD were given 20+ sessions of TMS + PT simultaneously
TMS was delivered at 10 Hz (L) or 1 Hz (R); PT was based on CBT principles
BDI was assessed at each 5th treatment (until end of treatment) and at 6-month follow-up



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Donse L et al. Brain Stim. 2018;11:337-345.

Concurrent TMS & Unguided Digital CBT for TRD

6-week, Two-Arm Randomized Trial of TMS +/- iCBT

78 patients with TR-MDD were randomized to TMS + iCBT or TMS alone

iCBT (MoodGYM) – 5 modules – relationship between thoughts/emotions, cognitive distortions/negative thoughts, assertiveness/self-esteem training, BA, problem solving

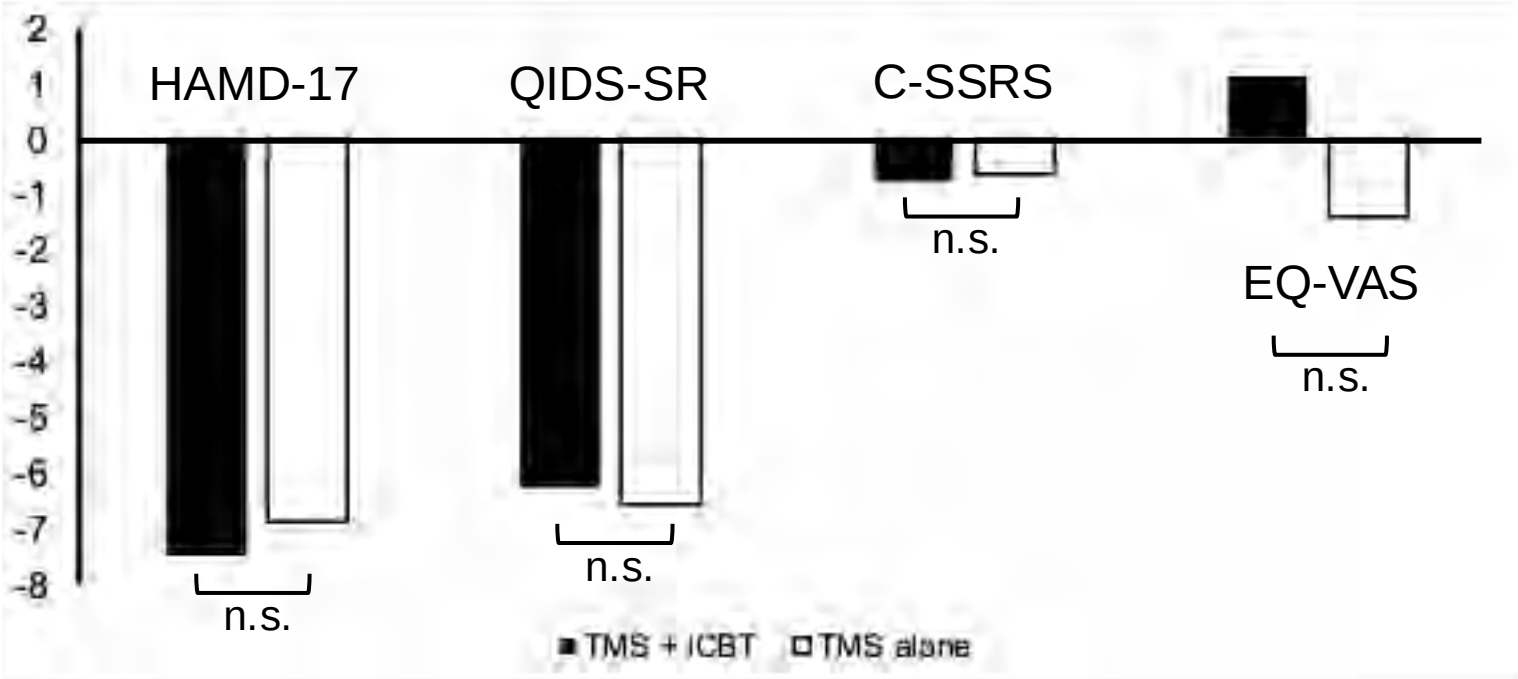
Participants instructed to complete 1-hr sessions on evening before/morning of TMS

Outcome Measures

Psychopathology (depression) -- HAMD-17, QIDS-SR

Suicidal ideations – C-SSRS (screen version)

Health status – EQ-VAS



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Adu MK et al. Brain Sci. 2023;13:293. DOI: 10.3390/brainsci13020293.

Behavioral Activation During TMS for MDD

Chart review study of BA administered during course of TMS

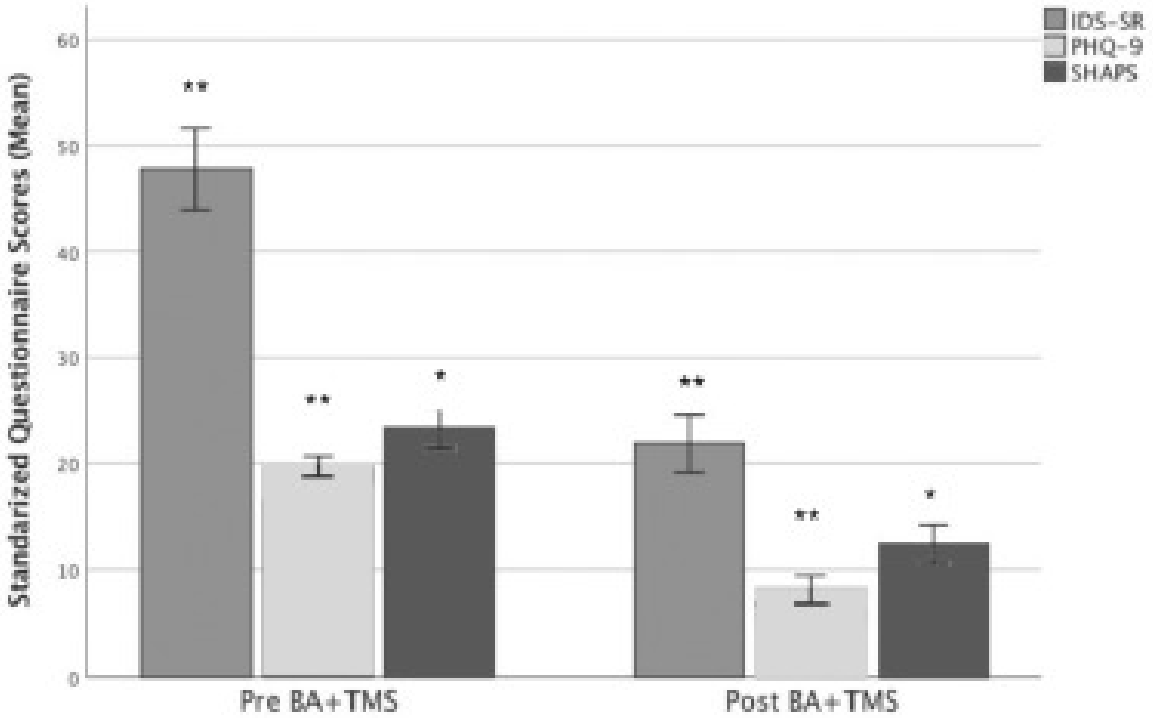
TMS was given over a standard course of 6 weeks
BA protocol was adapted for TMS sessions and was delivered by trained physicians & nurses
BA goal setting, review of BA progress, & discussion of obstacles occurred during stimulation

Outcome measures

IDS-SR, PHQ-9, SHAPS

Main results

Six (55%) met criteria for positive treatment response; average improvement clinical ratings was 47% for IDS, 55% for PHQ-9, and 39% for SHAPS; 77% of subjects completed or exceeded therapeutic goal(s)



Russo GB et al. J Affect Disord. 2018;236:101-104.

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Part 3B.
RAADs + Psychotherapy

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RAADs + Psychotherapy: Search Strategy

- RAADs:
  - Include: TMS, rTMS, TBS, iTBS/cTBS, tDCS
  - Exclude: ECT, VNS, DBS, MST

- Psychotherapy:
  - Include: Evidence-based psychotherapy, supportive therapy/ psychological support, coaching

MeSH Terms	TIAB terms
"Ketamine" "Hallucinogens" "Psilocybin" "Lysergic Acid Diethylamide" "N,N-Dimethyltryptamine"	ketamine, esketamine, arketamine, Spravato, "rapid-acting antidepressant*", "rapid acting antidepressant*", RAAD, NMDA, psychedelic*, hallucinogen*, psychoplastogen*, "psychedelic-assisted", "psychedelic assisted", "psilocybin-assisted", "psilocybin assisted", psilocybin, psilocin, LSD, "lysergic acid diethylamide", DMT, "N,N-dimethyltryptamine", ayahuasca, mescaline, MDMA, "3,4-methylenedioxymethamphetamine"

MeSH Terms	TIAB terms
"Psychotherapy" "Cognitive Behavioral Therapy" "Behavior Therapy" "Acceptance and Commitment Therapy" "Mindfulness-Based Cognitive Therapy" "Interpersonal Psychotherapy" "Psychotherapy, Brief" "Psychotherapy, Group" "Psychotherapy, Psychodynamic" "Psychosocial Intervention" "Counseling" "Motivational Interviewing" "Therapeutic Alliance"	psychotherap*, "psychological treatment*", "psychological therap*", "talk therap*", "evidence-based psychotherap*", "evidence based psychotherap*", CBT, "cognitive behavioral therap*", "cognitive behavioural therap*", "behavioral activation", BA, ACT, "acceptance and commitment therap*", MBCT, "mindfulness-based cognitive therap*", "mindfulness based cognitive therap*", IPT, "interpersonal psychotherap*", "psychodynamic therap*", "brief psychotherap*", "group psychotherap*", "supportive therap*", "supportive psychotherap*", "supportive counseling", "psychological support", ""non-directive support", coach*, "behavioral coaching", "health coaching", "wellness coaching", "recovery coaching", "therapeutic coaching"

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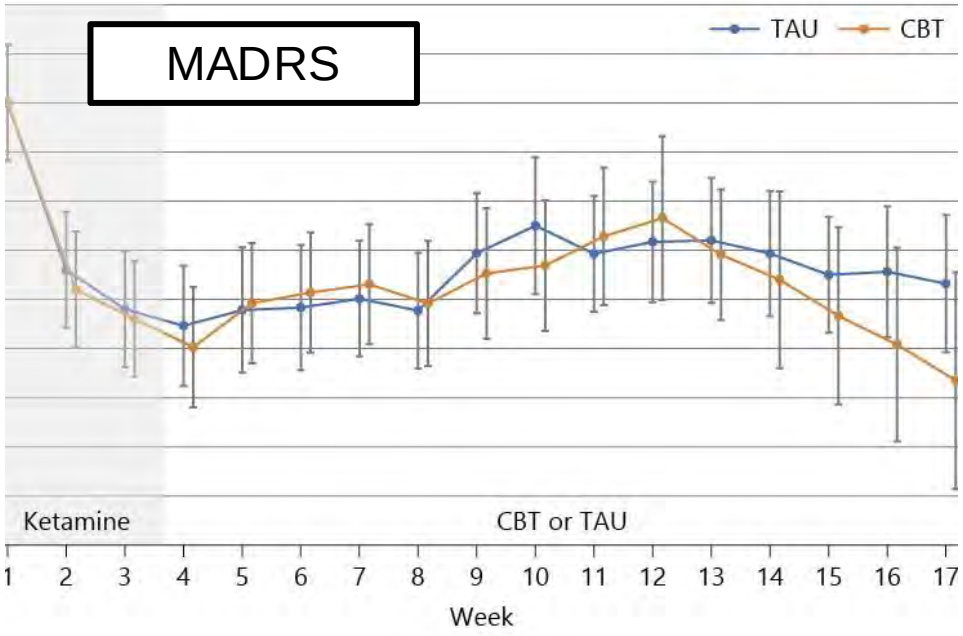

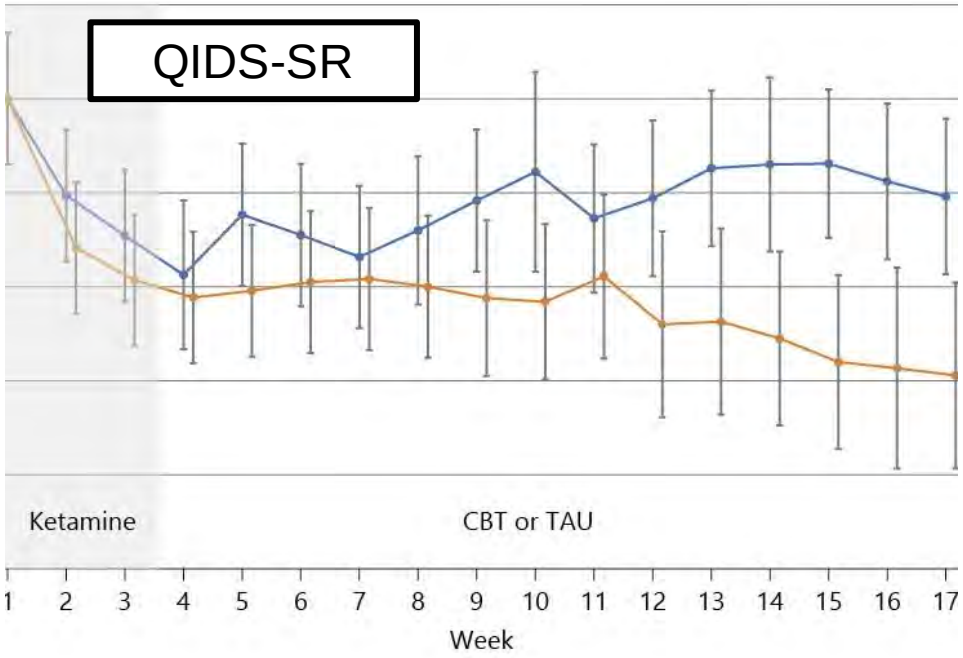

CBT for Sustaining Acute Ketamine Effects in Patients with TRD

Randomized proof-of-concept study

28 patients with TRD responded after 6 IV infusions of KET over 3 weeks and were then randomized to either cognitive-behavioral therapy (CBT) or treatment as usual (weekly/biweekly medication management)

Summary of Results

Significant group x time interaction effect favoring CBT over 14 weeks for QIDS* ($F=4.58$, $p=0.03$, Cohen's d 0.71 [-0.30, 1.70]) but not MADRS

Ketamine responders showed improvement in tests of cognitive flexibility* (emotional N-back, $t[8]=2.33$, $p<0.05$) and cognitive control (n.s.)

Wilkinson ST et al. Psychother Psychosom. 2021;90:318-327.

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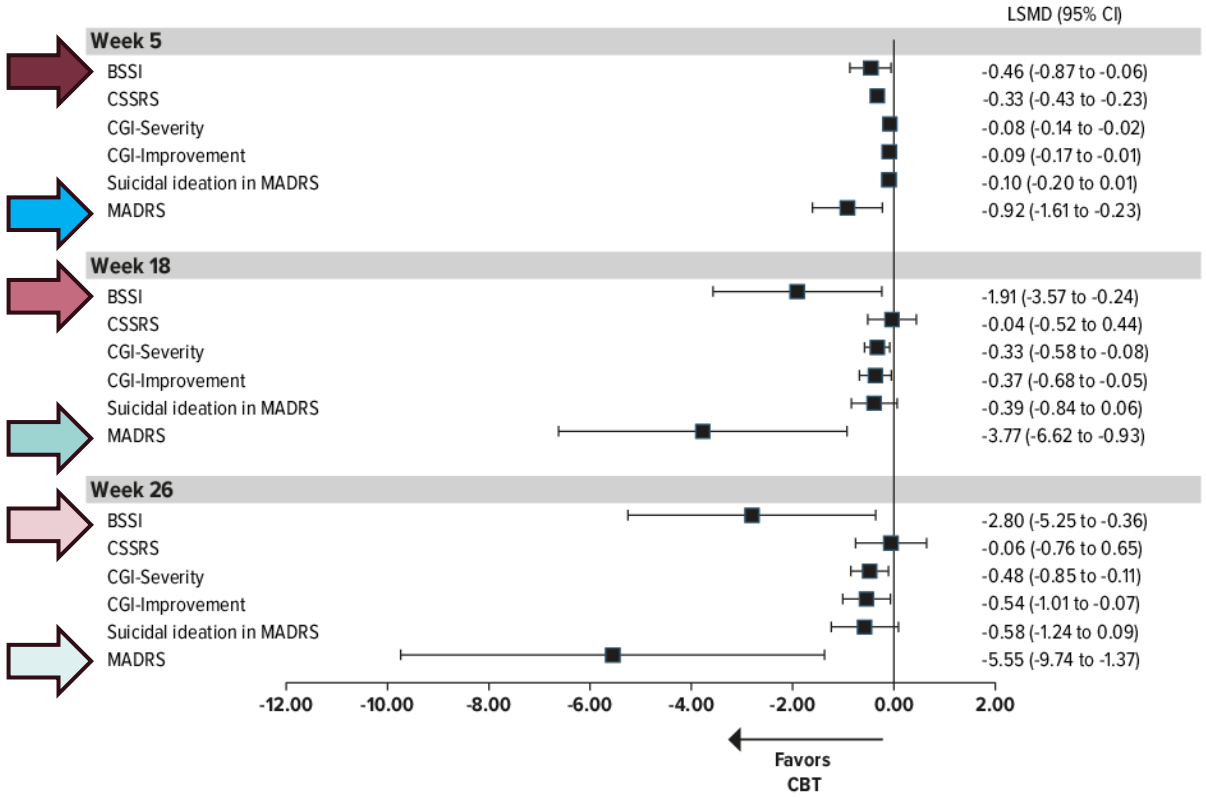
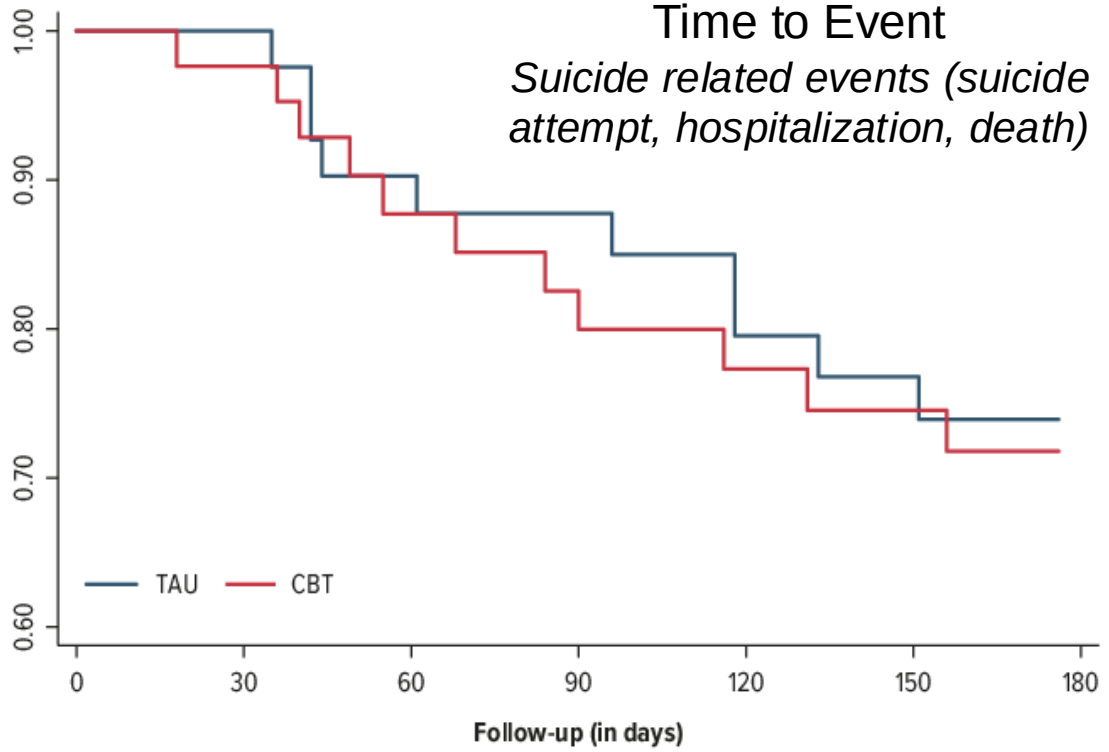
CBT Following Esketamine Treatment in MDSI

The CBT-ENDURE Randomized Trial

Randomized, rater-blinded feasibility trial (93 randomized subjects with MDSI)
Patients received ESK plus CBT or ESK plus treatment as usual





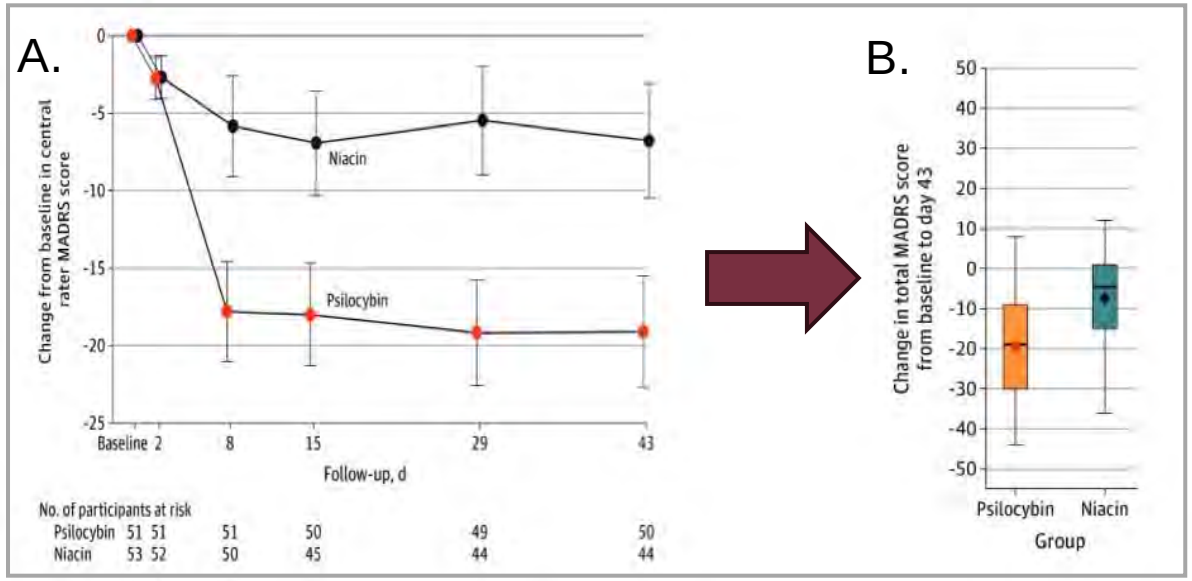
Wilkinson ST et al. J Clin Psychiatry. 2026;87:25m16285.

Psilocybin + Psychological Support for MDD & TRD

Two-Arm, Phase 2, Randomized, Niacin-Controlled Trial

104 subjects with DSM-5 MDD
Patients received psilocybin 25 mg or niacin 100 mg with psychosocial support and integration sessions

Primary outcome – 43-day change in MADRS

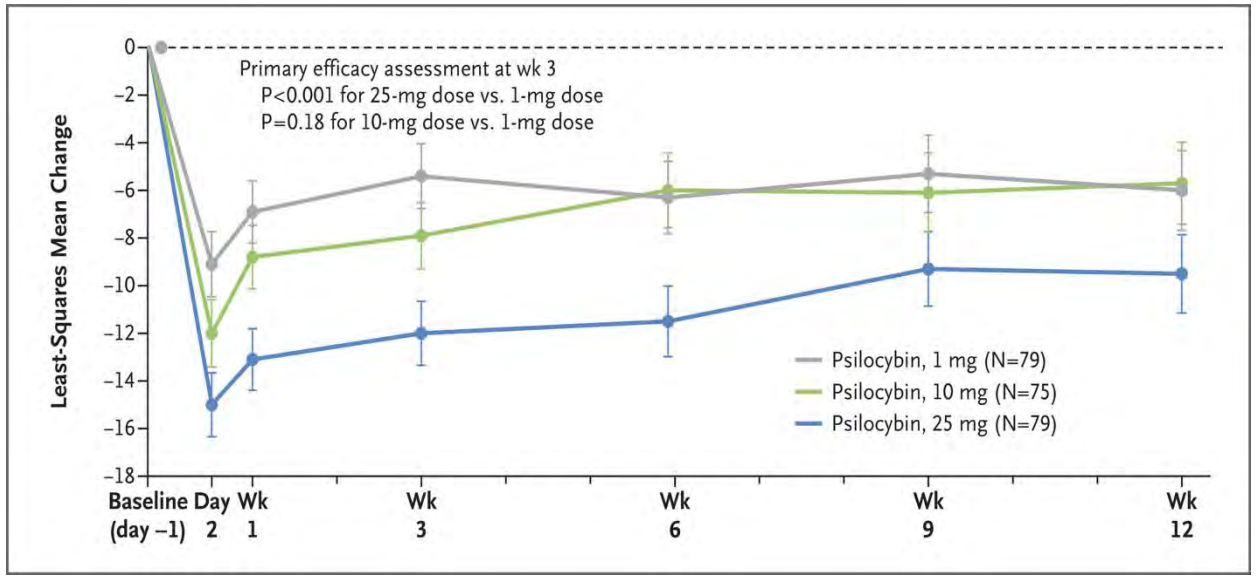


Raison CL et al. JAMA. 2023;330:843-853.

Three-Arm, Phase 2, Randomized Controlled Trial

233 subjects with DSM-5 MDD (TRD)
Patients received psilocybin 25-, 10- or 1 mg with psychosocial support and integration sessions

Primary outcome – 3 wk. change in MADRS

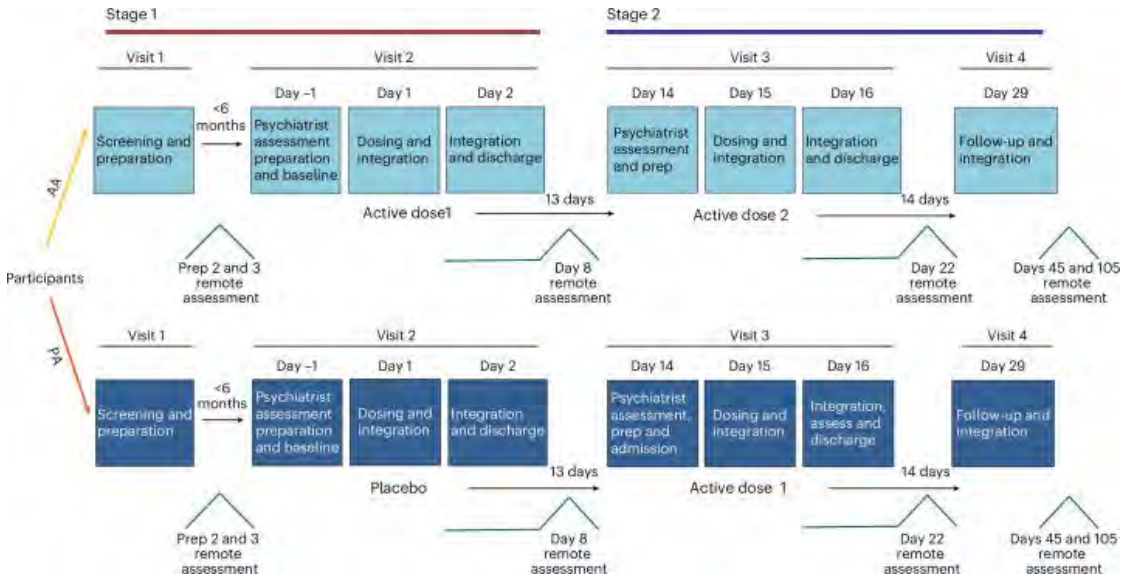


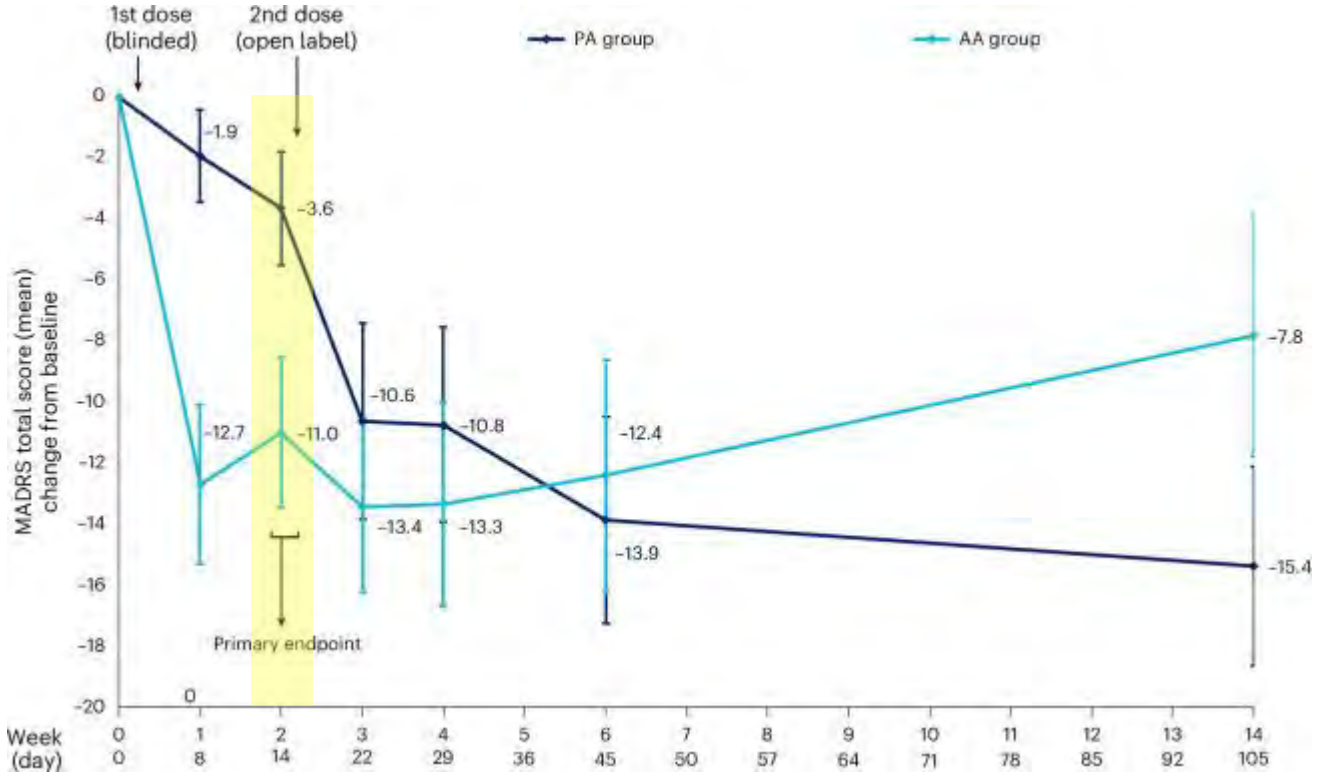
Goodwin GM et al. N Engl J Med. 2022;387:1637-1648.

Dimethyltryptamine-Assisted Psychotherapy/Support for Treatment-Resistant Major Depression

Two-Arm, Phase 2a, Randomized, Niacin-Controlled Trial

34 subjects with moderate to severe TRD (2 failed trials)
Patients received IV DMT 21.5 mg or IV PLC + “supportive psychotherapeutic support”





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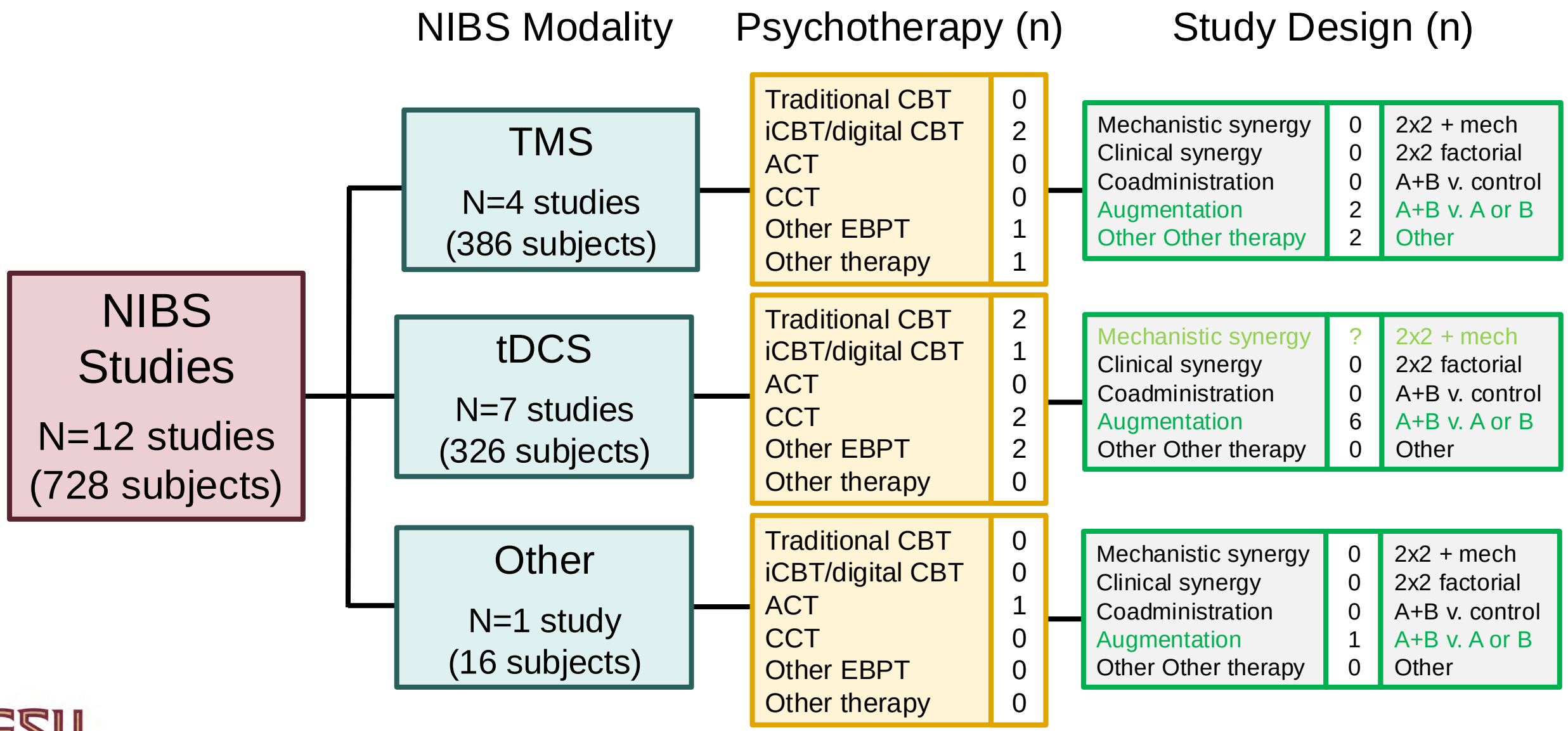
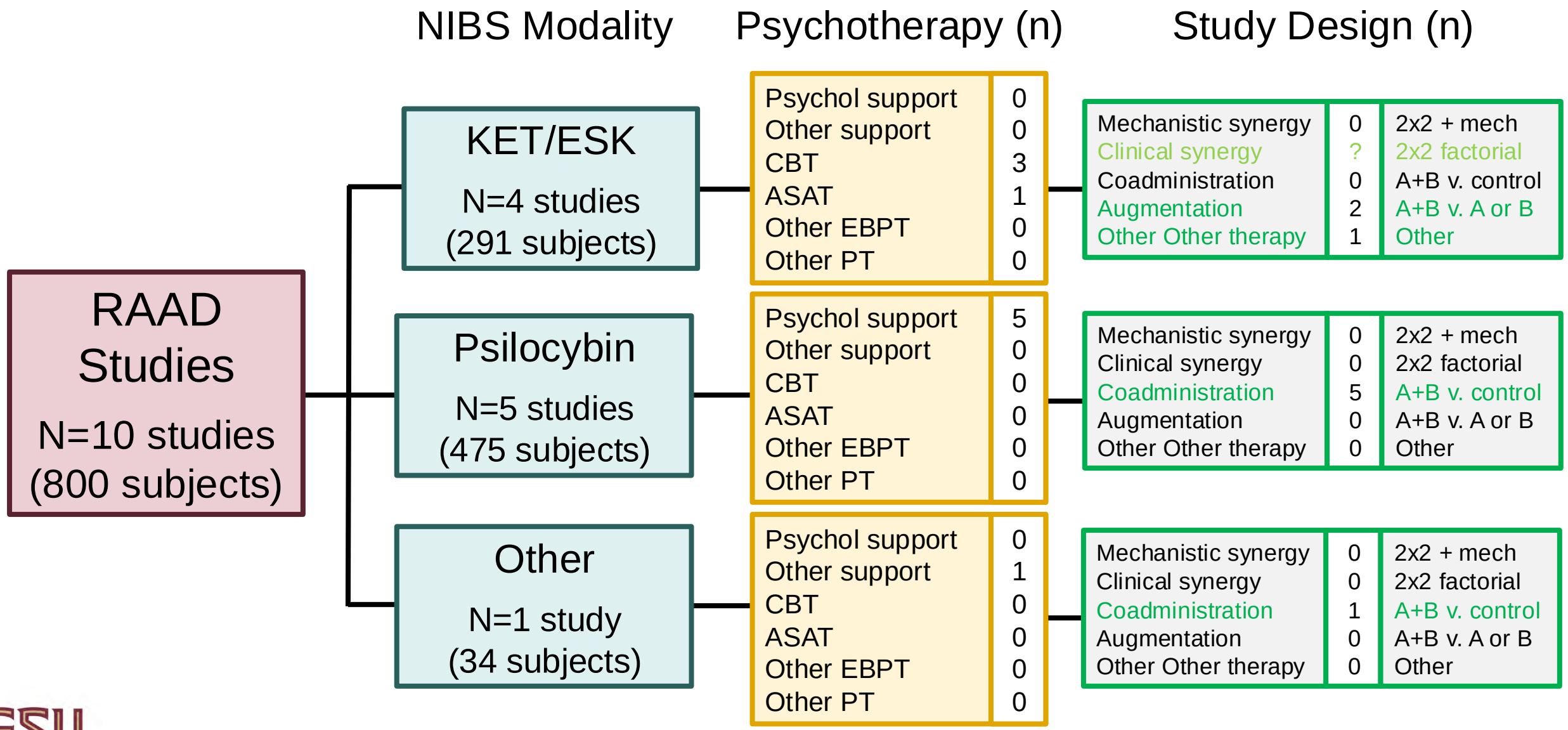
Erritzoe D et al. Nat Med. 2026;32:591-598.

Comparative Evidence: NIBS + Psychosocial Treatment



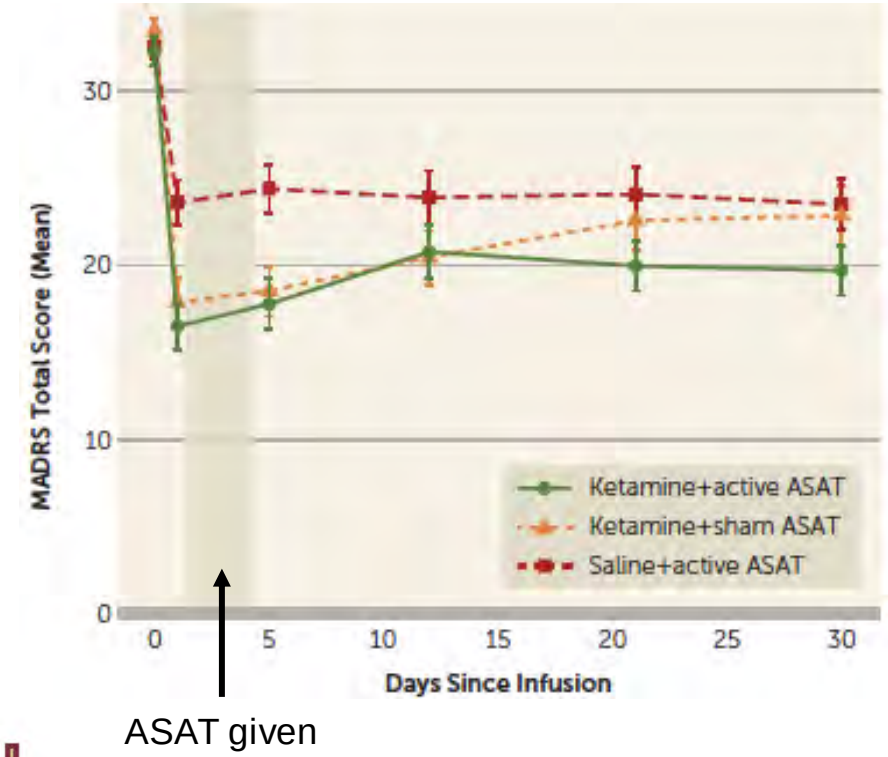
Comparative Evidence: RAADs + Psychosocial Treatment



Automated Self-Association Training (ASAT) for Extending Acute Antidepressive Effects of Ketamine

Two-Arm, Randomized, Double-Blind Trial

154 subjects with moderate to severe MDD and lower-than-normative self-esteem
Patients received IV KET + ASAT, KET + sham-ASAT, or IV PLC + ASAT



Automated Self-Association Training (ASAT)
Computerized cognitive training program that pairs self-relevant stimuli (photo, self-related words) with positive cues/positive words to make positive self-evaluations more automatic.

Main Results
Rapid antidepressive effects from a single KET infusion were sustained with ASAT but not with sham-ASAT; weaker acute antidepressive effects were observed with IV saline PLC + ASAT

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Price RB et al. Am J Psychiatry. 2022;179:959-968.

Part 4.
Limitations & Future Directions

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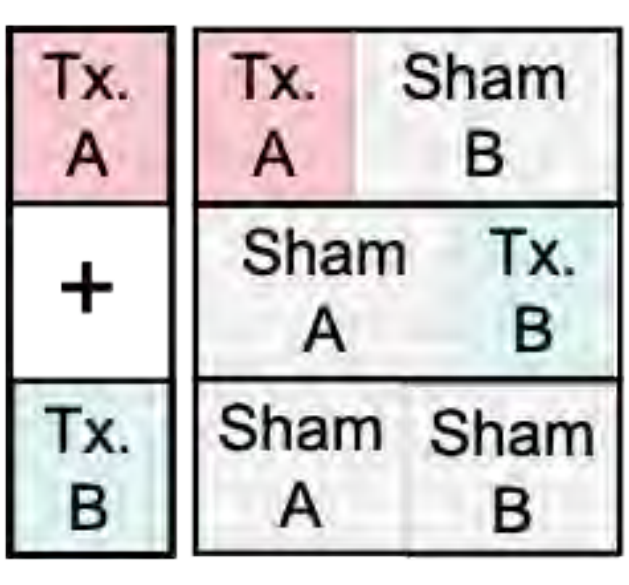
Limitations

1. Few truly factorial designs, so cannot test interactions (e.g., A+B works, but are they truly synergistic?
2. Weak isolation of PT contribution (especially for psychedelic trials).
3. Expectancy and blinding are often inadequately handled (many studies under review may be functionally unblinded).
4. Insufficient mechanistic investigation (e.g., few studies with a priori plasticity target tested as mediator, specific effects of psychotherapy not accounted for).
5. Timing of PT relative to biological therapeutics (especially NIBS) requires testing.
6. Generalizability limited (small studies, exclusions, academic centers, etc.).

Next-Generation Trials



Clinical Outcome

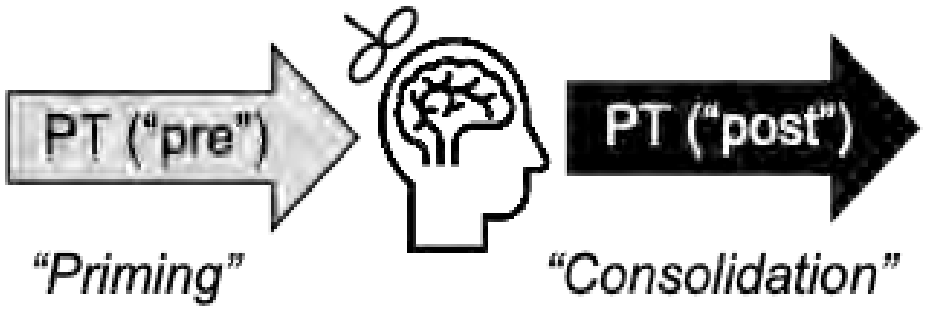
Mediator → Clinical Outcome

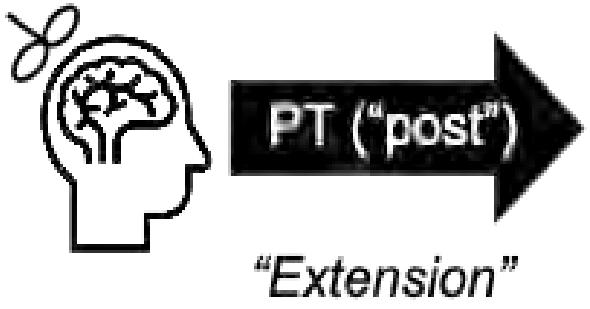
Clinical Outcomes:

- Rating scale scores
- Anhedonia/abnormal reward learning
- High rumination/low cognitive control
- Relapse after rapid response

Clinical Outcomes:

- Biomarkers – reward task fMRI, resting state connectivity, DLPFC striatal connectivity, DMN connectivity, sleep/activity rhythms, etc.
- Psychomarkers – effort-based decision making, rumination/cognitive flexibility, reward learning, emotional/experiential avoidance, etc.





Expectancy

Blinding

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Clinical Implications

- It is reasonable to combine evidence-based neuromodulation and psychosocial treatment on clinical grounds.
- Such decisions should be based on clinical judgment, clinical response patterns and tolerability, patient preference, and other factors within shared decision-making model.
- Mechanistic convergence is biologically plausible but not yet fully established.
- At this stage, neuromodulation and psycho-social treatments can be considered complimentary, but mechanistic synergy is not yet proved.

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Broad Summary

- It is exciting to speculate on how N/M therapeutics can change the brain's readiness to learn.
- It is equally exciting to speculate on how PT can best activate and shape that new learning within a more malleable neurobiological milieu.
- But these narratives are only aspirational based on current evidence.
- Future trials are needed that intentionally test interaction, timing of interventions, target engagement, and mediation.

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Thank you for your attention!

Questions?

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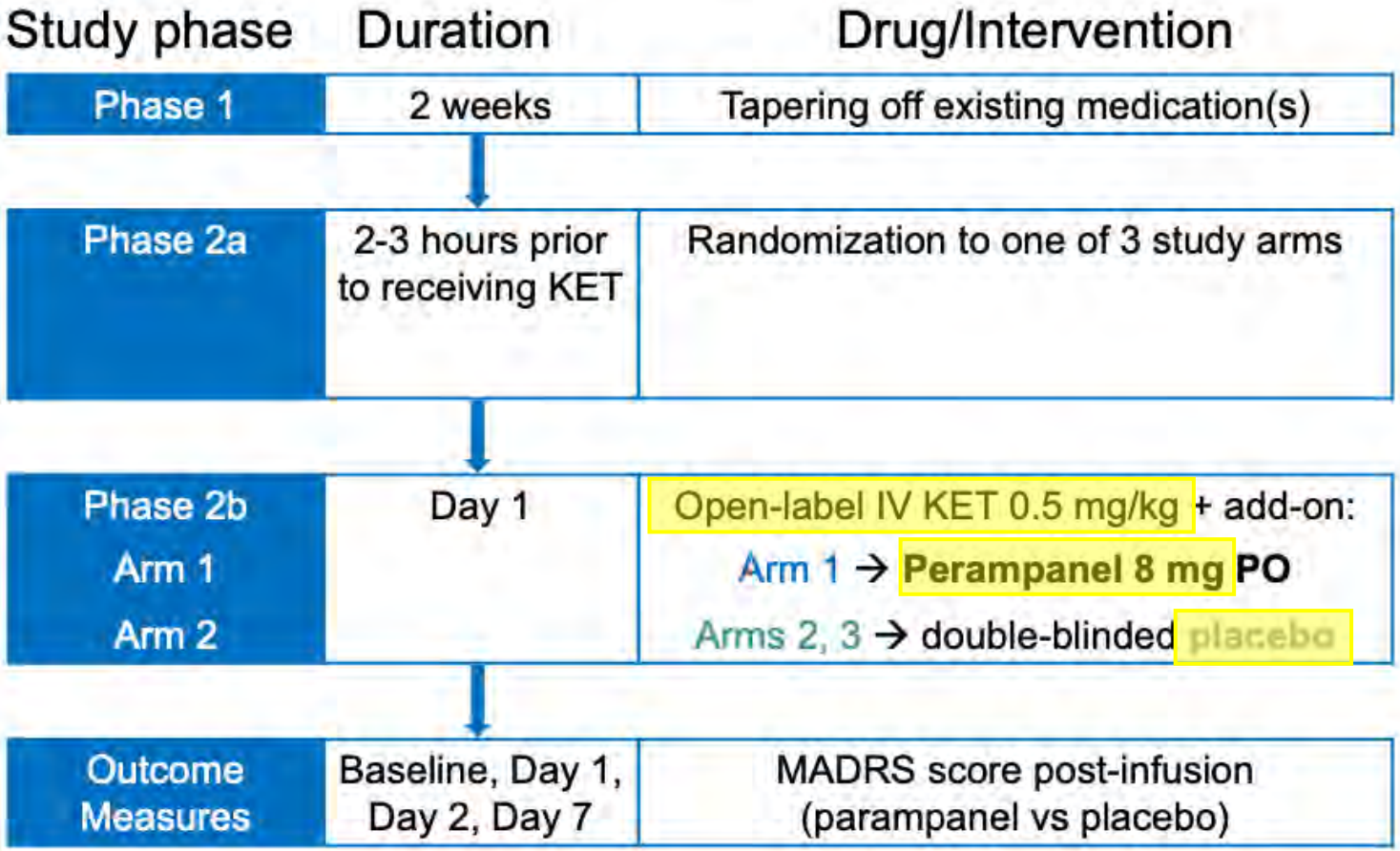
Mechanism of Action for KET's Antidepressant Effects: The AMPA Throughput Theory in Patients With TRD



Hypotheses:

There will be significantly higher (worse) MADRS scores in the perampanel group than the PLC group by days 1 and 2.

Implications if upheld:

AMPA throughput is necessary for the rapid-onset therapeutic antidepressant activity of IV racemic ketamine.

Biomarkers:

Polysomnogram/EEG, sEEG, TMS, magnetoencephalography

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NCT03973268. ClinicalTrials.gov. Accessed on 9/10/2025.

TRD definition:

Nonresponse to ≥ 2 AD's in the current MDE.

Influence of NIBS Modality, Temporal Alignment of Stimulation/PT, Diagnostic Category, & PT Delivery Method

Systematic review and meta-analysis of 28 randomized trials (1,506 subjects)
All trials included subjects randomized to NIBS (TMS, tDCS) + PT vs. sham NIBS + PT

Category	Label	SMD	Lower CI	Upper CI	Significance
NIBS type	tDCS	-0.20	-0.88	0.47	Not Significant
	rTMS	-0.47	-0.80	-0.13	**Significant**
Diagnosis	Addiction	-0.08	-0.48	0.33	Not Significant
	Anxiety	-0.70	-1.26	-0.14	**Significant**
	Depression	-0.39	-1.24	0.47	Not Significant
	OCD	-0.81	-2.10	0.49	Not Significant
	Pain	-0.32	-3.95	3.32	Not Significant
	Personality	-0.47	-1.10	0.17	Not Significant
	PTSD	0.08	-1.30	1.45	Not Significant
	Transdiagnostic	-0.76	-0.84	-0.68	**Significant**[†]
Therapy	CBT	-0.48	-0.78	-0.17	**Significant**
	Exposure	-0.35	-0.94	0.24	Not Significant
	Mindfulness	-0.22	-1.45	1.01	Not Significant
Evidence-based	No	-0.41	-0.90	0.08	Not Significant
	Yes	-0.33	-0.59	-0.07	**Significant**
Therapy delivery	Computerized	-0.18	-1.87	1.52	Not Significant
	Mixed	-0.28	-0.98	0.43	Not Significant
	Human	-0.50	-0.78	-0.21	**Significant**
Timing	Not concurrent	-0.56	-0.94	-0.18	**Significant**
	Concurrent	-0.11	-0.61	0.39	Not Significant

Beynel L et al. medRxiv Preprint. 2026. DOI: 10.64898/2026.02.19.26346650.