Neuroscience Education Institute

THE GLU HOLDING THINGS TOGETHER: GLUTAMATERGIC MODULATION FOR PSYCHIATRIC DISORDERS

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Chairman Emeritus, Neuroscience Education Institute

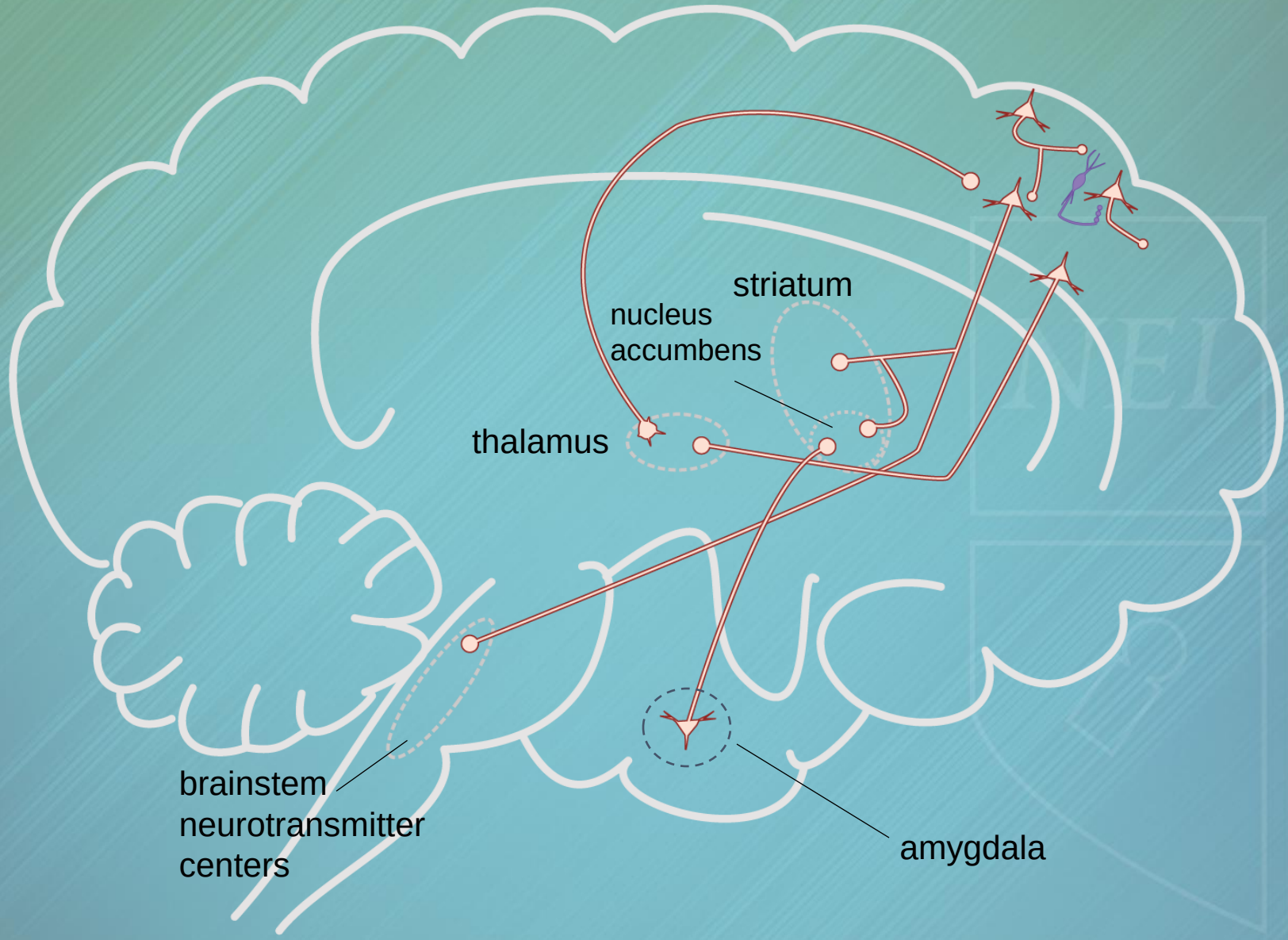
Presented at 2024 NEI Congress

Learning Objectives

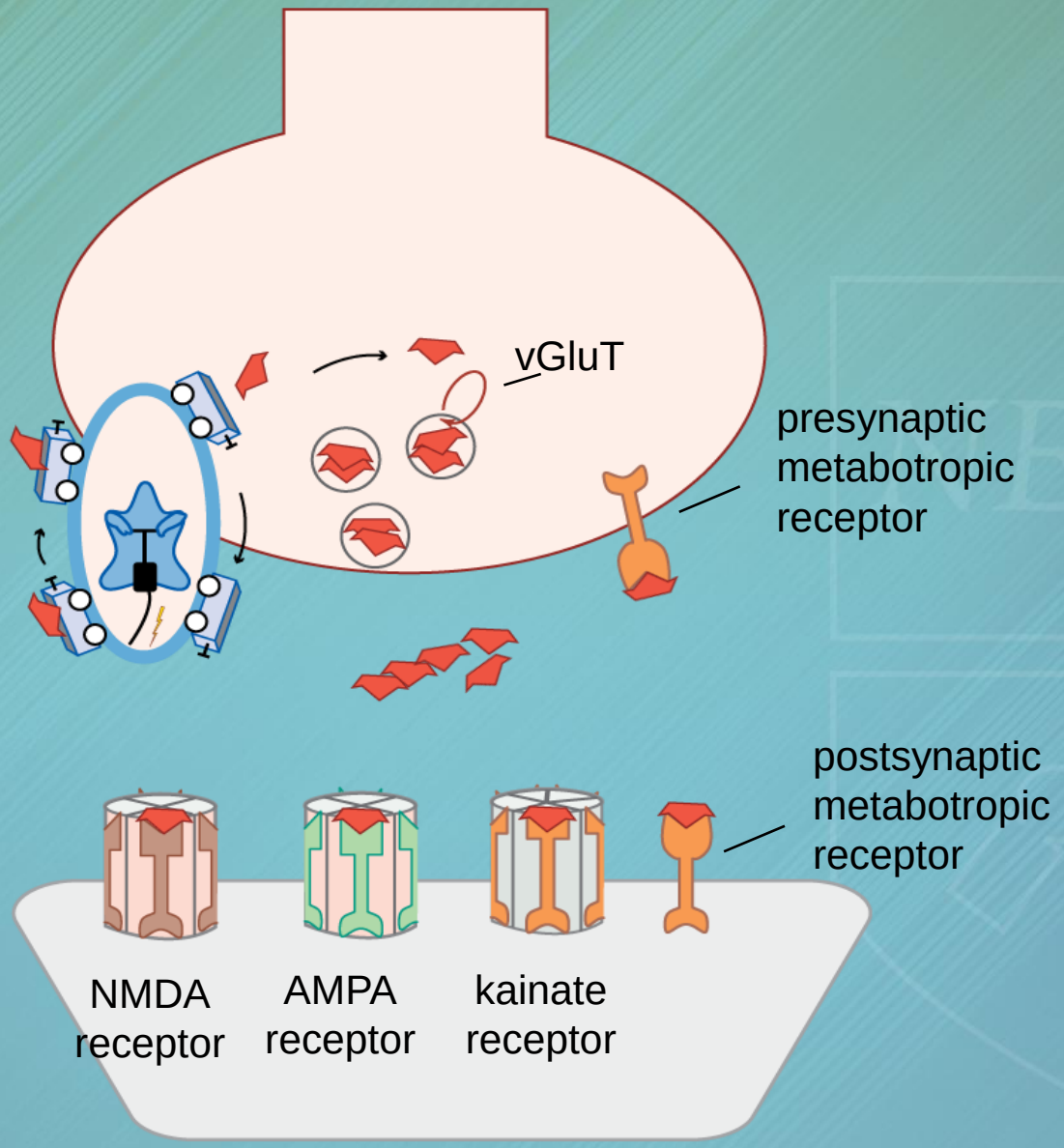
1. List how glutamatergic dysregulation may be involved in various psychiatric conditions
2. Implement appropriate glutamate-targeting psychopharmacological agents in the treatment of psychiatric disorders

Overview of Pathways and Receptors

Key Glutamate Pathways

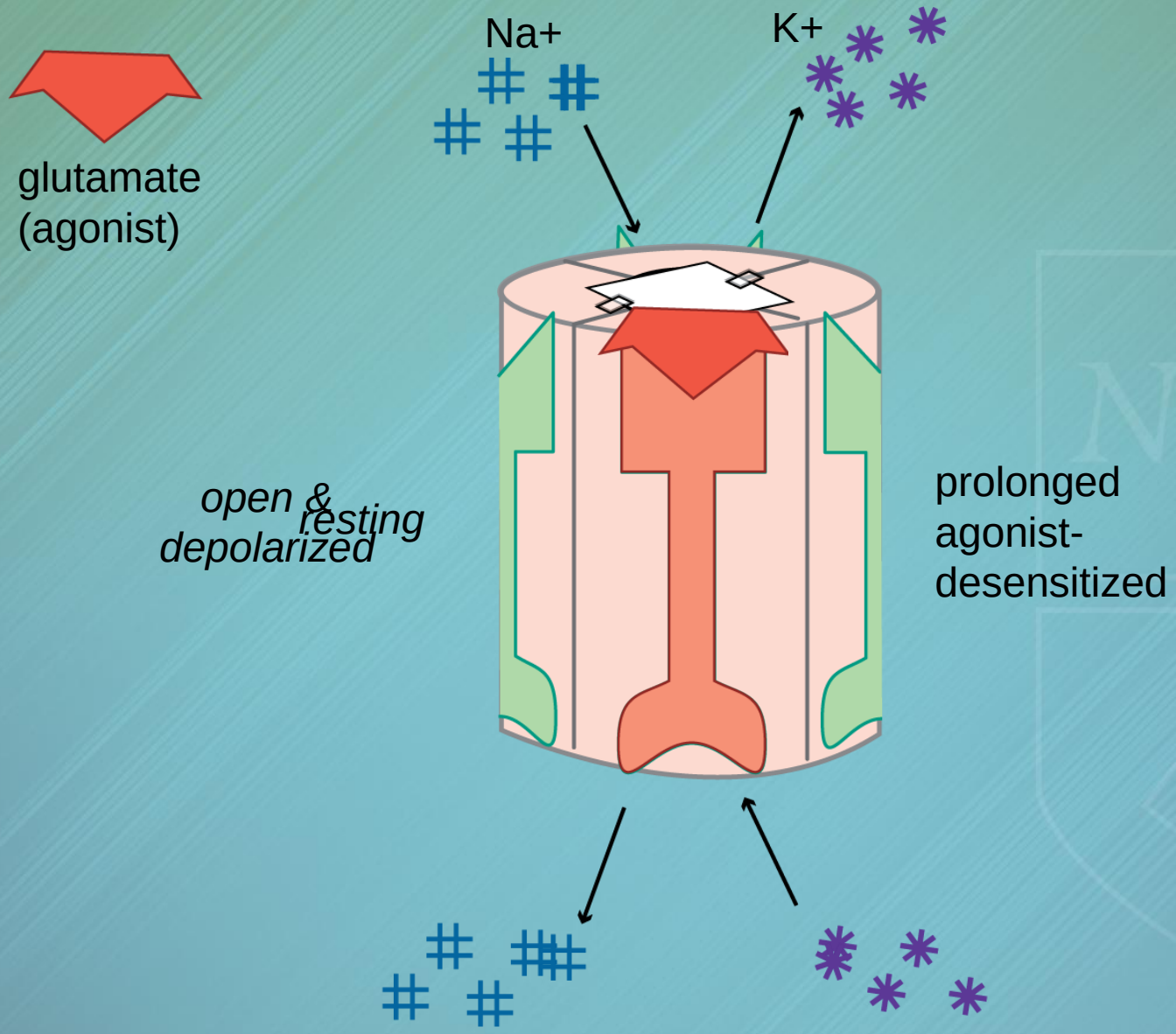


Glutamate Receptors



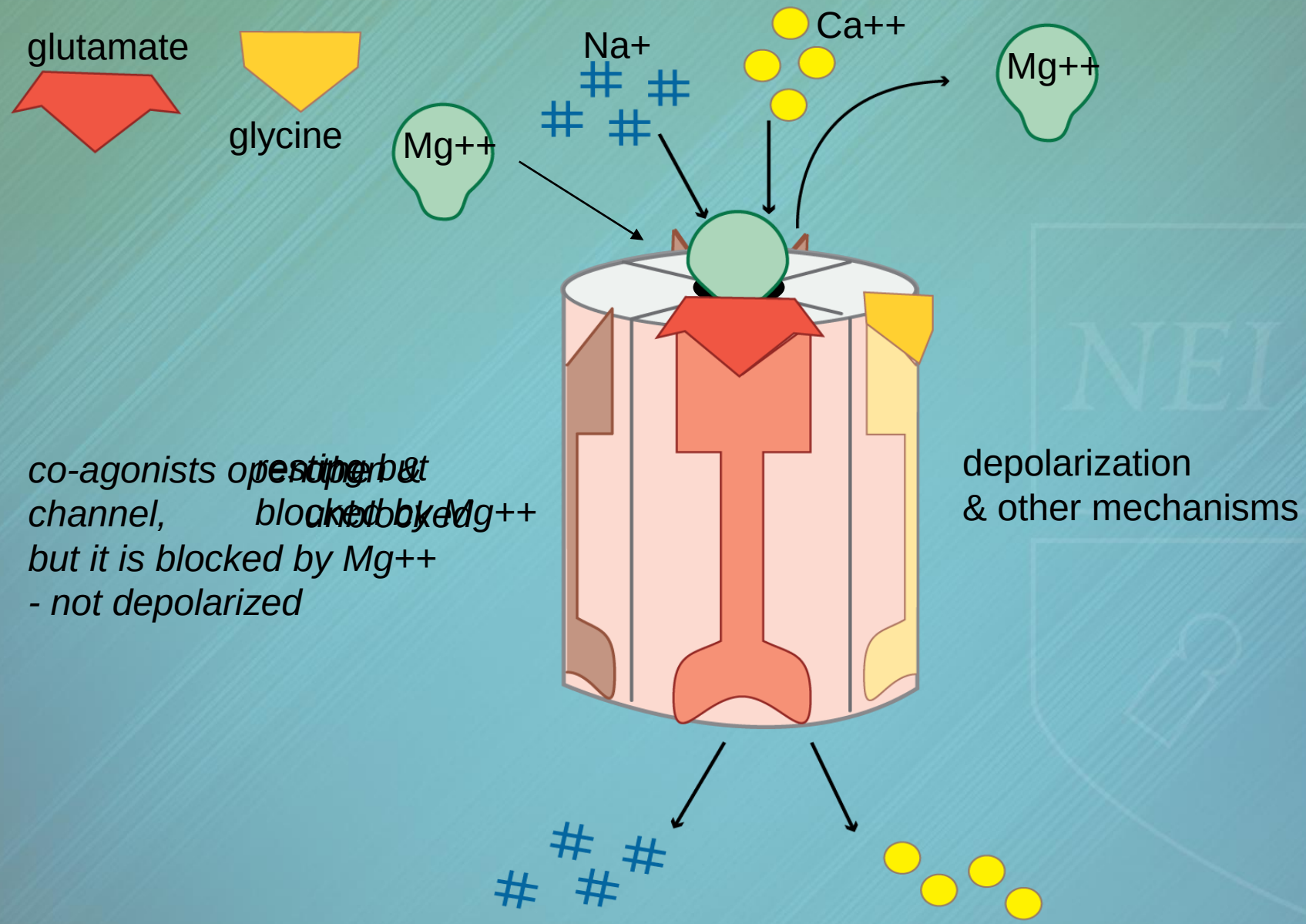
AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, *N*-methyl-D-aspartate; vGluT, vesicular glutamate transporter

AMPA & Kainate Receptors



AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; K^+, potassium; Na^+, sodium

NMDA Receptors



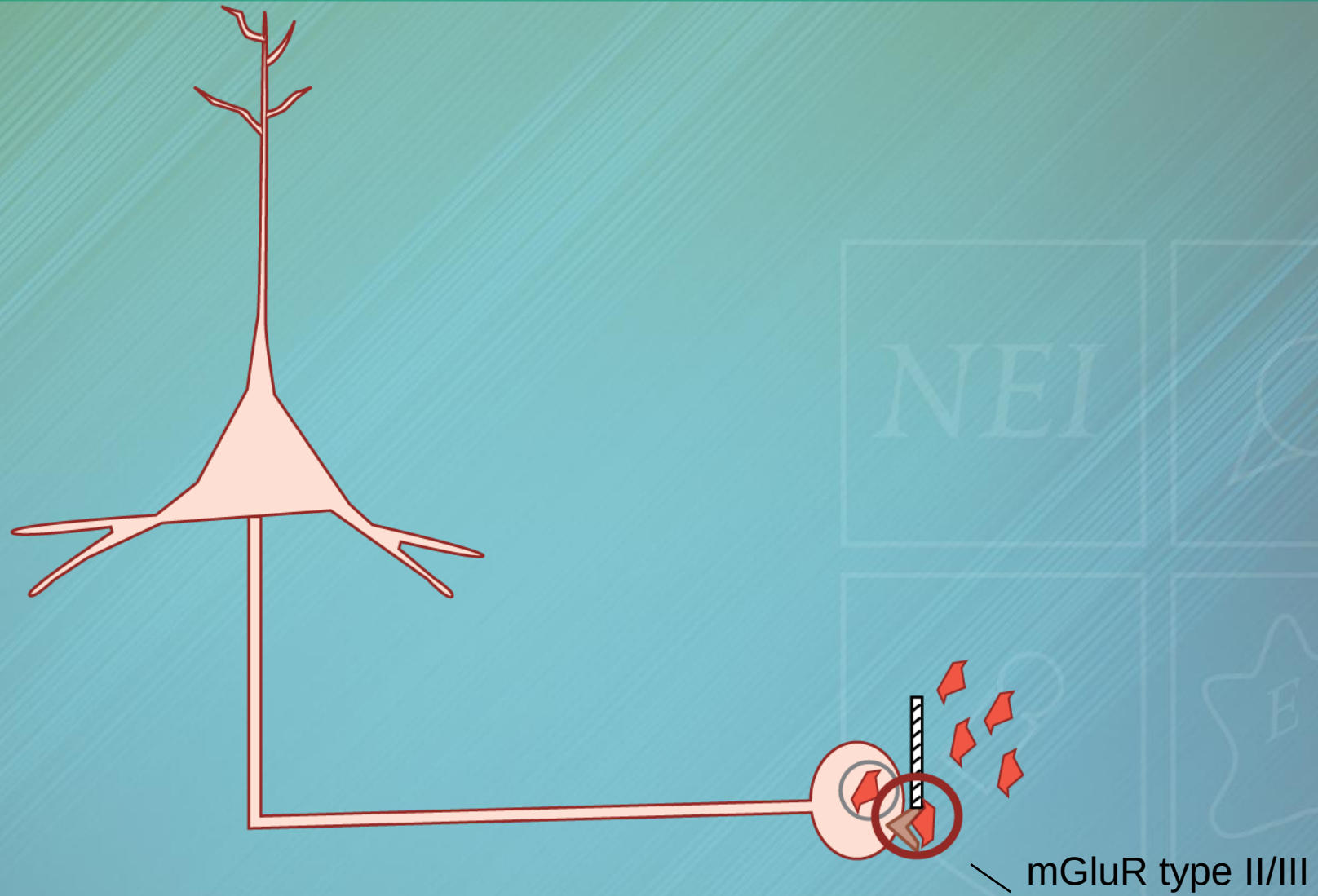
co-agonists open channel, but it is blocked by Mg++ - not depolarized

resting & blocked by Mg++

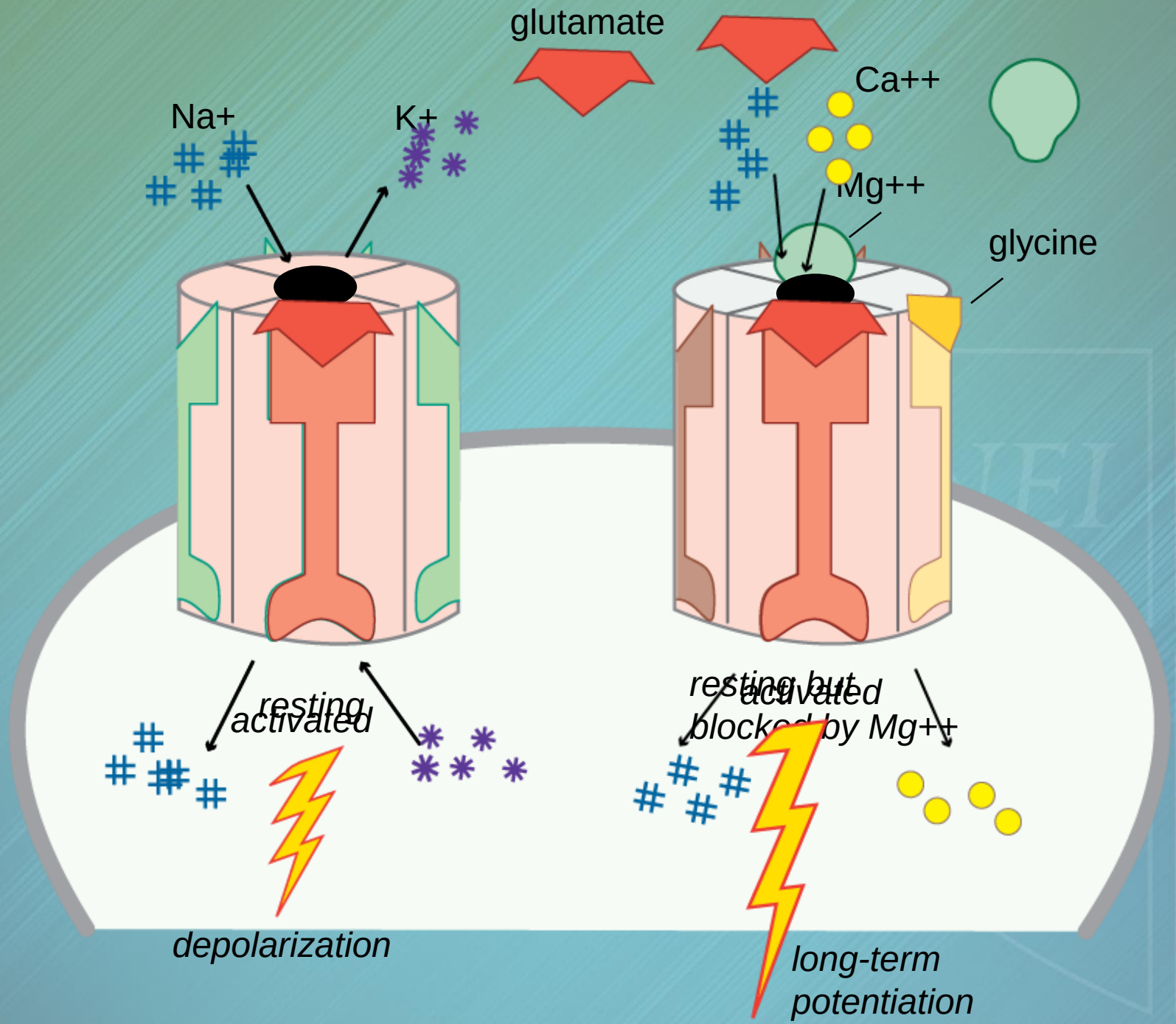
activated & unblocked

depolarization
& other mechanisms

mGlu Presynaptic Autoreceptors

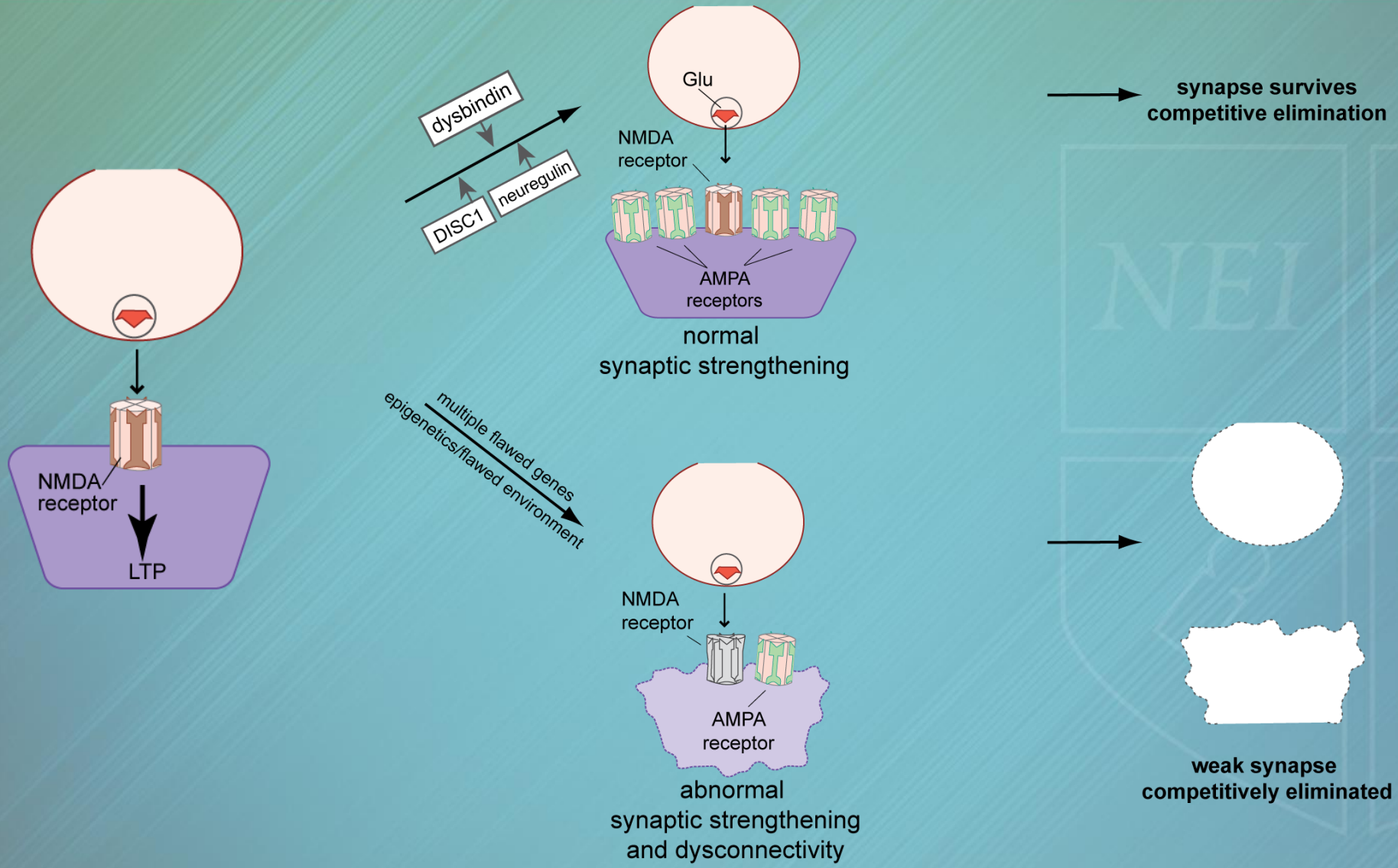


mGluR, metabotropic glutamate receptor



Ca^{++}, calcium; K^{+}, potassium; Mg^{++}, magnesium; Na^{+}, sodium

Glutamate Synapses Play a Key Role in Regulating Normal Development



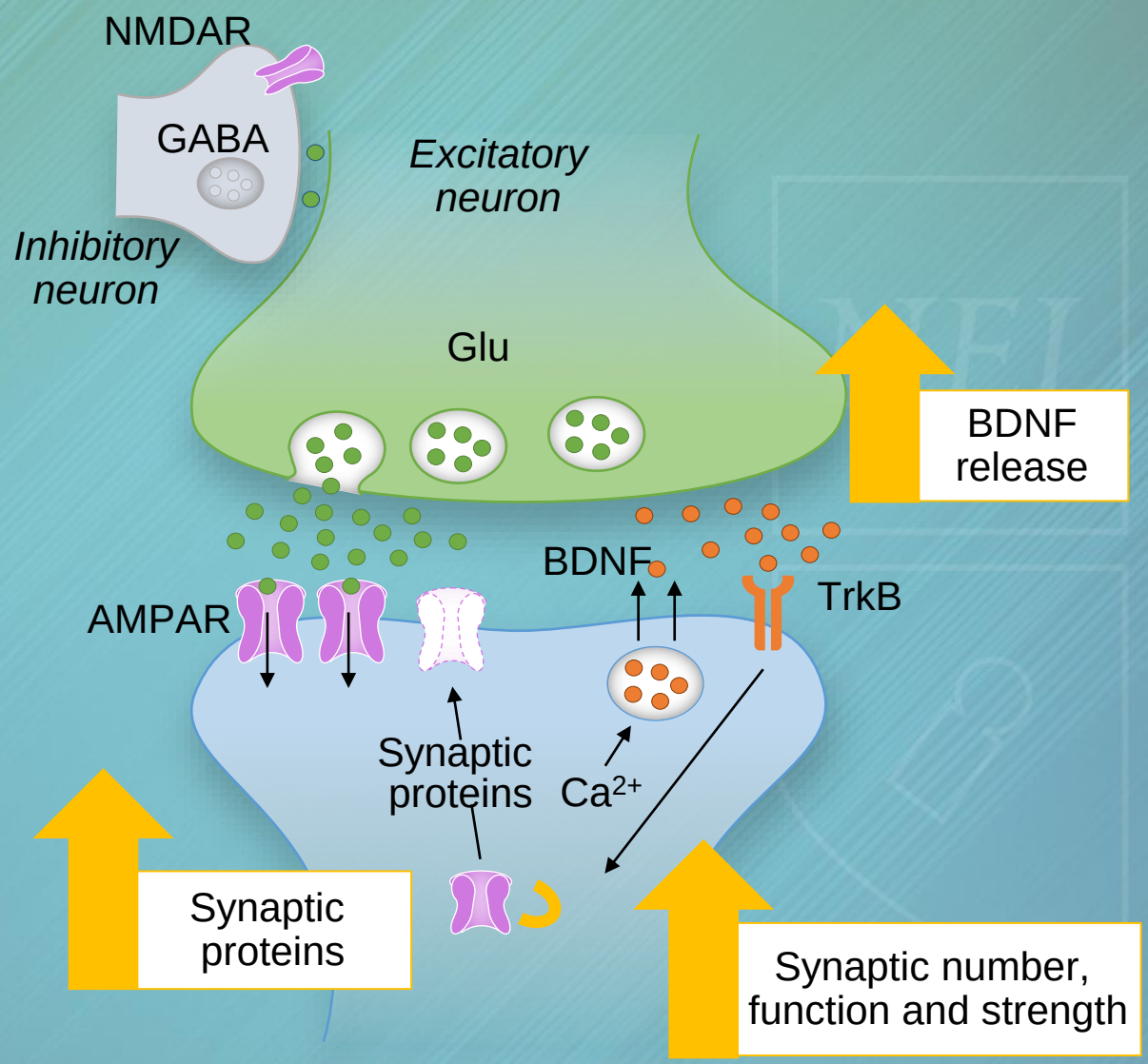
The Role of Glutamate in Depression

The Role of the Glutamatergic System in Depression

Glutamate is a major excitatory neurotransmitter that plays an important role in maintaining synaptic connections[1–4]

AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; Glu, glutamate; MDD, major depressive disorder; NMDAR, *N*-methyl-D-aspartate receptor; TrkB, tropomyosin-related kinase B.

1. Murrough JW et al. Nat Rev Drug Discov 2017;16:472-86.
2. Sanacora G et al. Neuropharmacology 2012;62:63-77.
3. Duman RS. Dialogues Clin Neurosci 2014;16:11-27.
4. Duman RS et al. Nat Med 2016;22:238-49.



Normal

The Role of the Glutamatergic System in Depression

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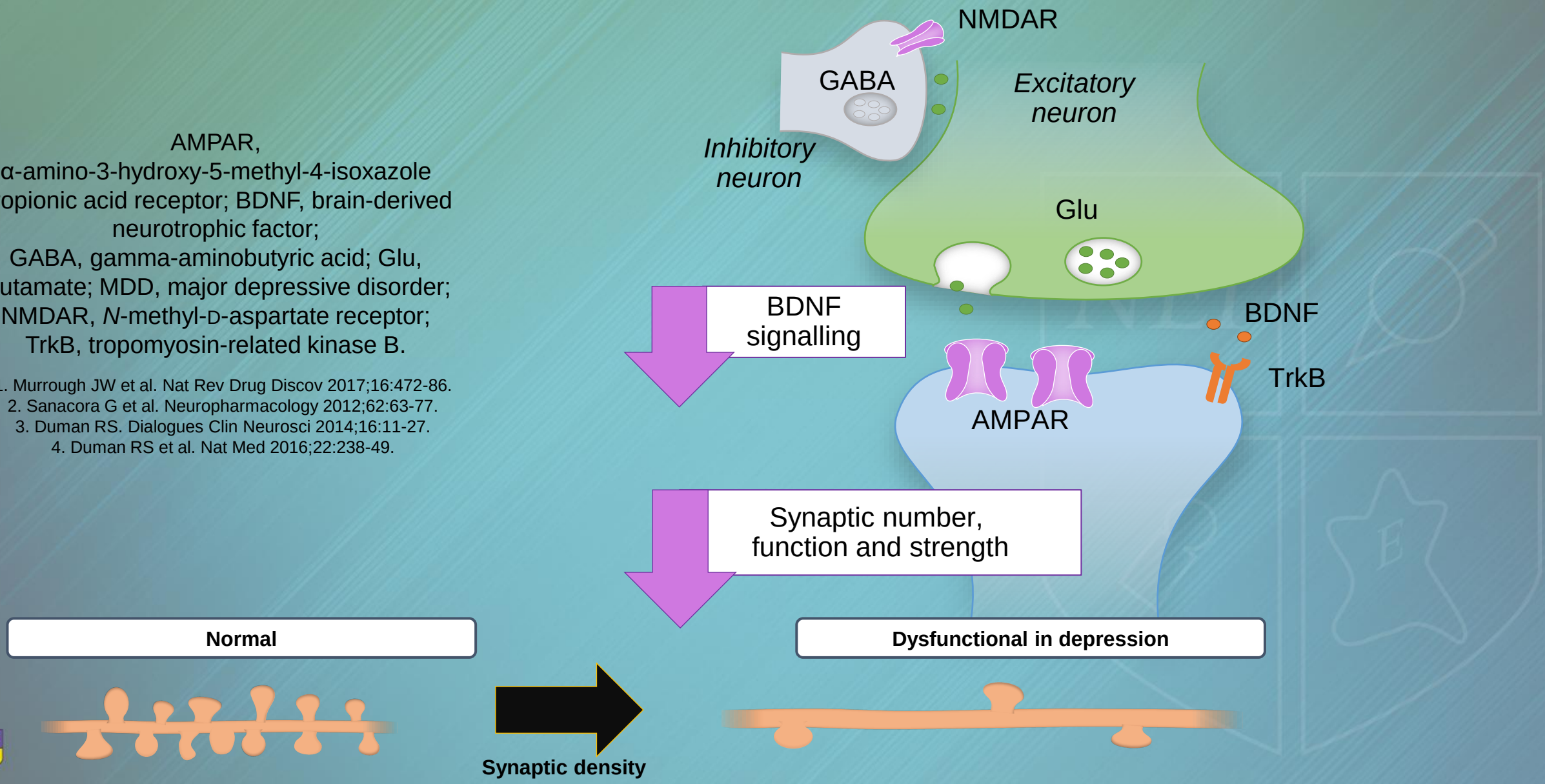


Glutamate and Depression

- Hyperactive NMDARs play an important role in the pathophysiology of MDD

Nondepressed brain	Depressed brain
Regulated NMDAR signaling	Dysregulated NMDAR signaling

- Targeting hyperactive NMDAR dysfunction in MDD offers a novel therapeutic approach that differs from existing treatments

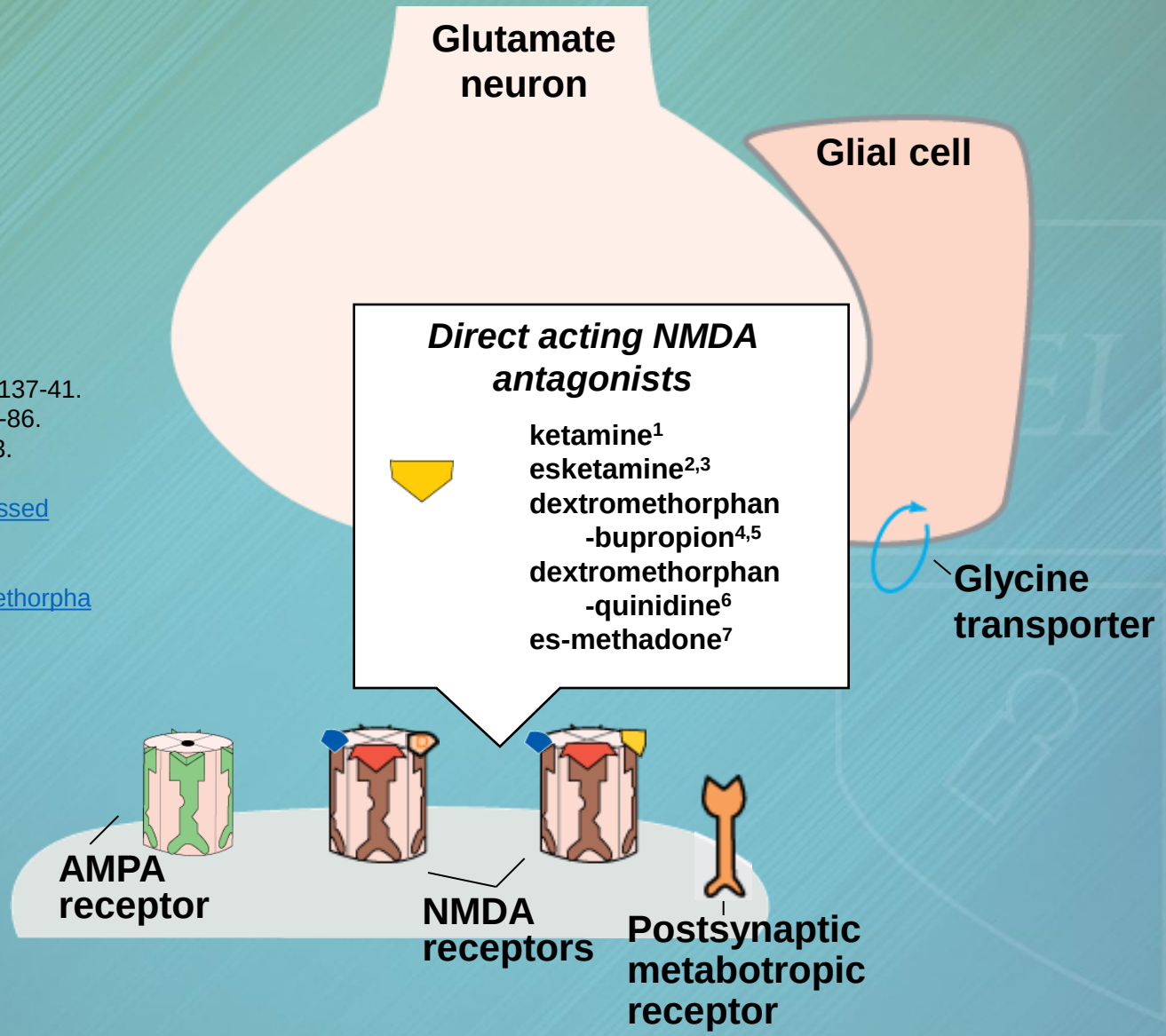
BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder; NMDAR, *N*-methyl-D-aspartate receptor

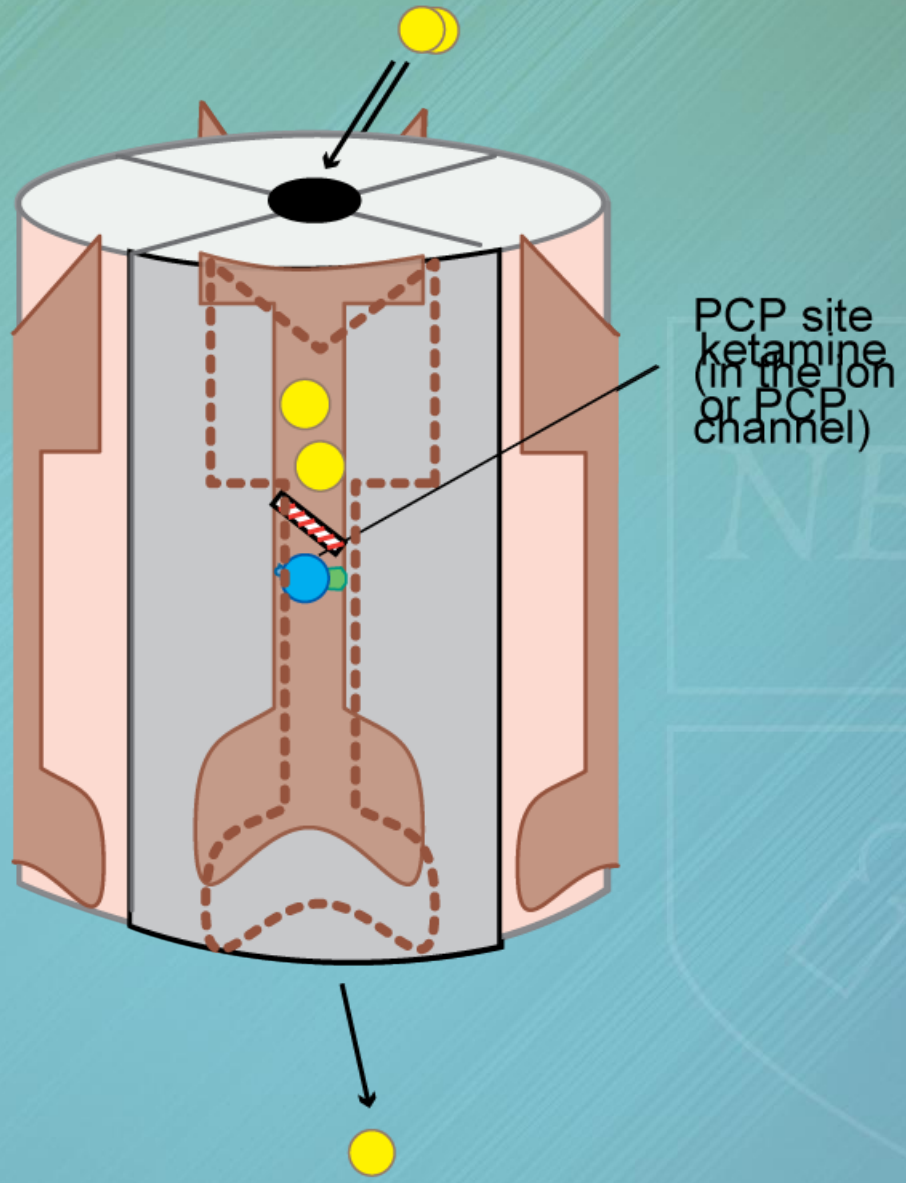
Murrough JW et al. Nat Rev Drug Discov 2017;16(7):472-86.

Novel Treatment Mechanisms: Glutamate

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid;
NMDA, *N*-methyl-D-aspartate

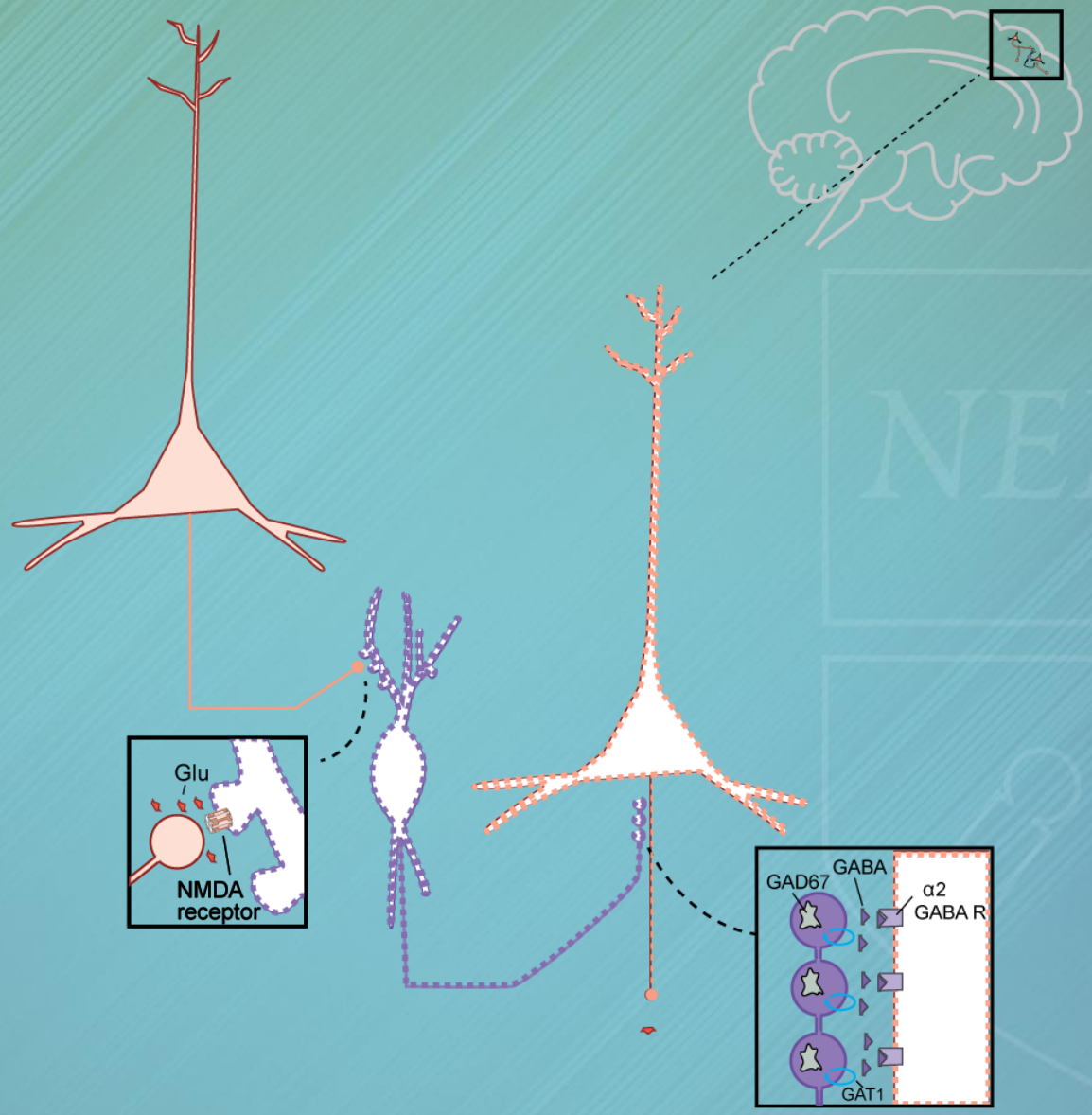
1. Zhang JC et al. Pharmacol Biochem Behav 2014;116:137-41.
2. Murrough JW et al. Nat Rev Drug Discov 2017;16:472-86.
3. Salahudeen M et al. Ther Adv Drug Saf 2021;11:71-93.
4. Clinicaltrials.gov. NCT04019704. https://clinicaltrials.gov/ct2/show/NCT04019704. Accessed May 2022.
5. PubChem. Dextromethorphan Compound Summary. https://pubchem.ncbi.nlm.nih.gov/compound/Dextromethorphan. Accessed May 2022.
6. Stahl SM. CNS Spectr 2013;18:225-7.
7. Fava M et al. Am J Psychiatry 2022;179:122-31.



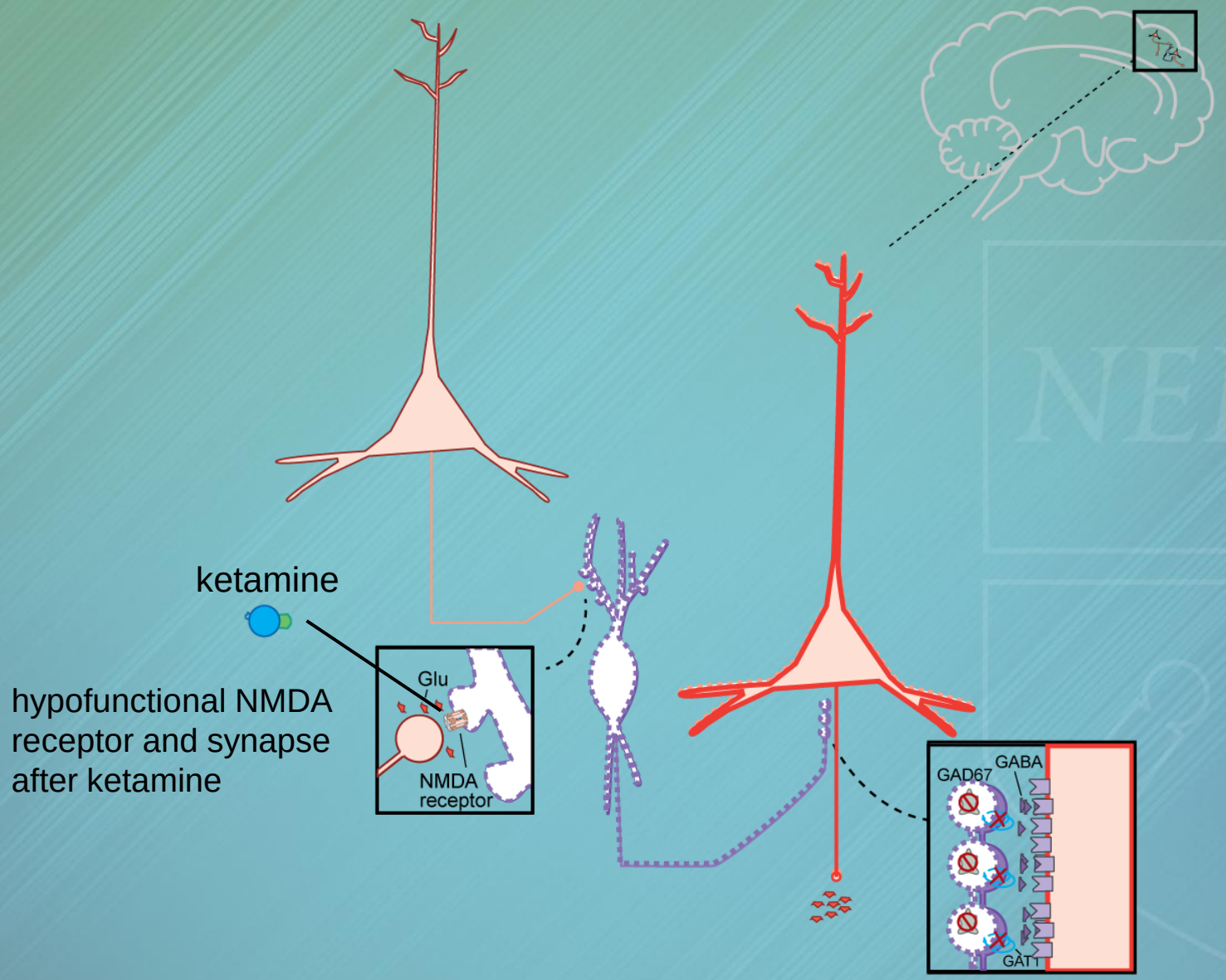


PCP, phencyclidine

Glutamate “Burst” Hypothesis



Glutamate “Burst” Hypothesis



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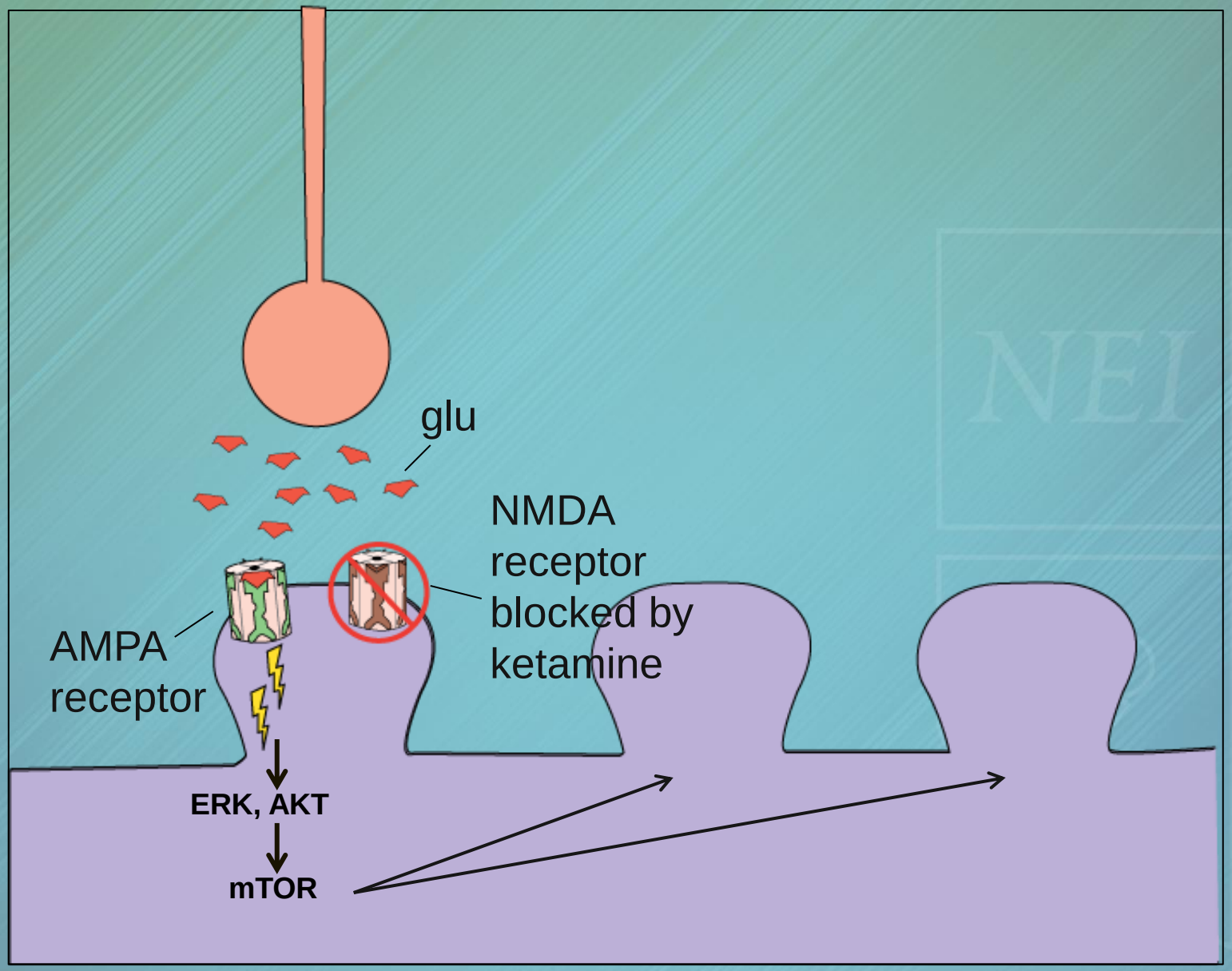


AKT, protein kinase B; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ERK, extracellular signal-regulated kinase; glu, glutamate; mTOR, mechanistic target of rapamycin; NMDA, *N*-methyl-D-aspartate

Esketamine Effect on Glutamate

It is proposed that esketamine modulates glutamate neurotransmission, restoring synaptic function[2]

Evidence suggests that through NMDA receptor blockade, esketamine* produces a surge in glutamate release[3–6]

↓

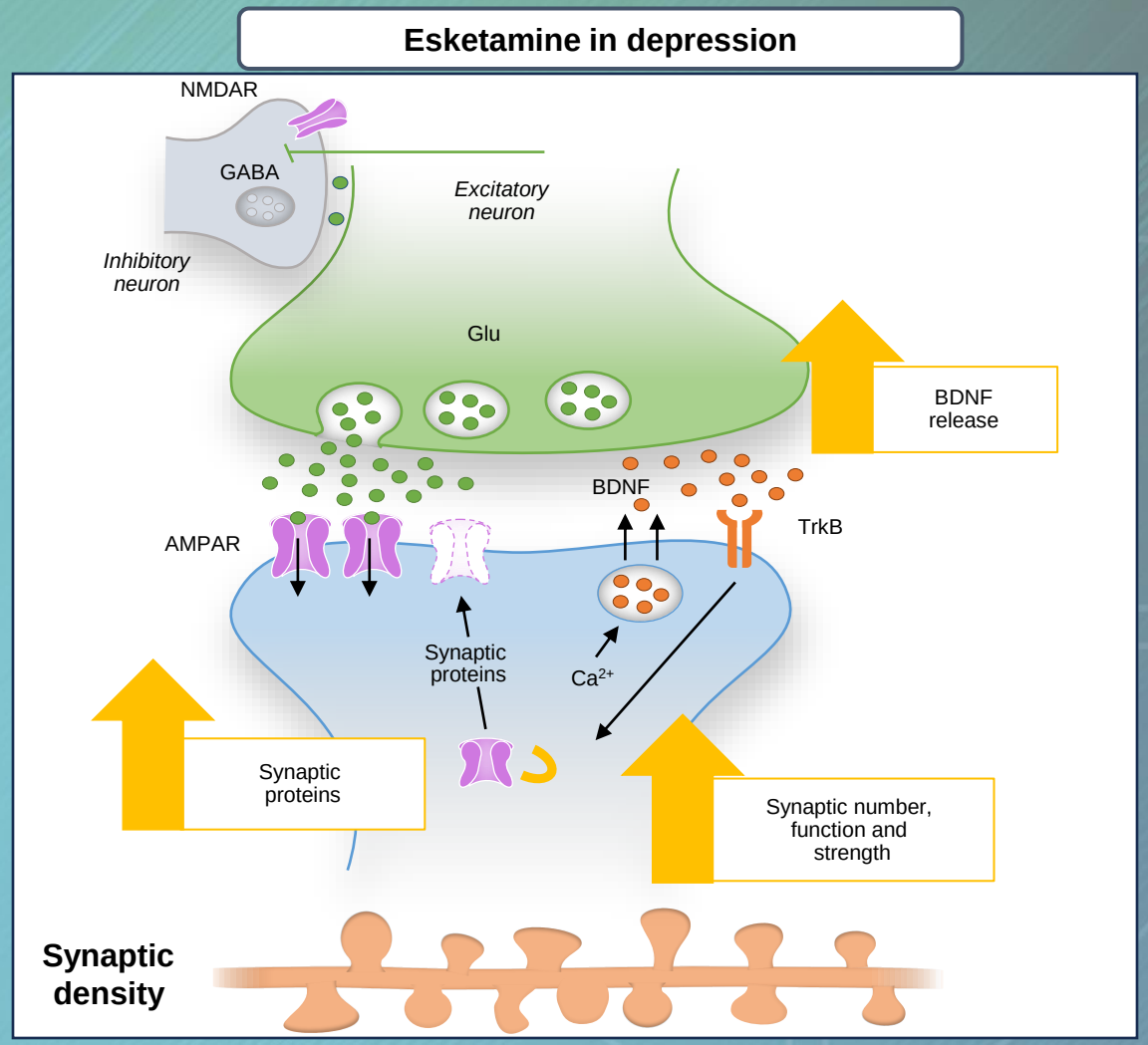
This surge in glutamate transmission leads to increased AMPA receptor stimulation[3,5,6]

↓

AMPA receptor stimulation leads to a release of BDNF, activating downstream neurotrophic signalling to increase synaptic protein synthesis synaptogenesis[3–6]

↓

Restoring synaptic function[3–6]

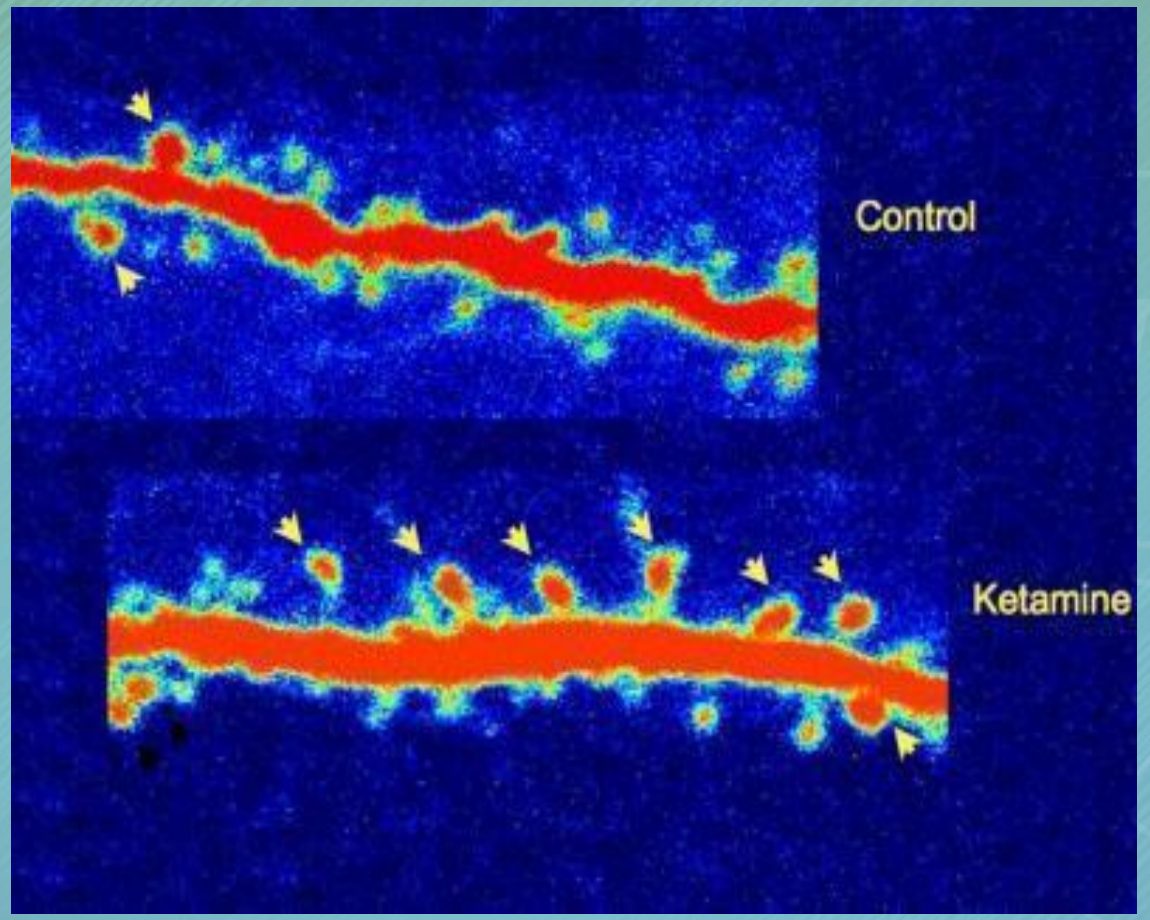


*First approved by US FDA, March 2019[1]

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; Glu, glutamate; NMDA, N-methyl-D-aspartate; NMDAR, *N*-methyl-D-aspartate receptor; TrkB, tropomyosin receptor kinase B.

1. Janssen Press Release, March 2019: https://www.jnj.com/janssen-announces-u-s-fda-approval-of-spravatotm-esketamine-ciii-nasal-spray-for-adults-with-treatment-resistant-depression-trd-who-have-cycled-through-multiple-treatments-without-relief. Accessed May 2022; 2. Duman RS et al. Mol Psychiatry 2019;24:1816-32; 3. Murrough JW et al. Nat Rev Drug Discov 2017;16:472-86; 4. Sanacora G et al. Neuropharmacology 2012;62:63-77; 5. Duman RS et al. Nat Med 2016;22:238-49; 6. Dale E et al. Biochem Pharmacol 2015;95:81-97.

Ketamine Rapidly Increases the Density and Function of the Dendritic Spines of Layer V Pyramidal Neurons in the Prefrontal Cortex



Bottom slide shows regeneration of synaptic connections in group receiving ketamine compared to control group

(Courtesy of Yale University)

Investigational Compounds on the Horizon

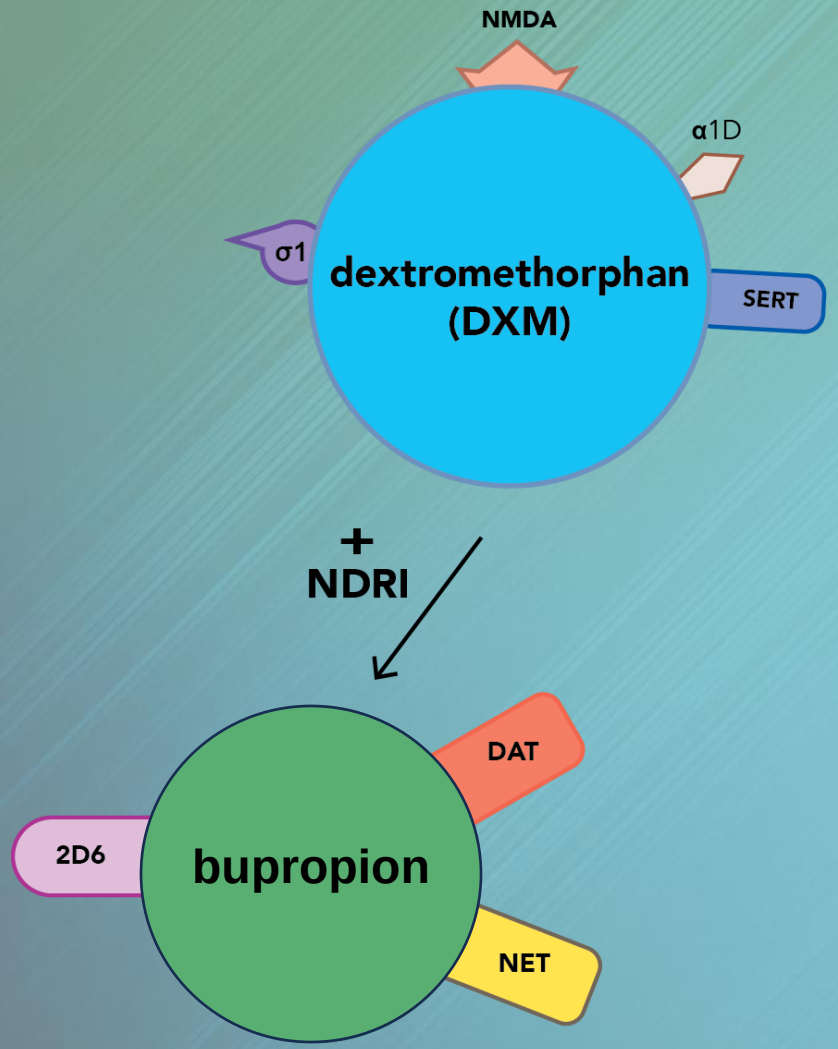
AXS-05

Combination of bupropion with dextromethorphan, a sigma-1 receptor agonist and NMDA receptor antagonist, rapid onset MDD[2,3], agitation in Alzheimer's disease[4]

Esmethadone

NMDA antagonist, weak mu opioid agonist, rapid onset MDD[6,7]

Dextromethorphan-Bupropion

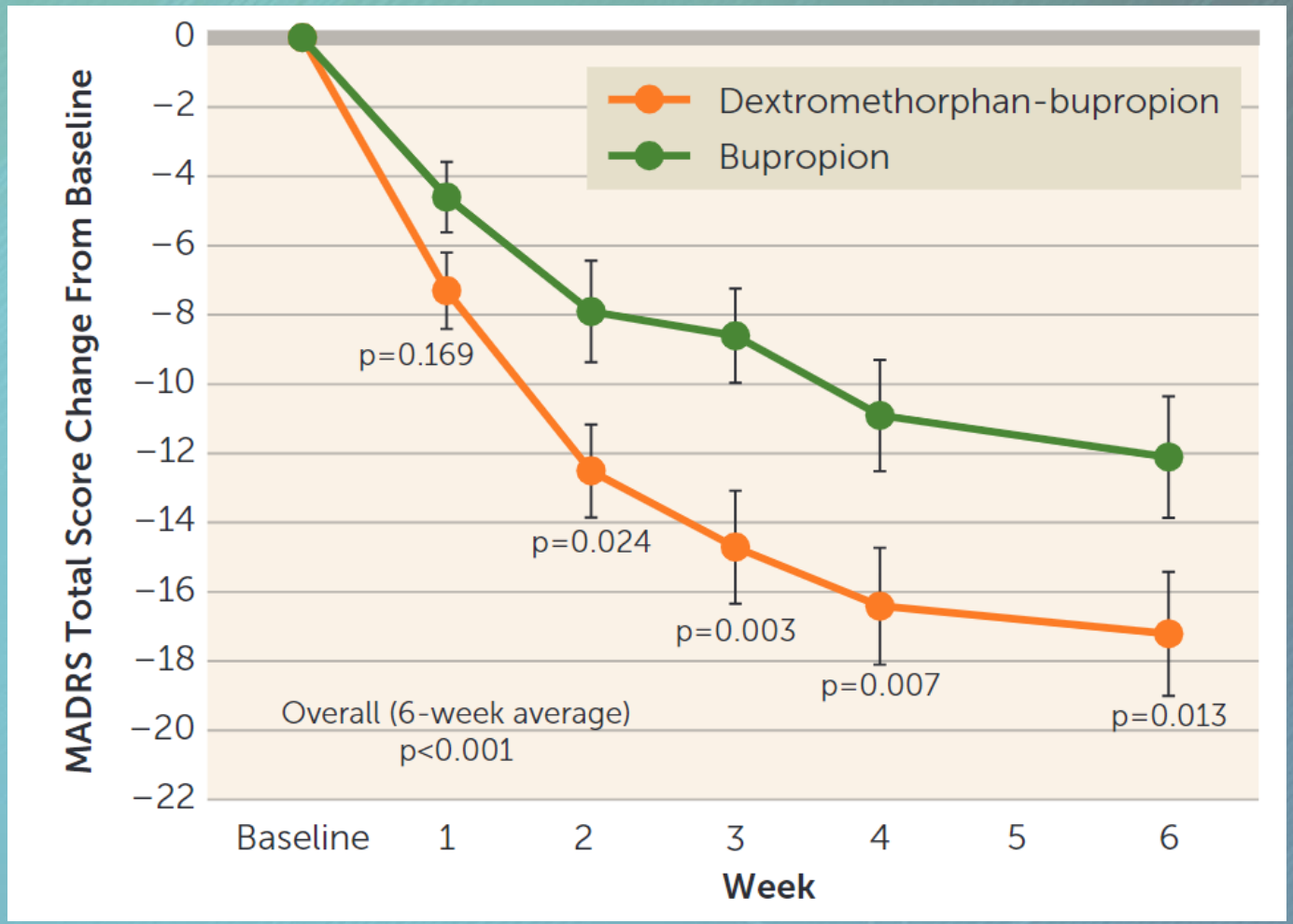


- Dextromethorphan (DXM) is a **moderate** NMDA antagonist, a strong sigma-1 agonist, and has at least moderate binding to SERT (SRI activity)
  - The metabolite dextrorphan is a **strong** NDMA receptor antagonist
- It is rapidly metabolized by CYP450 2D6, making it difficult to achieve therapeutic blood levels without concomitant administration of a CYP2D6 inhibitor (e.g., bupropion)
- The FDA approved dextromethorphan-bupropion sustained-release tablets for treatment of MDD in adults in 2022

Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021.

Dextromethorphan 45 mg/Bupropion 210 mg vs Bupropion 300 mg

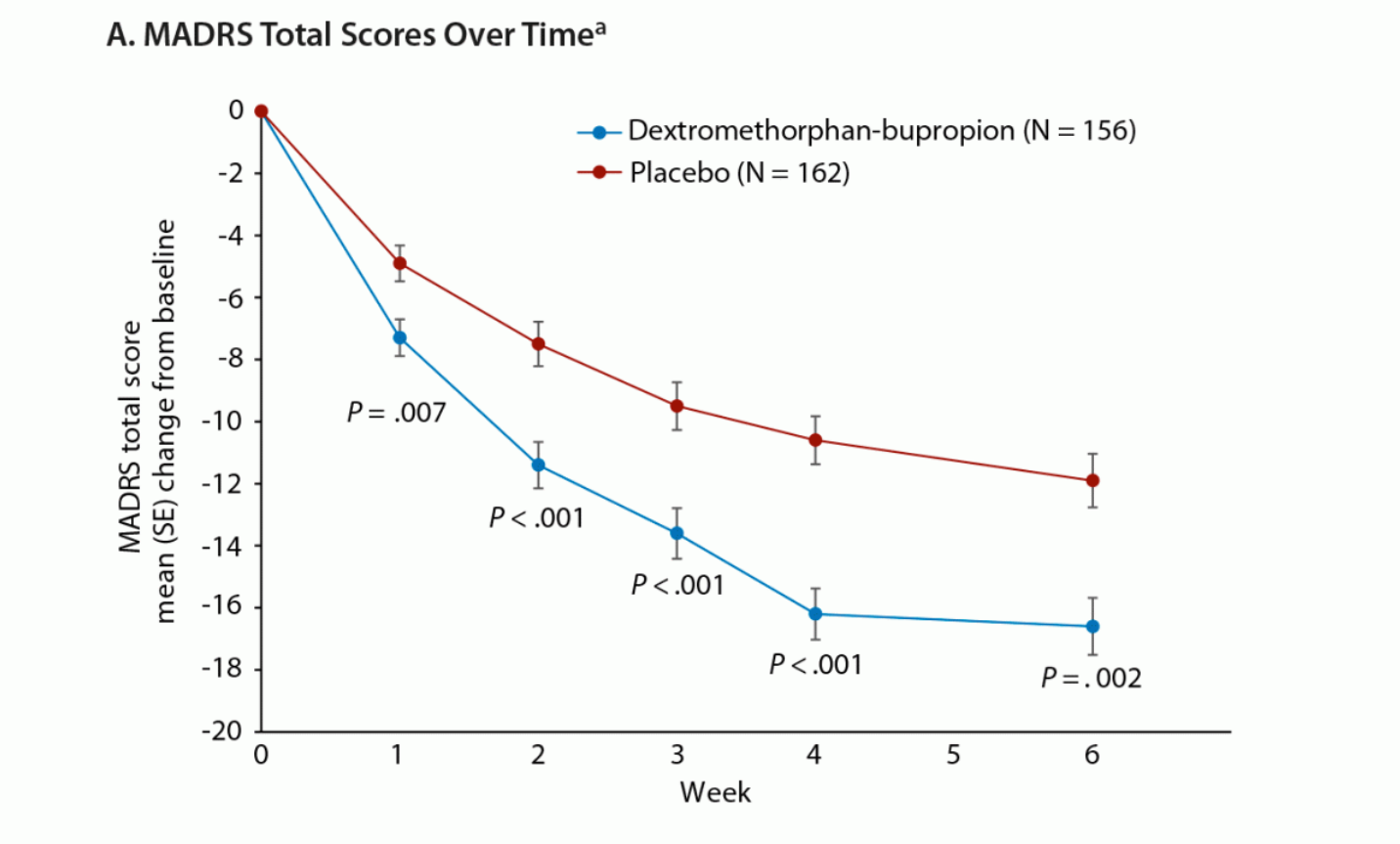
- Week 1 CGI-I: separated; *P* = .045
- Week 6 MADRS remission: 47% vs 16%; *P* = .0004



Tabuteau H et al. Am J Psychiatry 2022;179(9):490-9.

Combination DXM-Bupropion Effective in the Treatment of Adults With MDD

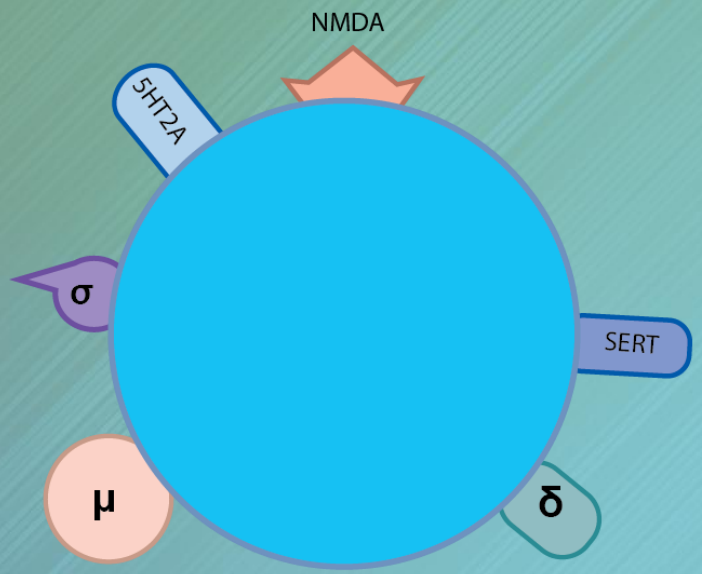
GEMINI Study (phase 3, randomized, double-blind, placebo-controlled)

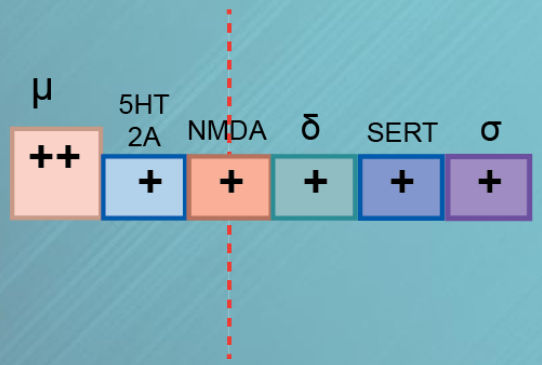


Treatment with DXM-bupropion resulted in rapid and statistically significant improvements in depressive symptoms and function and quality of life across multiple efficacy endpoints, compared to placebo

Iosifescu DV et al. J Clin Psychiatry 2022;83(4):21m14345.

Dextromethadone/S-methadone

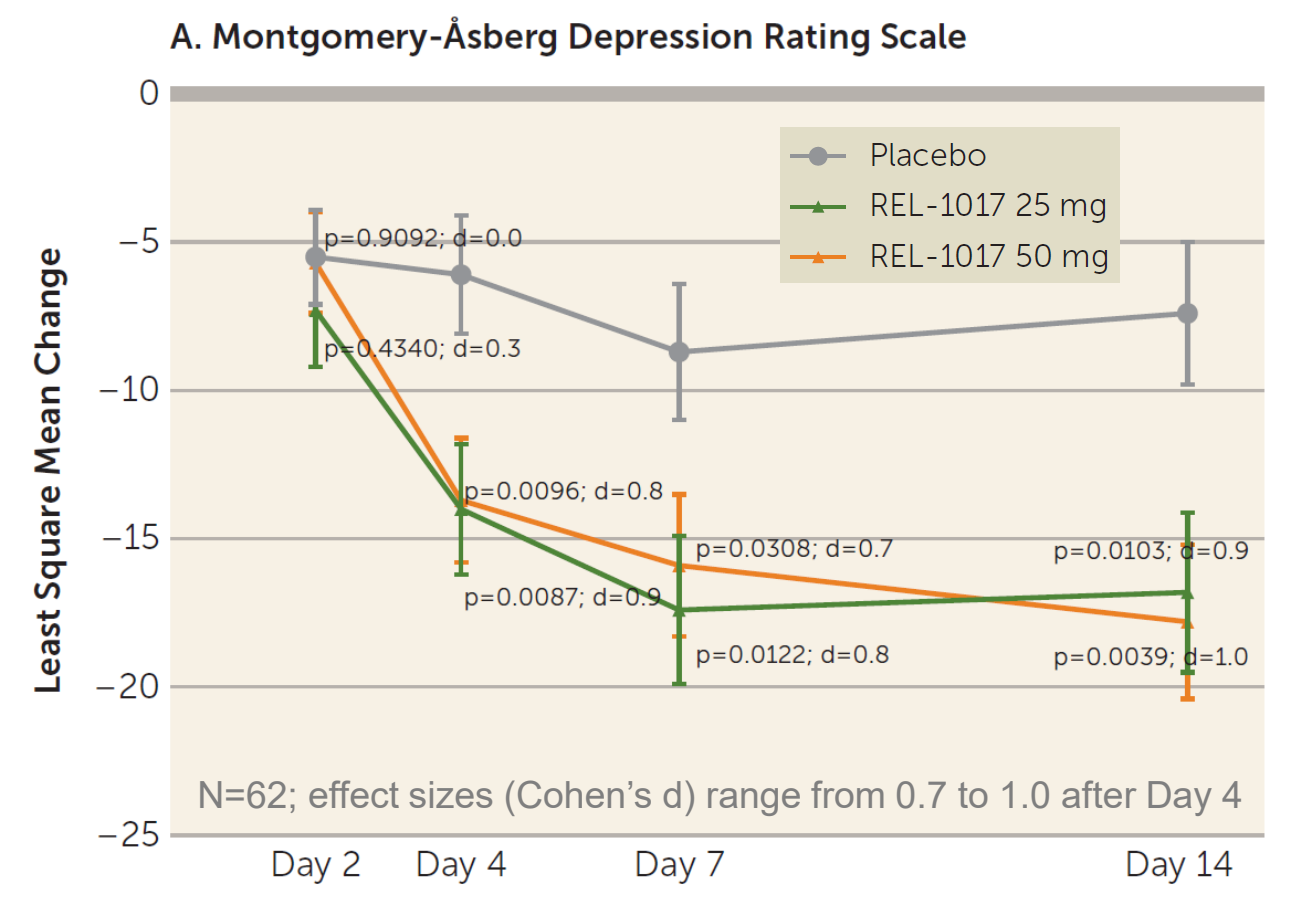




- Dextromethadone (REL-1017) is the (S)-enantiomer of methadone
- The dextro-enantiomer is a moderate NMDA receptor antagonist and has much less potent mu-opioid agonism
- In clinical development as an oral rapid-onset treatment

Stahl SM. Stahl's Essential Psychopharmacology, 5th ed; 2021.

Dextromethadone as Adjunctive Treatment in MDD: A Phase 2a Randomized Double-Blind Trial

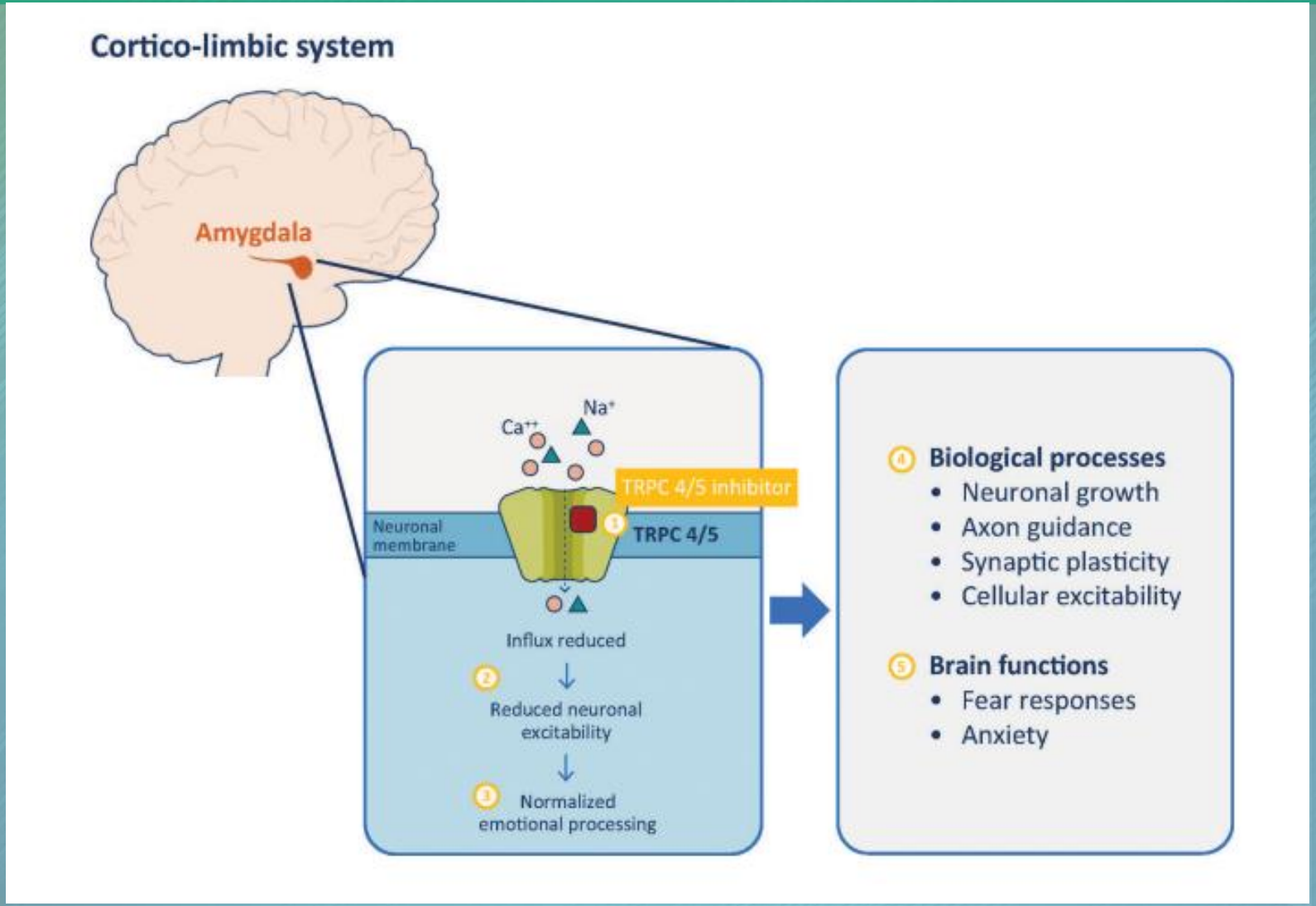


- The NNT to achieve remission on day 14 was 4 for the 25-mg group and 3 for the 50-mg group
- The most common treatment-emergent adverse events that occurred in at least 5% of all patients were headache, constipation, nausea, and somnolence
- No evidence of dissociative or psychotomimetic effects, opioid effects, or withdrawal signs and symptoms

Fava M et al. Am J Psychiatry 2022;179(2):122-31.

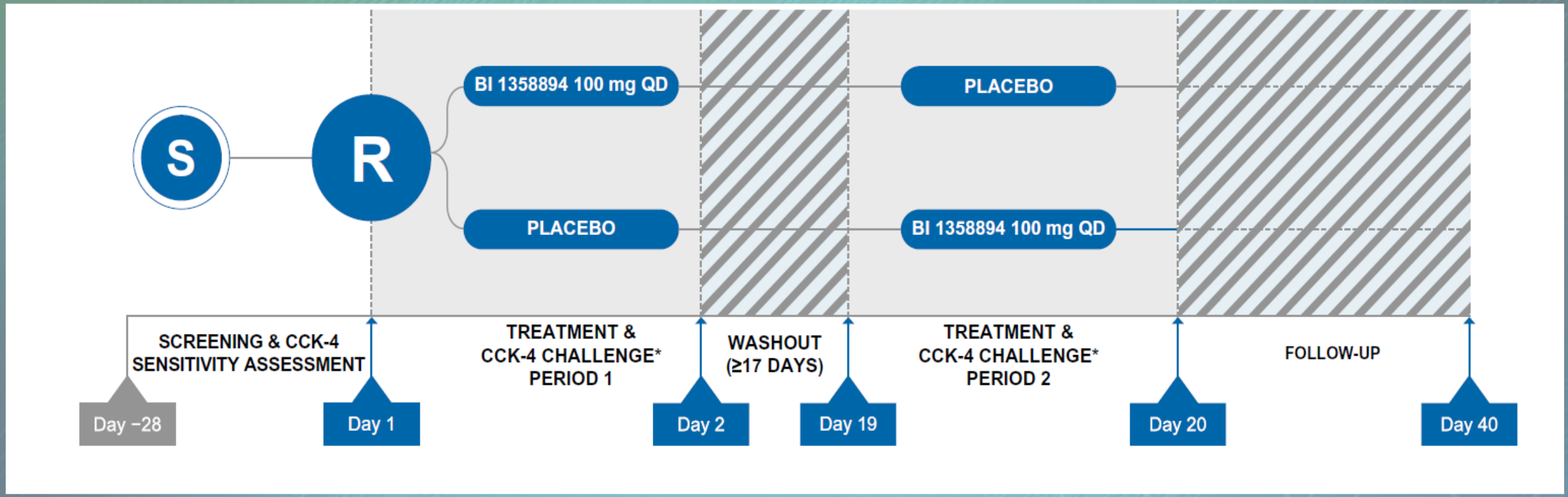
Glutamate as a Target for Depression & PTSD

Transient Receptor Potential Canonical 4/5 Inhibitor BI 1358894 Mechanism



Davis LL, Hamner MB. Front Psychiatry 2024;15:1356563.

BI 1358894 Reduces Stress Response in CCK4 Challenge

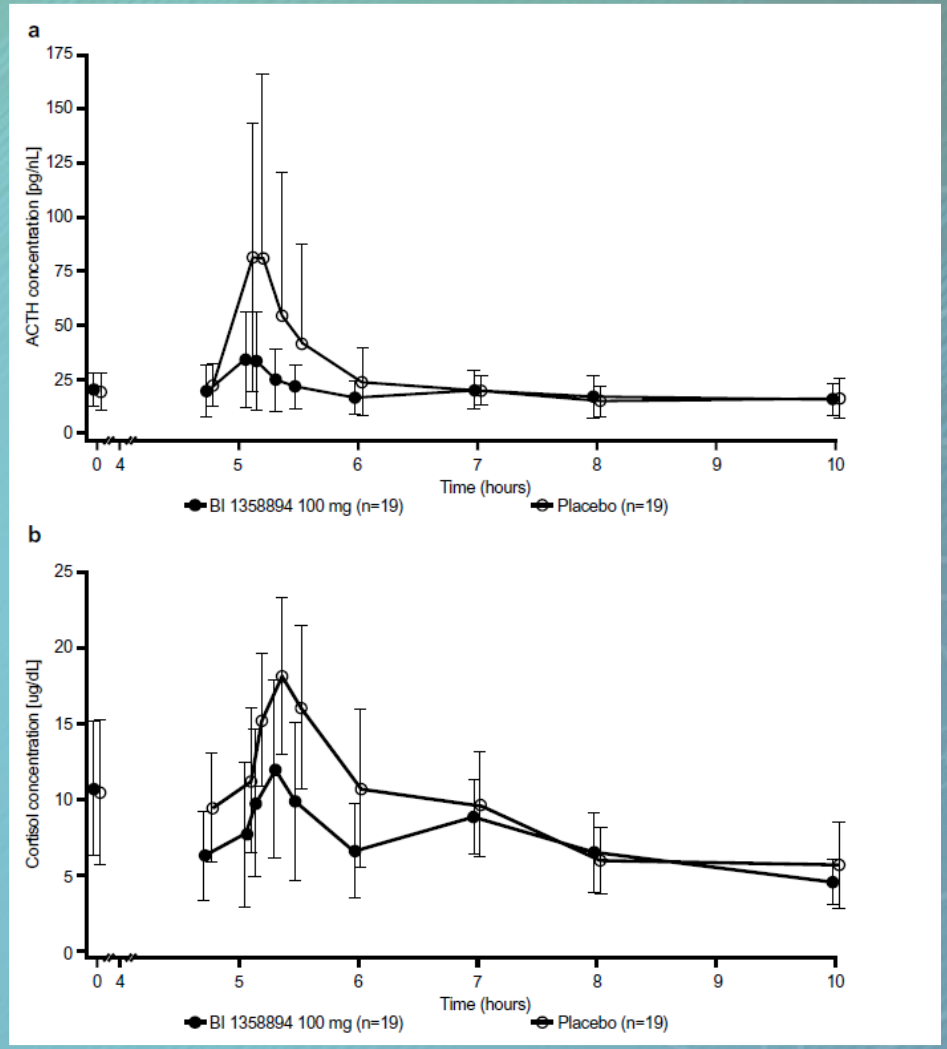


Goettel M et al. CNS Drugs 2023;37(12):1099-109.

BI 1358894 Reduces Stress Response in CCK4 Challenge

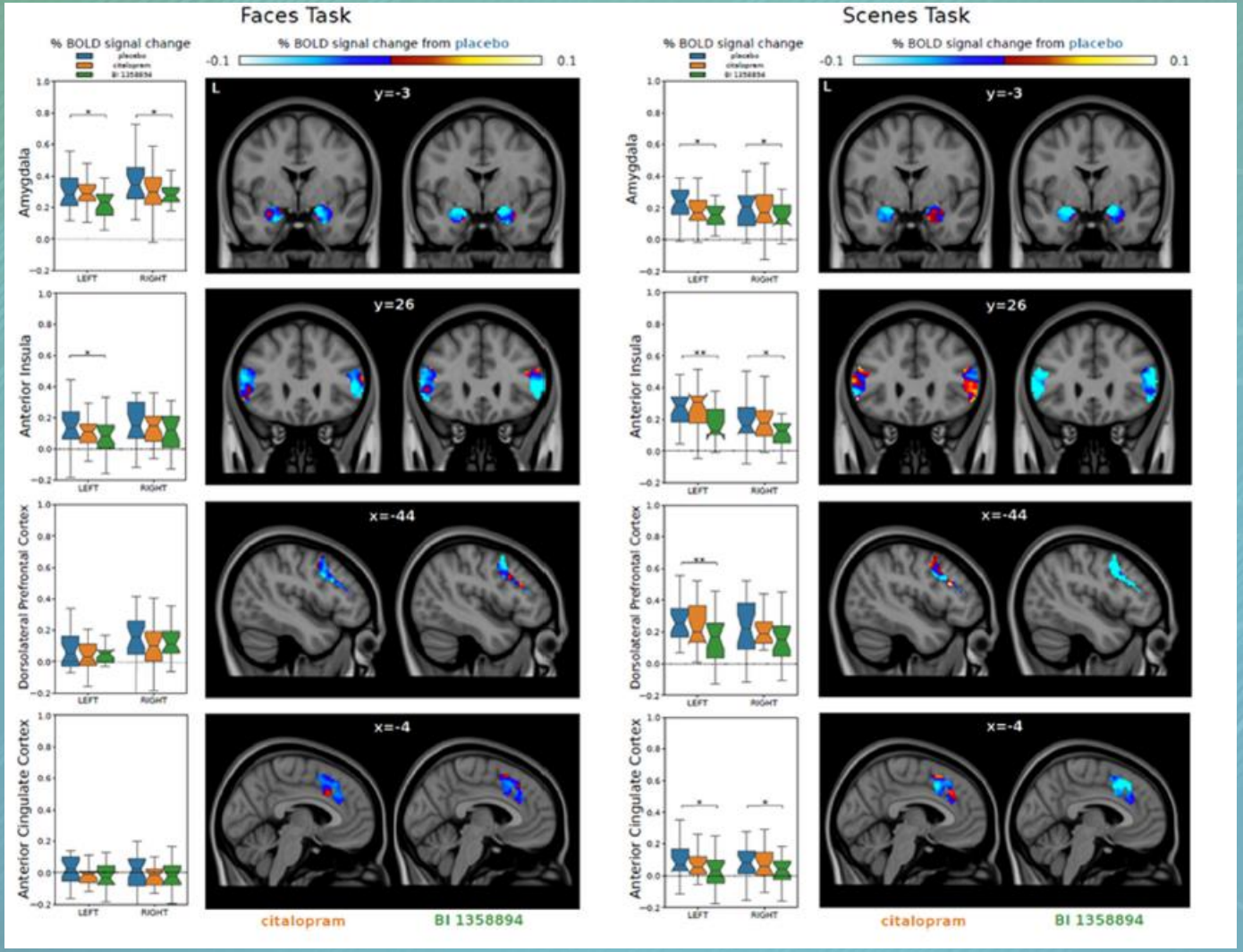
BI 1358894 group did not show increase in adrenocorticotropic hormone (ACTH)

BI 1358894 group did not show increase in cortisol



Goettel M et al. CNS Drugs 2023;37(12):1099-109.

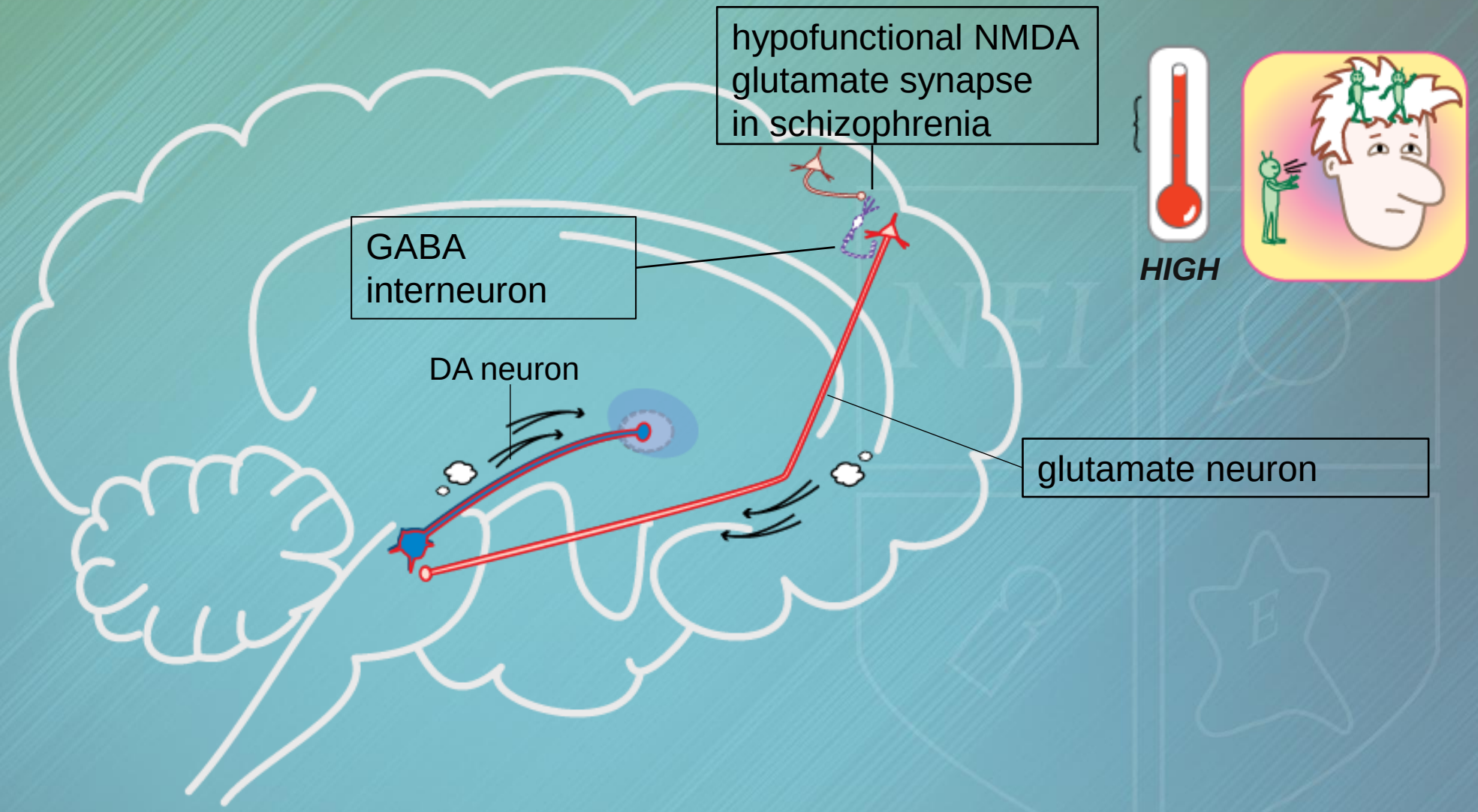
TRPC 4/5 Inhibitor BI 1358894 Decreases Cortico-Striatal Loop Activity in Response to Negative Stimuli



Grimm S et al. Eur Neuropsychopharmacol 2022;65:44-51.

The Role of Glutamate in Schizophrenia and Cognitive Impairment

The Role of Glutamate in Schizophrenia



The Role of Glutamate in Schizophrenia

hypofunctional NMDA glutamate synapse

mesocortical DA pathway

Glutamate hyperactivity causes key GABA interneurons to inhibit DA releases

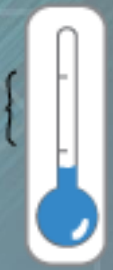
lack of energy

apathy

anhedonia

negative symptoms

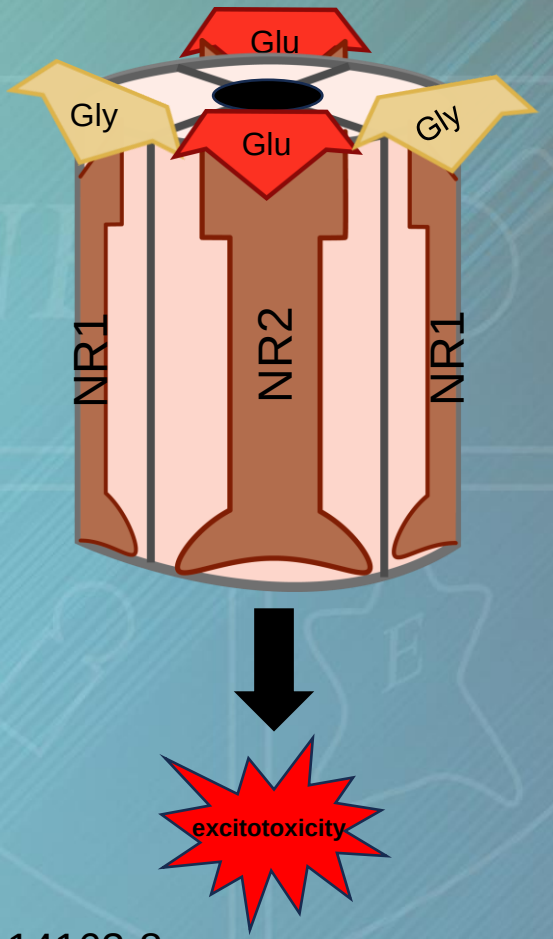
affective symptoms



LOW

Enhance NMDA/Glutamatergic Signaling? What About Excitotoxicity?

- The NMDA receptor has three distinct subunit types
  - NR1
    - Glycine binding site
    - Less associated with excitotoxicity
  - NR2
    - Glutamate binding site
    - Associated with excitotoxicity
  - NR3
    - Glycine binding site
    - Less known and less common
  - Most NMDA receptors consist of two NR1 and two NR2 subunits



Ulbrich MH, Isacoff EY. Proc Natl Acad Sci U S A 2008;105(37):14163-8;
Coyle JT, Puttfarcken P. Science 1993;262(5134):689-95.

NMDA NR1 Glycine Agonists

- Serine, D-serine, and glycine—agonists
- D-cycloserine and sarcosine—partial agonists
- Relatively higher doses needed (gram quantities)
- Greater potential for side effects?

Kalia LV et al. Lancet Neurol 2008;7(8):742-55.

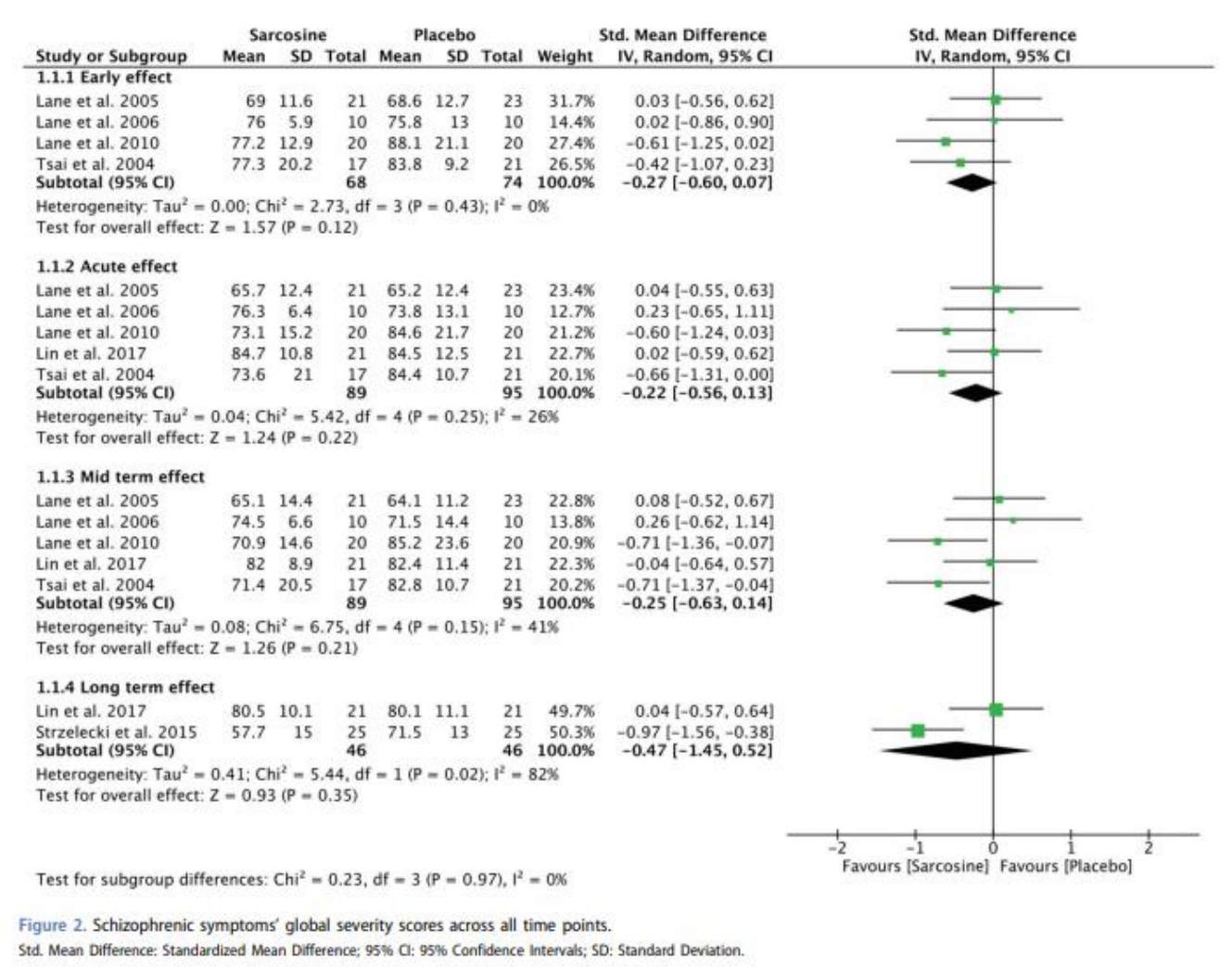
List of GlyT1 Inhibitors

	Compound
Sarcosine and sarcosine-based GlyT1 inhibitors	Sarcosine
	NFPS/ALX5407
	Org 25935
	AM747
	Org 24461
Currently undergoing clinical trials	Org 24598

	Compound
Non-sarcosine-based GlyT1 inhibitors	Iclepertin (BI 425809)
	Bitopertin
	SSR504734
	SSR103800
	GSK1018921
	ACPPB
	DCCCyB
	PF-03463275

de Bartolomeis A et al. Front Psychiatry 2020;11(369):1-20; March M et al. Exp Opin Drug Metab Toxicol 2021;17(4):483-93; Bugarski-Kirola et al. Biol Psychiatry 2017;82(1):8-16; Rosenbrock H et al. Eur Arch Psychiatry Clin Neurosci 2023;273(7):1557-66.

Meta-Analyses of Sarcosine (N-methyl-glycine) Added on to an FGA or SGA (Excluding Clozapine)



Study or Subgroup	Sarcosine Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Early effect								
Lane et al. 2005	69	11.6	21	68.6	12.7	23	31.7%	0.03 [-0.56, 0.62]
Lane et al. 2006	76	5.9	10	75.8	13	10	14.4%	0.02 [-0.86, 0.90]
Lane et al. 2010	77.2	12.9	20	88.1	21.1	20	27.4%	-0.61 [-1.25, 0.02]
Tsai et al. 2004	77.3	20.2	17	83.8	9.2	21	26.5%	-0.42 [-1.07, 0.23]
Subtotal (95% CI)			**68**			**74**	**100.0%**	**-0.27 [-0.60, 0.07]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.73$, df = 3 (P = 0.43); $I^2 = 0\%$								
Test for overall effect: Z = 1.57 (P = 0.12)								
1.1.2 Acute effect								
Lane et al. 2005	65.7	12.4	21	65.2	12.4	23	23.4%	0.04 [-0.55, 0.63]
Lane et al. 2006	76.3	6.4	10	73.8	13.1	10	12.7%	0.23 [-0.65, 1.11]
Lane et al. 2010	73.1	15.2	20	84.6	21.7	20	21.2%	-0.60 [-1.24, 0.03]
Lin et al. 2017	84.7	10.8	21	84.5	12.5	21	22.7%	0.02 [-0.59, 0.62]
Tsai et al. 2004	73.6	21	17	84.4	10.7	21	20.1%	-0.66 [-1.31, 0.00]
Subtotal (95% CI)			**89**			**95**	**100.0%**	**-0.22 [-0.56, 0.13]**
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 5.42$, df = 4 (P = 0.25); $I^2 = 26\%$								
Test for overall effect: Z = 1.24 (P = 0.22)								
1.1.3 Mid term effect								
Lane et al. 2005	65.1	14.4	21	64.1	11.2	23	22.8%	0.08 [-0.52, 0.67]
Lane et al. 2006	74.5	6.6	10	71.5	14.4	10	13.8%	0.26 [-0.62, 1.14]
Lane et al. 2010	70.9	14.6	20	85.2	23.6	20	20.9%	-0.71 [-1.36, -0.07]
Lin et al. 2017	82	8.9	21	82.4	11.4	21	22.3%	-0.04 [-0.64, 0.57]
Tsai et al. 2004	71.4	20.5	17	82.8	10.7	21	20.2%	-0.71 [-1.37, -0.04]
Subtotal (95% CI)			**89**			**95**	**100.0%**	**-0.25 [-0.63, 0.14]**
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 6.75$, df = 4 (P = 0.15); $I^2 = 41\%$								
Test for overall effect: Z = 1.26 (P = 0.21)								
1.1.4 Long term effect								
Lin et al. 2017	80.5	10.1	21	80.1	11.1	21	49.7%	0.04 [-0.57, 0.64]
Strzelecki et al. 2015	57.7	15	25	71.5	13	25	50.3%	-0.97 [-1.56, -0.38]
Subtotal (95% CI)			**46**			**46**	**100.0%**	**-0.47 [-1.45, 0.52]**
Heterogeneity: $Tau^2 = 0.41$; $Chi^2 = 5.44$, df = 1 (P = 0.02); $I^2 = 82\%$								
Test for overall effect: Z = 0.93 (P = 0.35)								
Test for subgroup differences: $Chi^2 = 0.23$, df = 3 (P = 0.97), $I^2 = 0\%$								

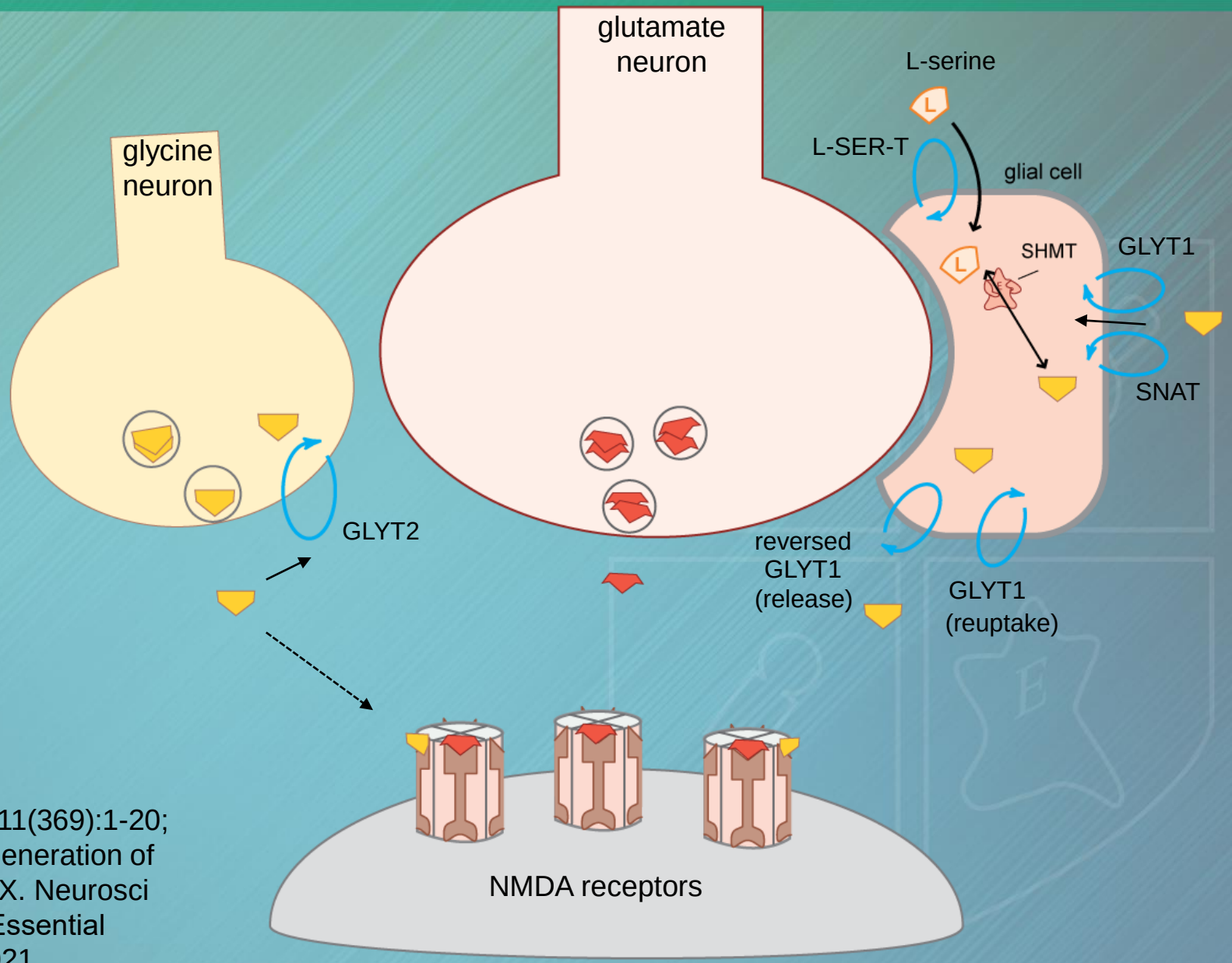
Figure 2. Schizophrenic symptoms' global severity scores across all time points.
Std. Mean Difference: Standardized Mean Difference; 95% CI: 95% Confidence Intervals; SD: Standard Deviation.

Results were potentially significant in the treatment-resistant subgroup analysis

Marchi M et al. Exp Opin Drug Metab Toxicol 2021;17(4):483-93.

Glycine Transporters (GlyTs)

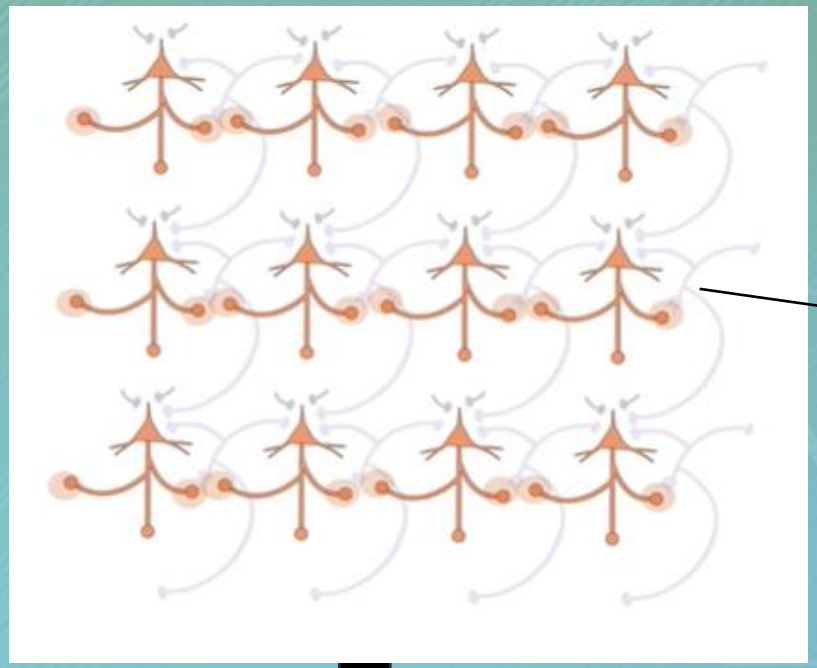
- GlyT1
  - Cortex, thalamus, and hippocampus
  - Expressed on astrocytes
- GlyT2
  - Spinal cord, cerebellum, and brainstem
  - Expressed on glycinergic and GABAergic terminals



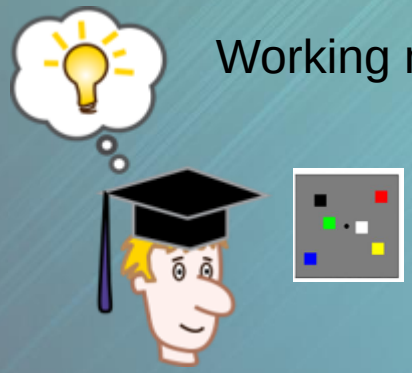
de Bartolomeis A et al. Front Psychiatry 2020;11(369):1-20; Bunney BG et al. Psychopharmacology-4th Generation of Progress ACNP 2000; Gomez RS, Pinto MCX. Neurosci Biobehav Rev 2020;118:97-110; Stahl's Essential Psychopharmacology, 5th edition; 2021.

PFC Network in Healthy Brain

Excitatory/Inhibitory (E/I) Balance



GABAergic interneuron



Working memory task

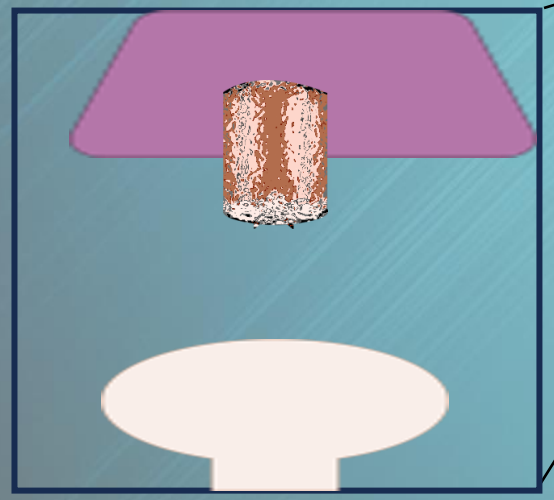
Gamma (30-100Hz) oscillations on cortical EEG

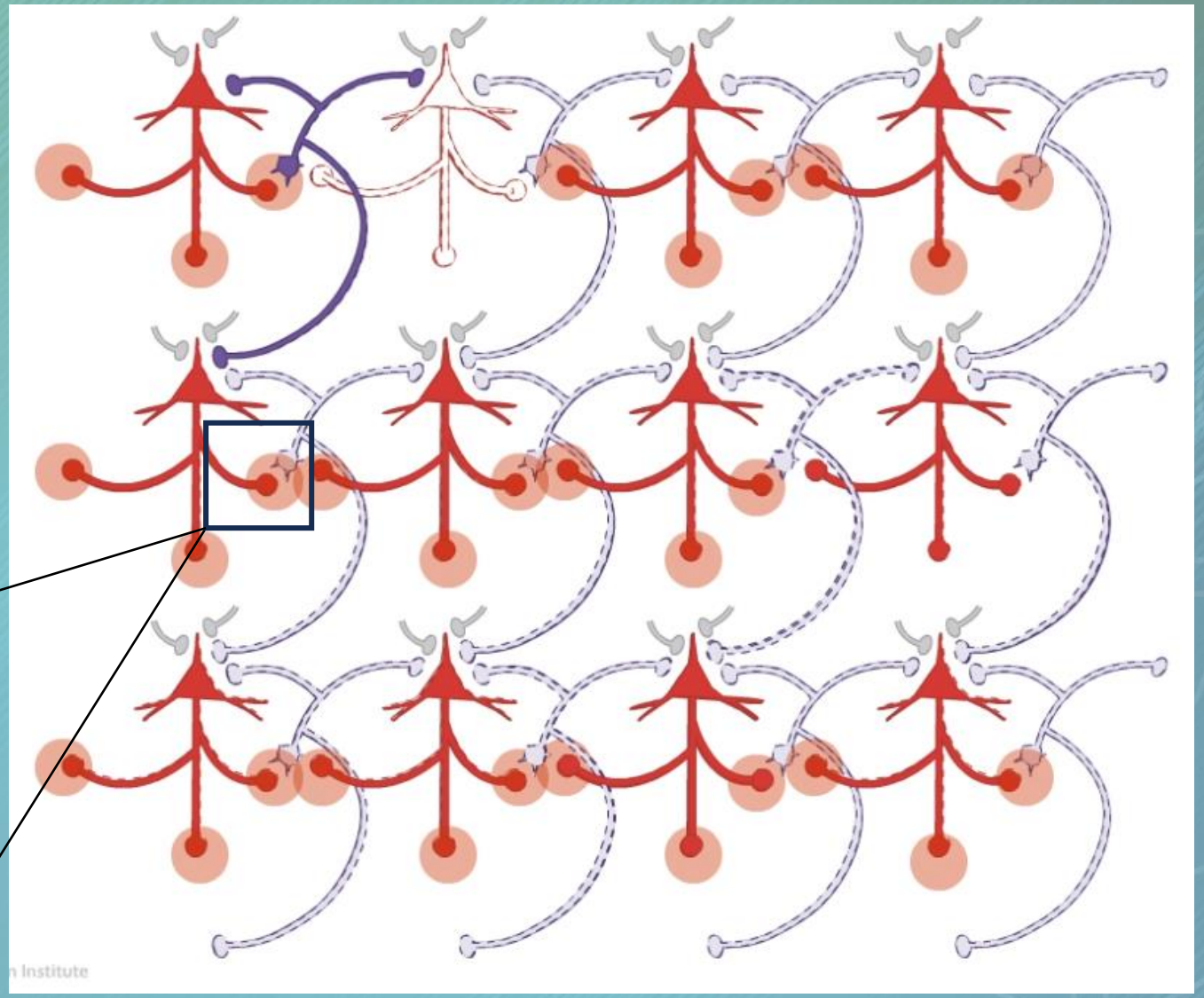
Excitation

Inhibition

PFC Network in Schizophrenia

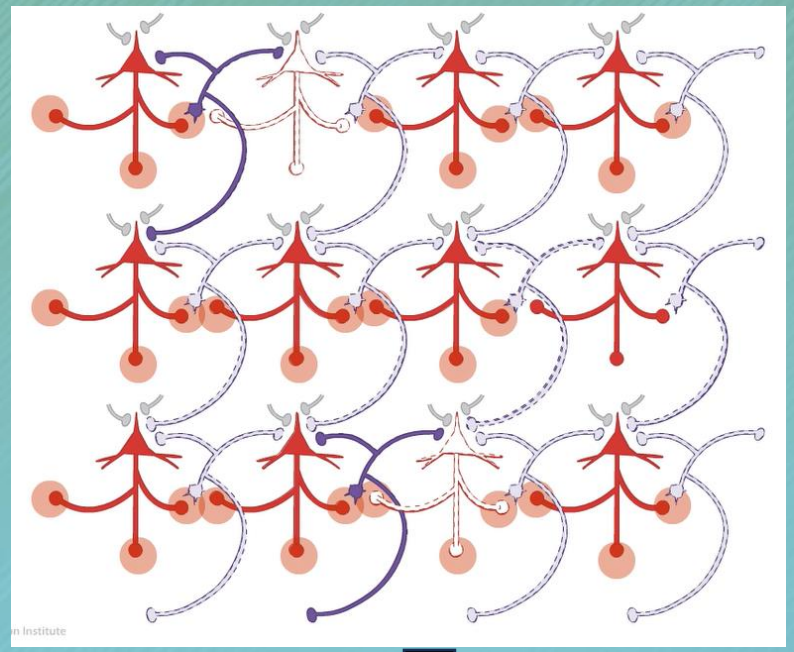
Hypofunctional NMDA receptor on
PV+ GABAergic interneuron





PFC Network in Schizophrenia

Excitatory/Inhibitory (E/I) *imbalance*

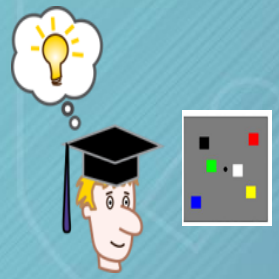


Working memory task

Disrupted gamma oscillations on cortical EEG

Healthy Brain

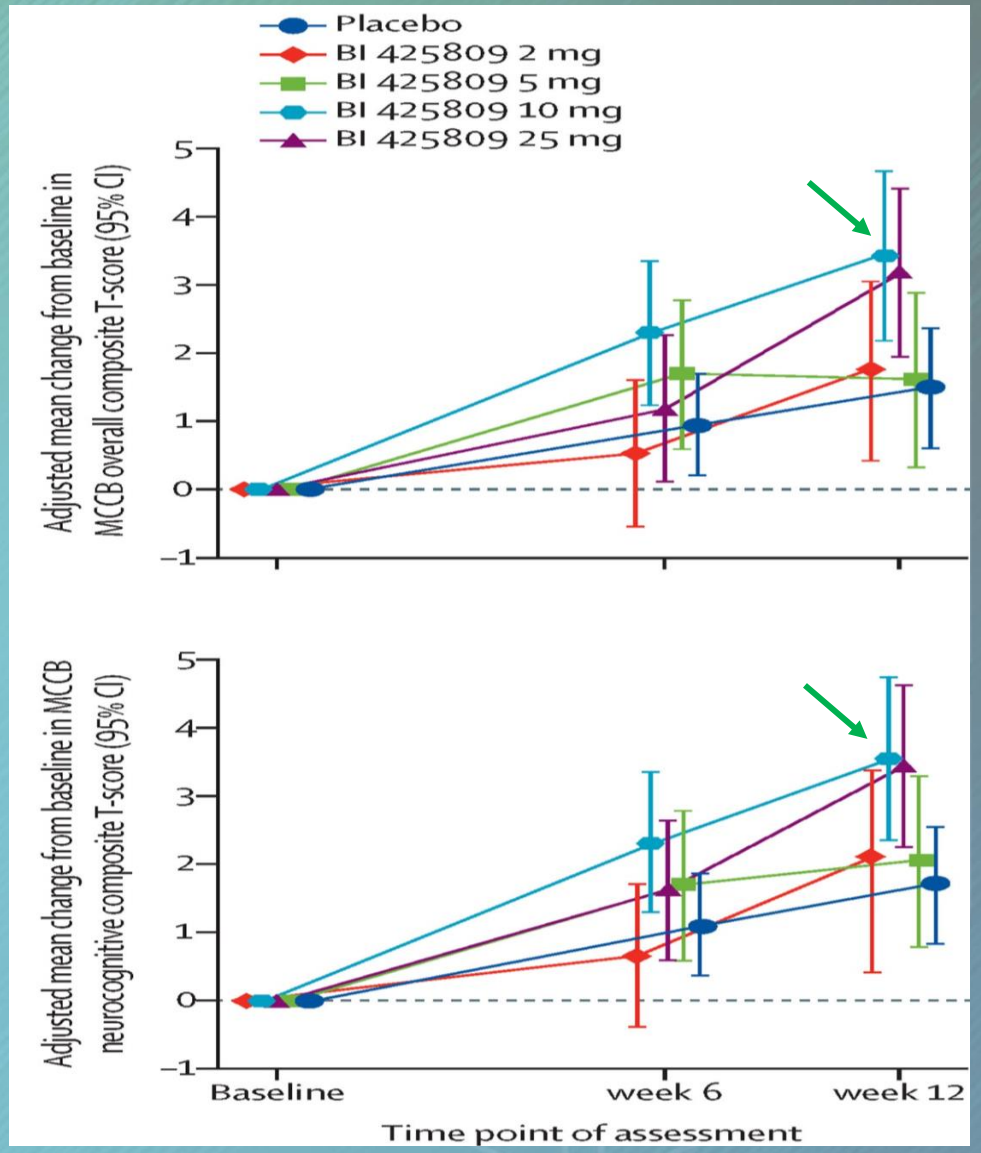
Working memory task



Gamma (30-100Hz) oscillations on cortical EEG

Iclepertin (BI 425809) Phase II Trials

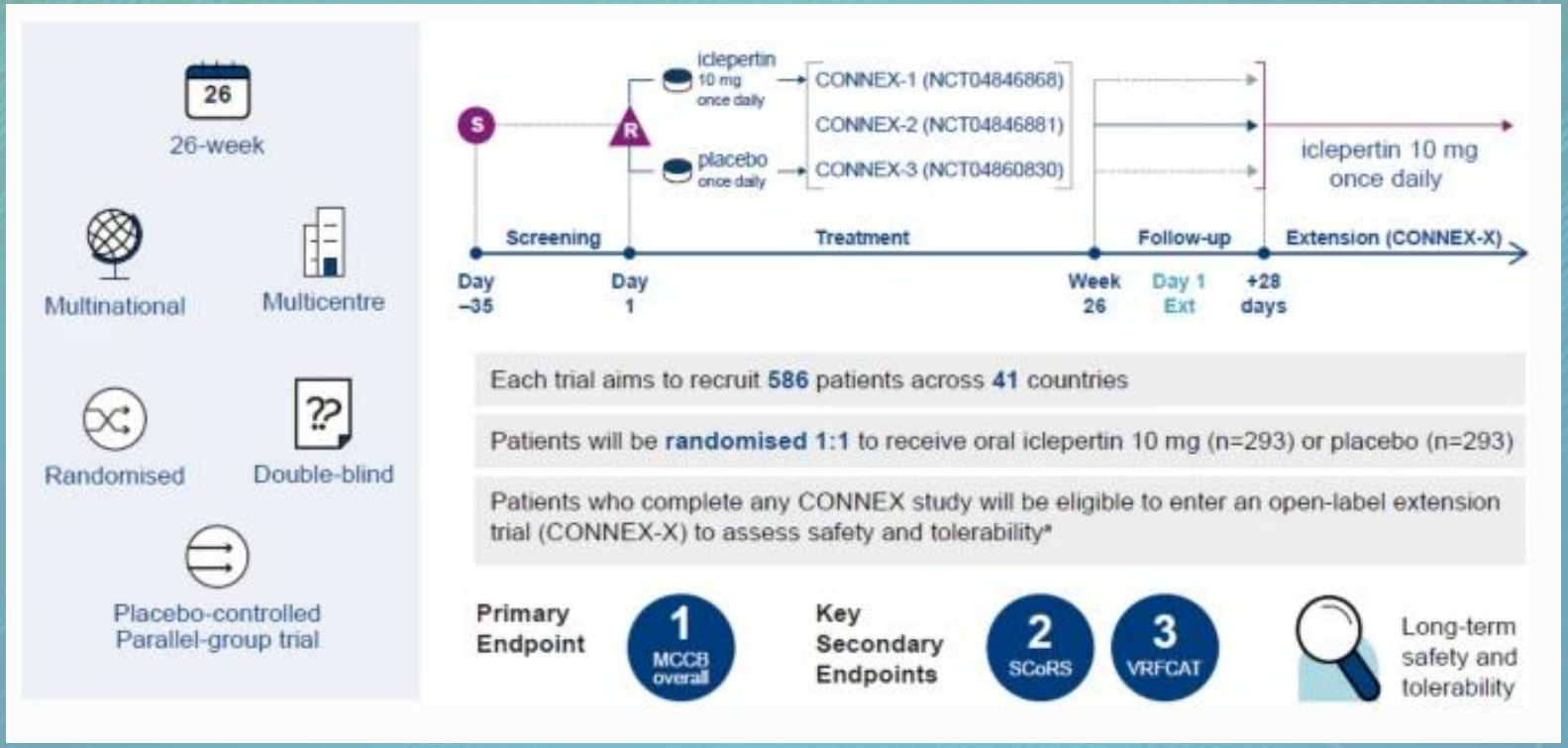
- 509 patients with schizophrenia randomly assigned to either 2, 5, 10, or 25 mg.
- Primary Endpoint was change from baseline in MATRICS Consensus Cognitive Battery (MCCB) overall composite T-score at week 12.
- 10 and 25 mg showed significant improvements from placebo, but 2 and 5 mg did not.



Fleischhacker, W Wolfgang et al. The Lancet Psychiatry (2021) 8(3), 191- 201

Iclepertin (BI 425809) Currently Collecting Phase III Data

- Granted “breakthrough therapy” designation (BTD) by the US FDA in 2021 for cognitive impairment associated with schizophrenia
- Phase III CONNEX trials



de Bartolomeis A et al. Front Psychiatry 2020;11(369):1-20; March M et al. Exp Opin Drug Metab Toxicol 2021;17(4):483-93; Bugarski-Kirola et al. Biol Psychiatry 2017;82(1):8-16; Rosenbrock H et al. Eur Arch Psychiatry Clin Neurosci 2023;273(7):1557-66.

Summary

- Glutamatergic synapses play a key role in regulating aspects of synaptic plasticity that contribute to psychiatric disorders like depression, anxiety, and cognitive impairment
- New drugs like ketamine and TRPC 4/5 inhibitors can modulate synaptic activity associated with glutamate to help treat psychiatric conditions
- Glutamatergic signaling can be modulated by glycine, which provides an important regulatory site that can be exploited for therapeutic gain as is the case for GLYT1 inhibitors

Posttest Question 1 of 3

Which of the following is true regarding the role of AMPA and NMDA receptors in long-term potentiation?

1. AMPA receptor depolarization displaces Mg2+ ion on NMDA receptors, resulting in LTP
2. NMDA receptor depolarization displaces Mg2+ ion on AMPA receptor, resulting in LTP
3. AMPA receptor depolarization allows for the influx of Mg2+ ions through the NMDA receptor, resulting in LTP
4. NMDA receptor depolarization allows for the efflux of Mg2+ ions through the AMPA receptor, resulting in LTP

Posttest Question 2 of 3

What is the result of the glutamate burst hypothesis associated with the therapeutic effects of ketamine?

1. Neurogenesis
2. Synaptogenesis
3. Increased NMDA receptor expression
4. Increased AMPA receptor expression

Posttest Question 3 of 3

From a neural circuitry perspective, which of the following accurately describes the mechanism of anxiety reduction by TRPC 4/5 inhibitors?

1. TRPC 4/5 inhibitors work in a similar way to ketamine to block NMDA receptor signaling
2. TRPC 4/5 inhibitors disinhibit amygdala pyramidal neurons
3. TRPC 4/5 inhibitors reduce cortico-striatal loop activity
4. TRPC 4/5 inhibitors prevent AMPA receptor signaling