Mechanisms of Rapid Antidepressant Efficacy:

Insights from Ketamine, its Isomers and Metabolites

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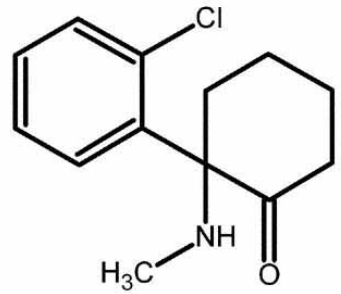

Disclosures

Sources of Research Support

1. Department of Veterans Affairs, VA National Center for PTSD
2. Department of Veterans Affairs/Department of Defense, Consortium for the Alleviation of PTSD
3. National Center for Advancing Translational Science, NIH
4. National Institute on Alcohol Abuse and Alcoholism
5. National Institute of Mental Health

Speaker's Bureau: None

Paid Editorial Relationship

Biological Psychiatry - Editor

Consulting Relationship (3 yr; >$5,000)

Biogen, Boehringer-Ingelheim, Cerevel, Janssen, Jazz, Neurocrine, Novartis, Takeda,

Stock Equity

Biohaven Pharmaceuticals, EpiVario
RBNC, Sage, Spring, Terran

Patents:

1. Glutamatergic treatments (licensed to Biohaven Medical Sci)
2. Intranasal ketamine for depression and suicide (licensed to Janssen Pharmaceuticals)
3. AMPA-R antagonist for alcoholism
4. Naloxone to reduce ketamine abuse liability
5. Decision support for antidepressant treatment

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BRAIN & BEHAVIOR RESEARCH FOUNDATION
Awarding NARSAD Grants

U.S. Department of Veterans Affairs

NIH National Institute of Mental Health

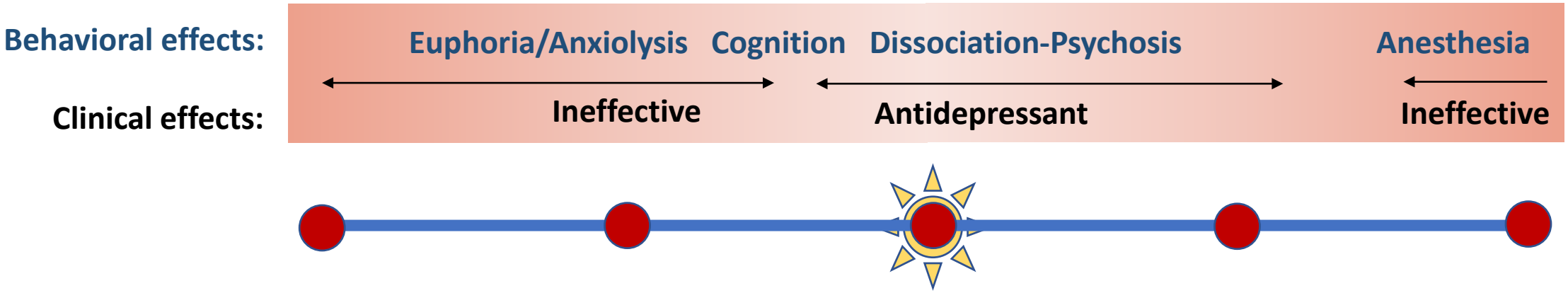
NIH National Center for Advancing Translational Sciences

NIH National Institute on Alcohol Abuse and Alcoholism

Outline

- How do we think R/S-ketamine (Ketamine) and S-ketamine (Esketamine) work?
- What other drugs are implicated? (R-ketamine, 2R,6R-HNK, etc.)

Dose-related R/S-ketamine effects in depression

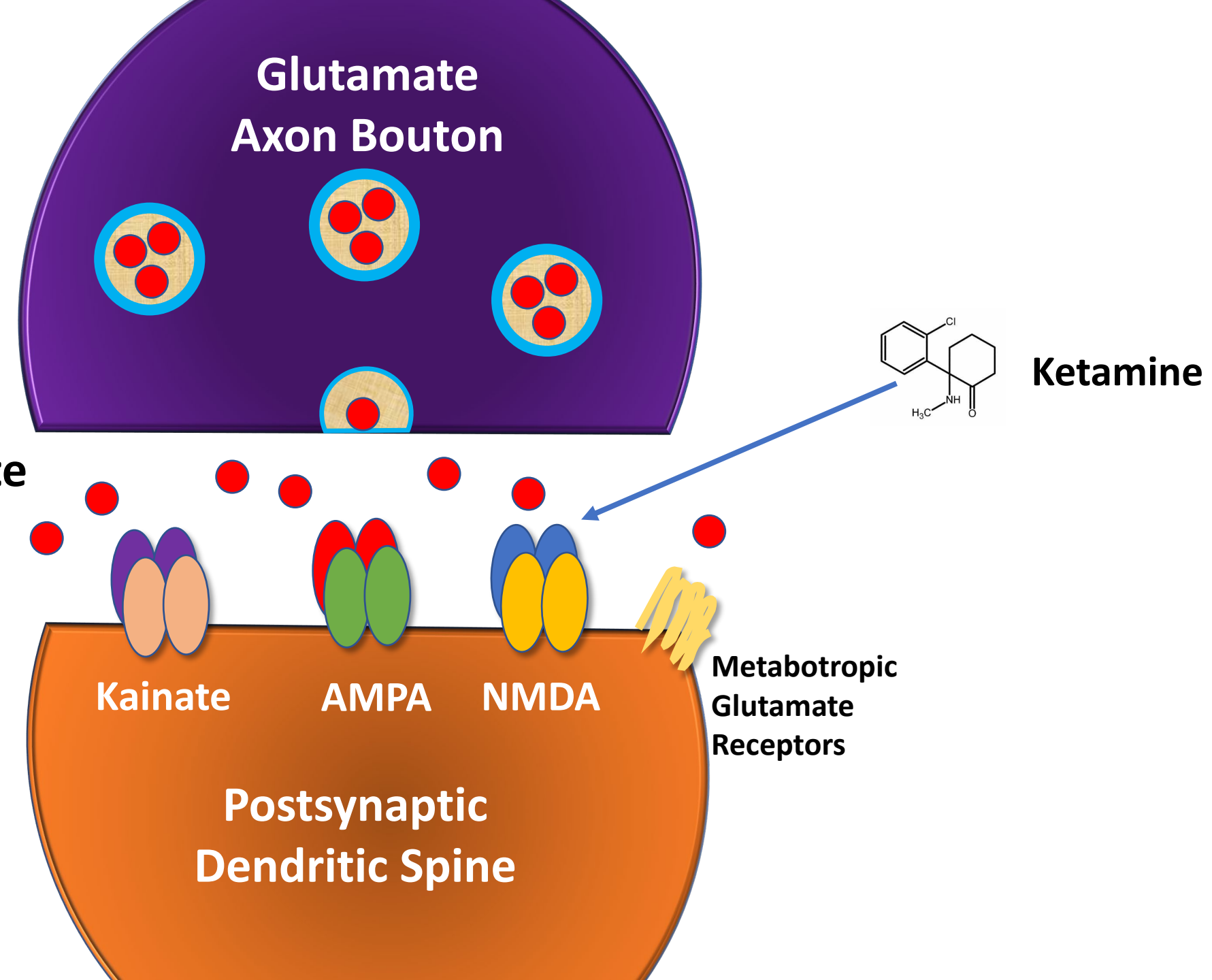


Dose*:	0 mg/kg	0.2 mg/kg	0.5 mg/kg	1.0 mg/kg	≥2.0 mg/kg
Plasma:	0 ng/ml	88 ng/ml	220 ng/ml	440 ng/ml	≥880 ng/ml
µM:	0 µM	0.2 µM	0.5 µM	1.0 µM	≥2.0 µM
% Occ:			~30-40%		

*: based on 40-minute i.v. infusion

Krystal et al. AGP 1994, Krystal et al. Psychopharm 1998, Krystal et al. Psychopharm 1999, Krystal et al. AGP 1998, Khlestova et al. J Neuroscience 2016, Shaffer et al. Neuropharm 2014, Berman et al. 2000, Su et al. NPP 2017, Fava et al. Mol Psychiatry 2020

Ketamine blocks the N-methyl-D-aspartate glutamate receptor



R/S-ketamine potencies (Ki)

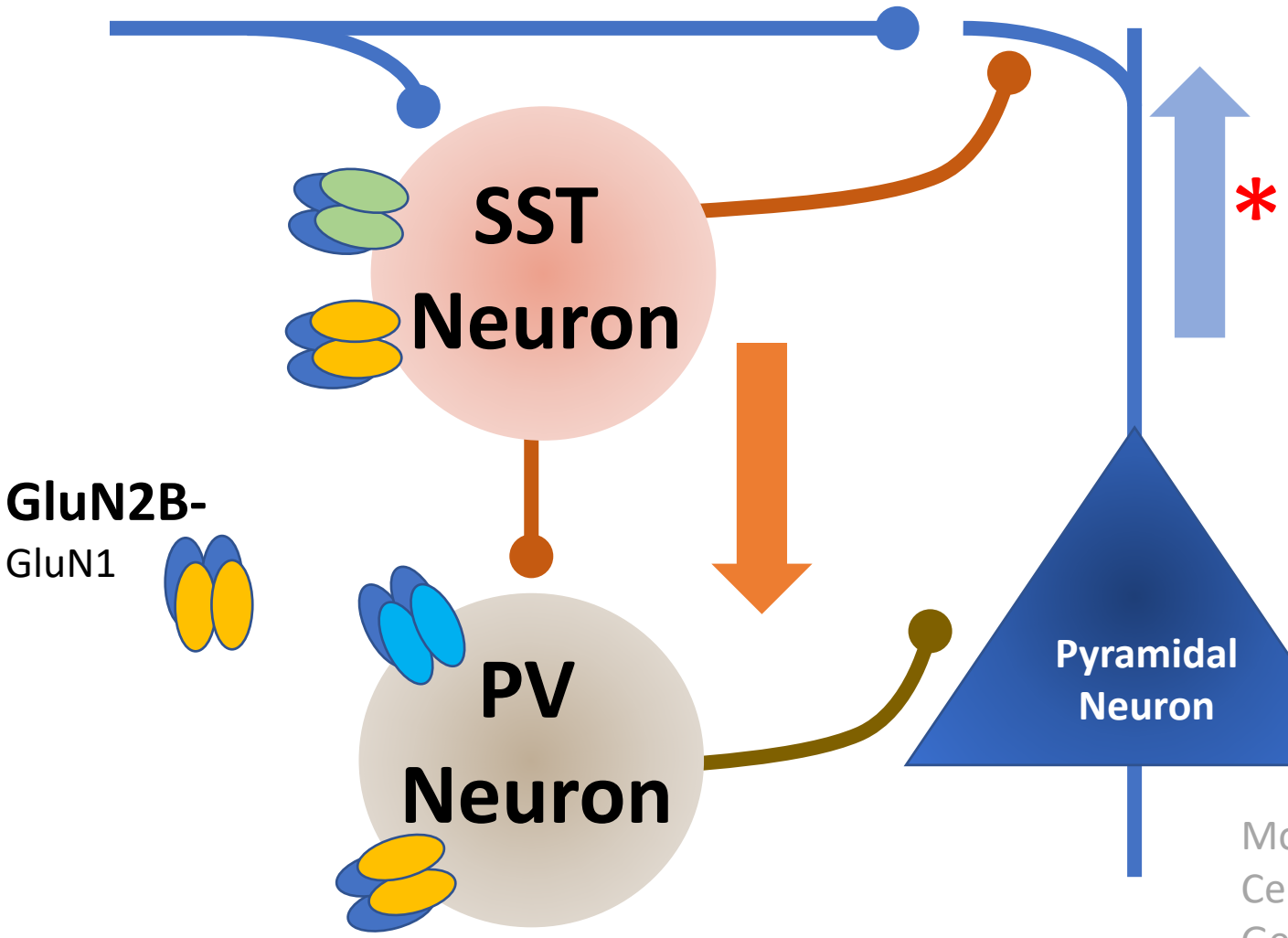
Site	Ki (μM)
NMDA: GluN2C	**1.18**
NMDA: Glun2D	**2.95**
NMDA: Glun2B	**5.08**
NMDA: Glun2A	**5.35**
TrkB	**1.05**
DRD2	**0.5* (high affinity state of DRD2)**
HCN1	10.0
5HT2A	15.0
nACHR (alpha/beta/gamma/delta)	18.7/15.2/20.4/19.4* (30% of ketamine's activity)
nACHR alpha7	20.0
M1/M2/M3	45/294/246
Voltage-gated sodium channel	146.7

Lower Mg+2 Affinity

Subanesthetic

Zanos P et al. JPET 2018, Chen X et al. J Neurosci 2009; Khlestova E et al. J Neurosci 2016; Lodge D et al. Neurosci Lett 1982; MacDonald et al. J Neurophysiol 1987; Orser et al. Anesthesiology 1997, Casarotto et al. Cell 2021

Ketamine antidepressant effects depend on transient inhibition of SST and PV inhibitory neurons



- Ketamine inhibition of inhibitory neurons (SST and PV neurons):
  - Increases glutamate release
  - KO of GluN2B occludes AD response
- NO effect on AD response:
  - KO of GluN2B on pyramidal neurons (Gerhard; but see Miller)
  - KO of GluN2A
- Psychedelics directly activate dendrites*

Monyer et al. Neuron 1994, von Engelhardt et al. Front Cell Neurosci 2015, Krystal et al. Biol Psych 2017; Gerhard et al. JCI 2019, Miller et al. 2017

Humans: Ketamine induced glutamate release is associated with dissociation and antidepressant response

- Increases cortical glutamate release in HS and depressed (13C-MRS/13C-glucose)
- Elevations in glutamate (1H-MRS) associated with psychosis-dissociation in HS
- Induced GLU release correlates with AD response (11C-ABP688, PET)

Abdallah et al. NPP 2018, Stone et al. Mol Psychiatry 2012, Esterlis et al. Mol Psychiatry 2018, Gilbert and Zarate PBB 2020

Initial effects vs. antidepressant effects on gene expression

“Intoxication”

First 120 minutes: Activation

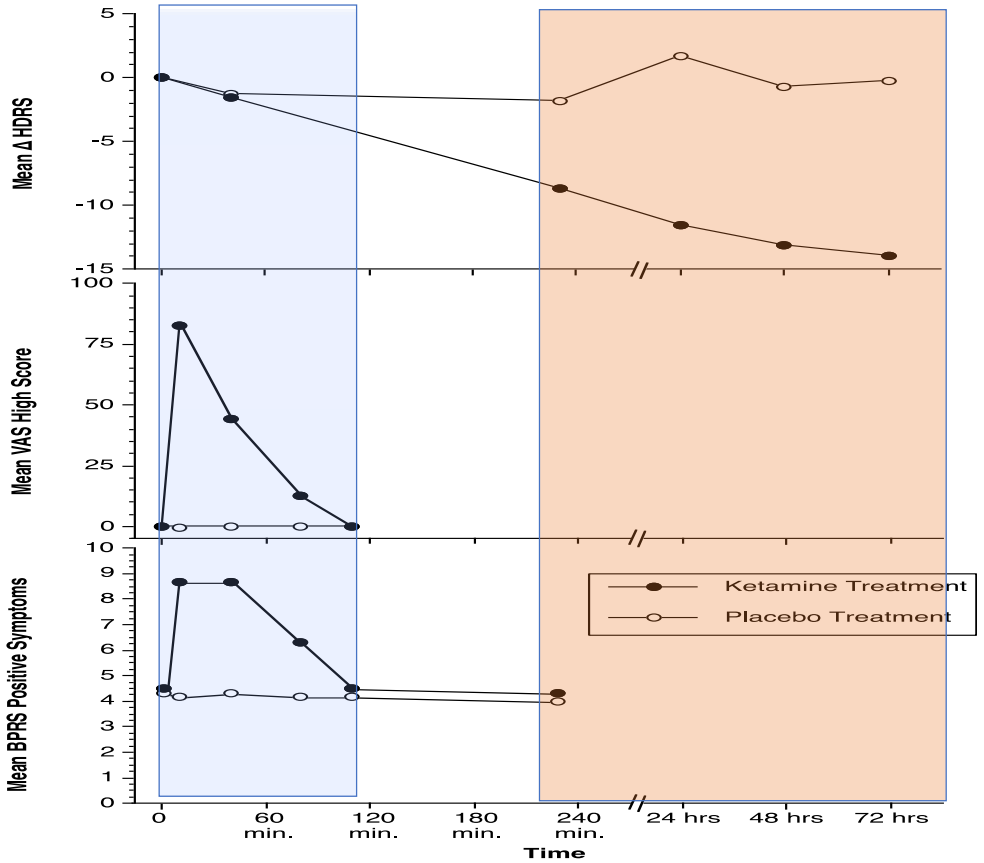
Genes: Arc, pERK, Akt/mTORC1

“Antidepressant”

6+ Hours: New Synapses

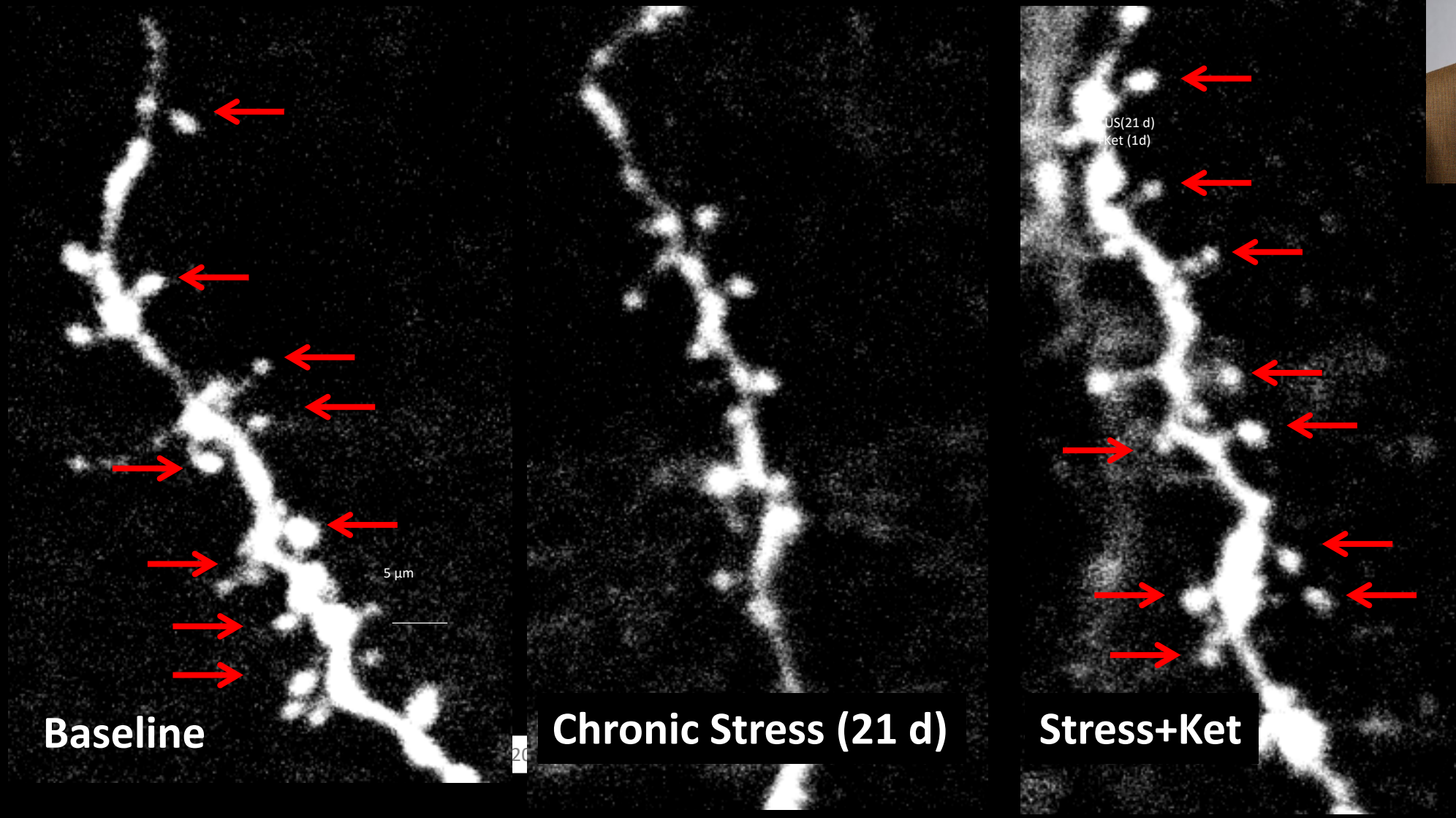
Presynaptic genes: Synapsin 1, SV2A

Postsynaptic Genes: PSD95, GluR1

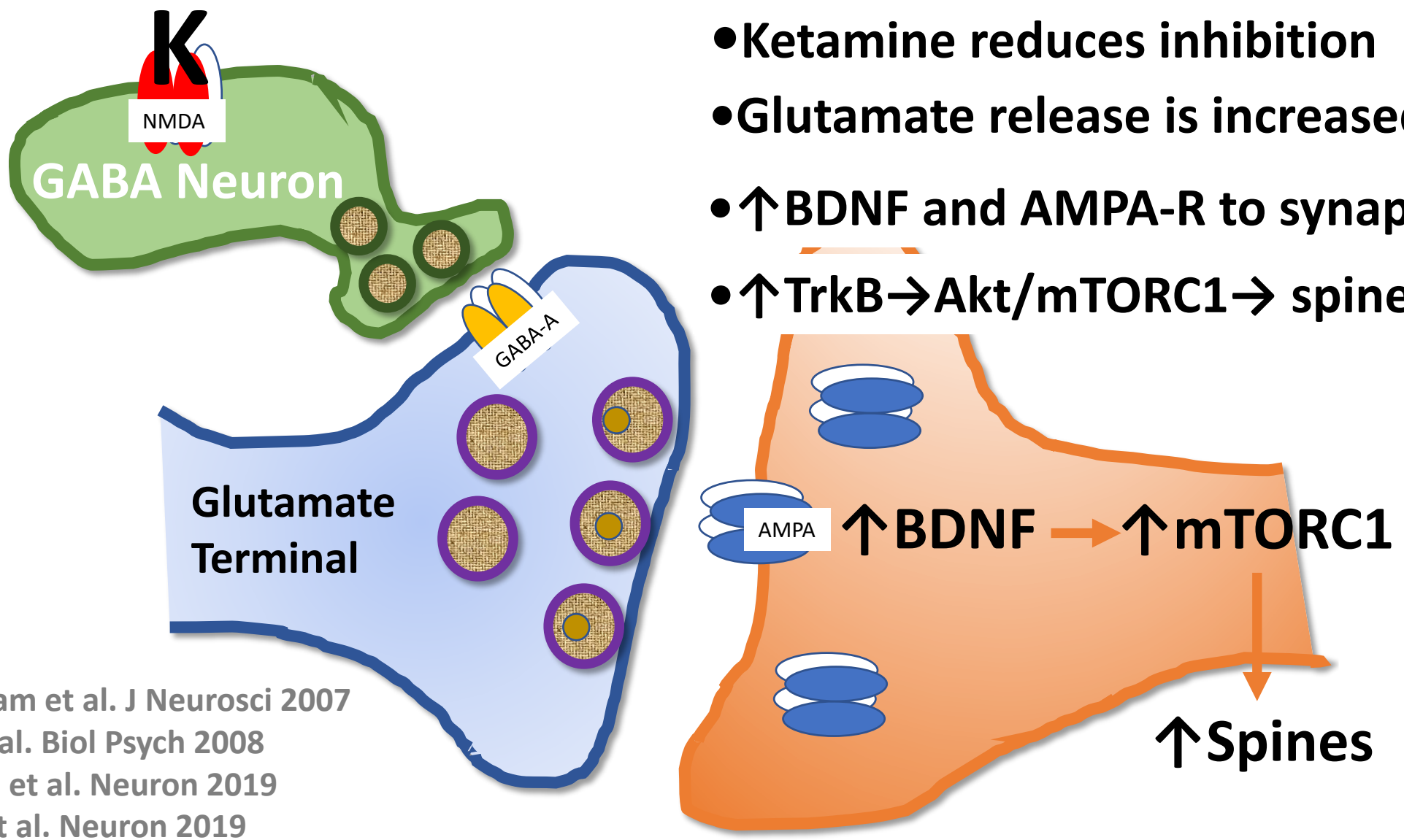


R. Berman et al. Biol Psychiatry 2000, Li et al. Science 2011, Muller et al. J Psych Res 2013

Ketamine stimulates rapid regrowth of synaptic connectivity in these regions
Duman and Aghajanian Science 2012



Presynaptic "Duman" Model:

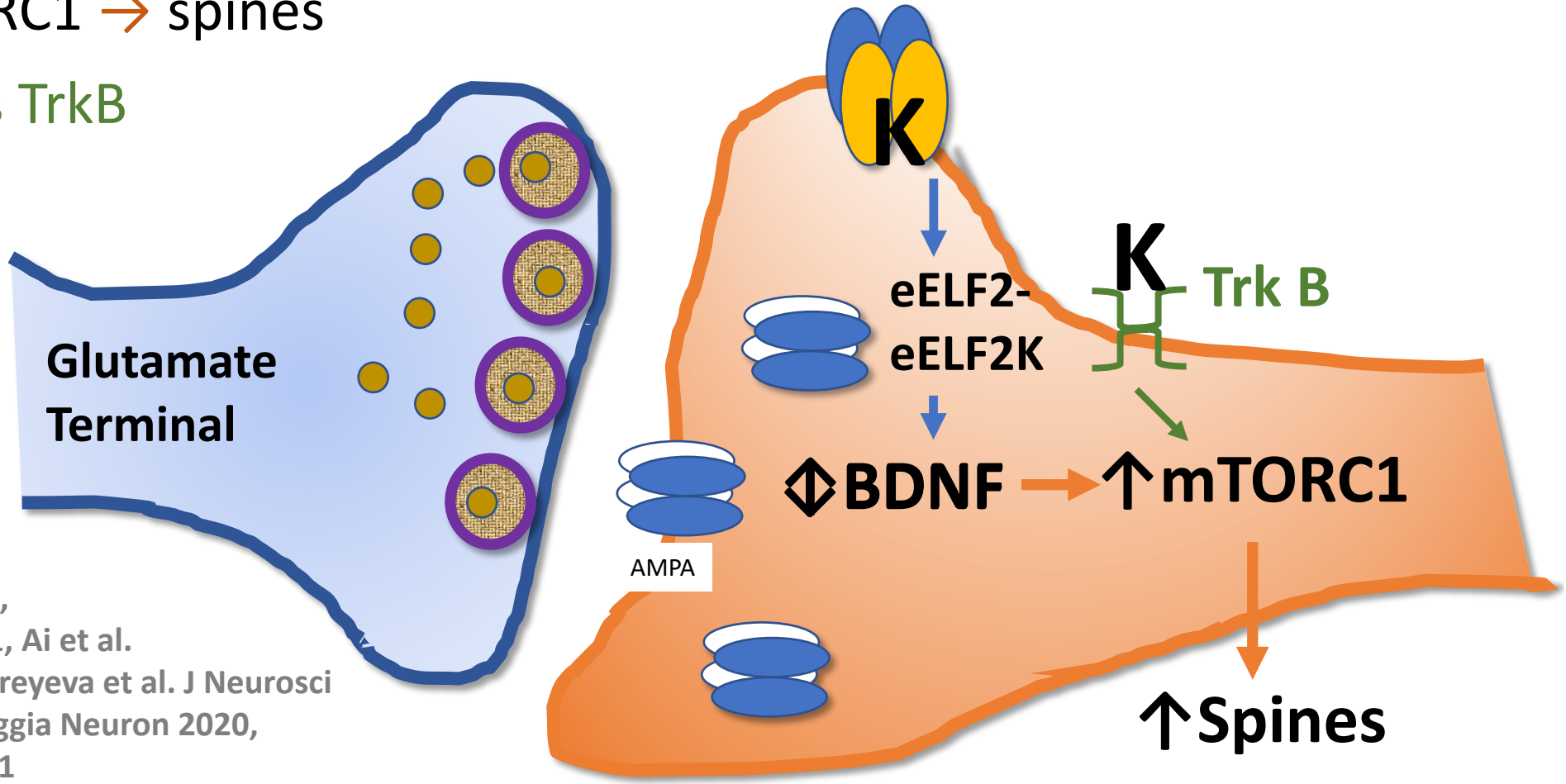


- Ketamine reduces inhibition
- Glutamate release is increased
- ↑BDNF and AMPA-R to synapse (onset)
- ↑TrkB→Akt/mTORC1→ spines (maint.)

Moghaddam et al. J Neurosci 2007
Maeng et al. Biol Psych 2008
Duman RS et al. Neuron 2019
Krystal J et al. Neuron 2019
Moda-Sava et al. Science 2019

Postsynaptic “Monteggia/Kavalali” Model:

- ↑Spontaneous Glu via GluN2B → ↑eELF2/eELF2K → ↓BDNF and ↓GluA1
- Ket block of GluN2B → ↑BDNF and AMPA-R to synapse
- ↑Akt/mTORC1 → spines
- K stimulates TrkB



Hardingham & Bading
Nat Rev Neuroscie 2010,
Autry et al. Nature 2011, Ai et al.
Neurosci Lett 2011, Nosreyeva et al. J Neurosci
2013, Kavalali & Monteggia Neuron 2020,
Casarotto et al. Cell 2021

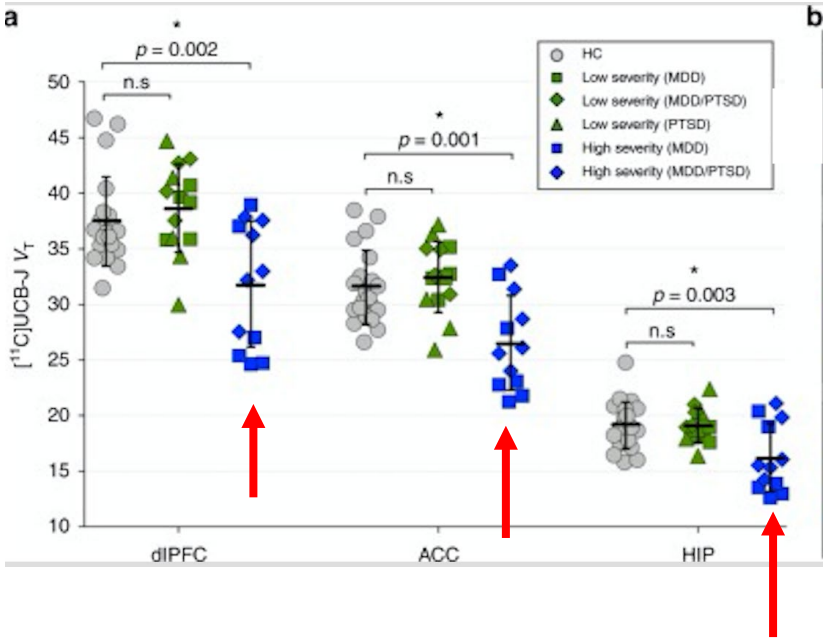
Different biology for initiation and maintenance of antidepressant effects

- **Initiation of AD effects:** enhanced function (AMPA)
- **Maintenance of AD effects** is spine-dependent
  - Lost spines are “restored” (no general spine increase)
  - Duration of AD response related to maintenance of spines
  - If restored spines were “permanent” would antidepressant response be “permanent”?

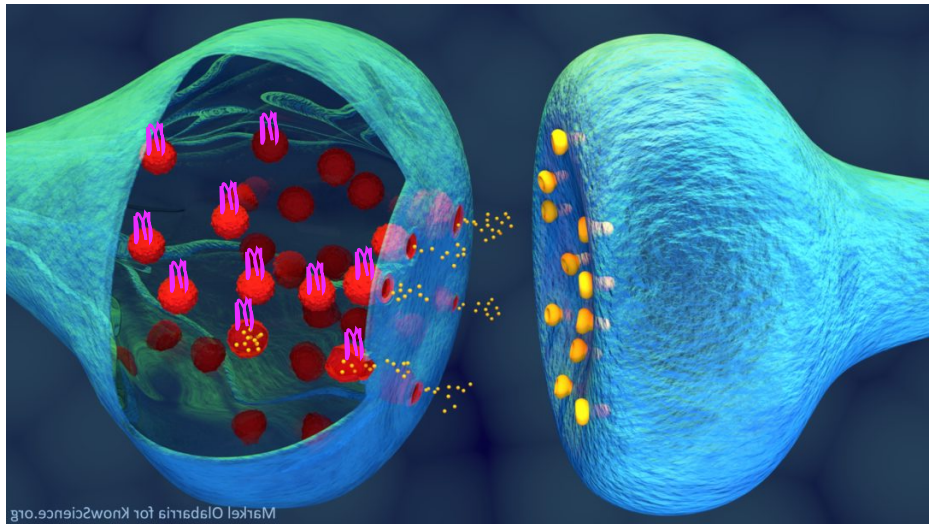
Phoumthipphavong et al. eNeuro 2016; Moda-Sava et al. Science 2019

Reductions in PET synaptic marker (SV2A) correlate with reduced fMRI cortical functional connectivity

Reduced 11C-UCB-J associated with severe depression



Synaptic Vesicle Protein 2A (SV2A)
Localized to Vesicles in Nerve Terminals



I. Esterlis

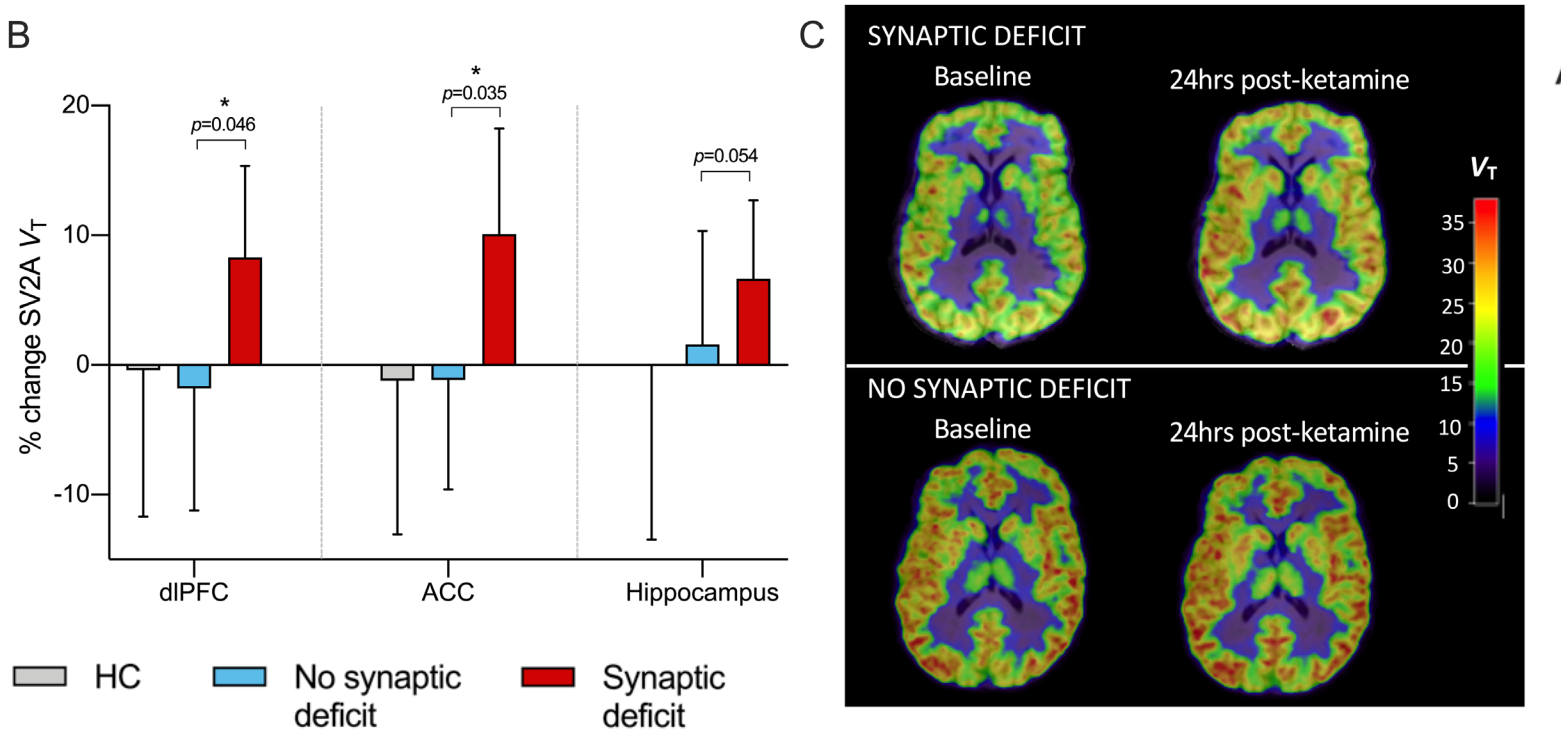
S. Holmes

Holmes et al. Nature Communcations 2019

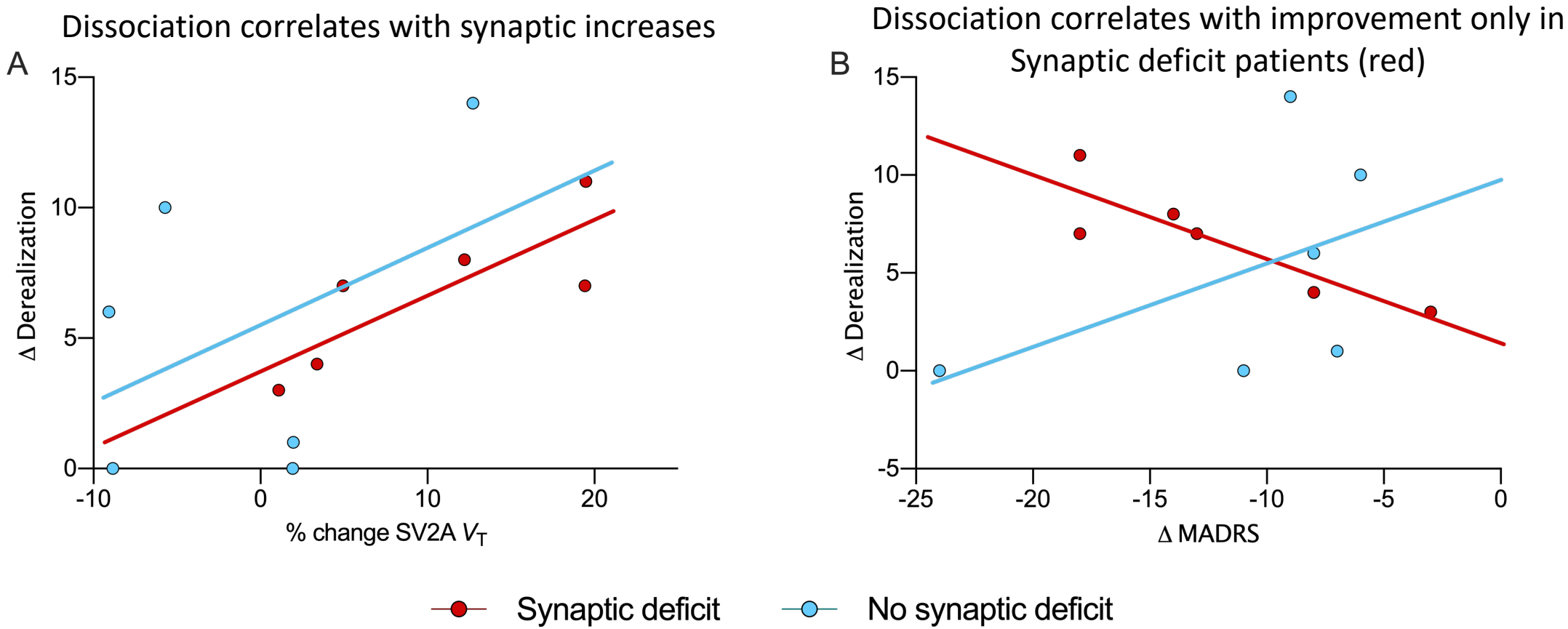
Ketamine restores synapses in TRD subgroup

Holmes et al. *in review,* 2021

Only increases synapses in TRD with synaptic deficits (PET: 11C–UCB-J; SV2A)

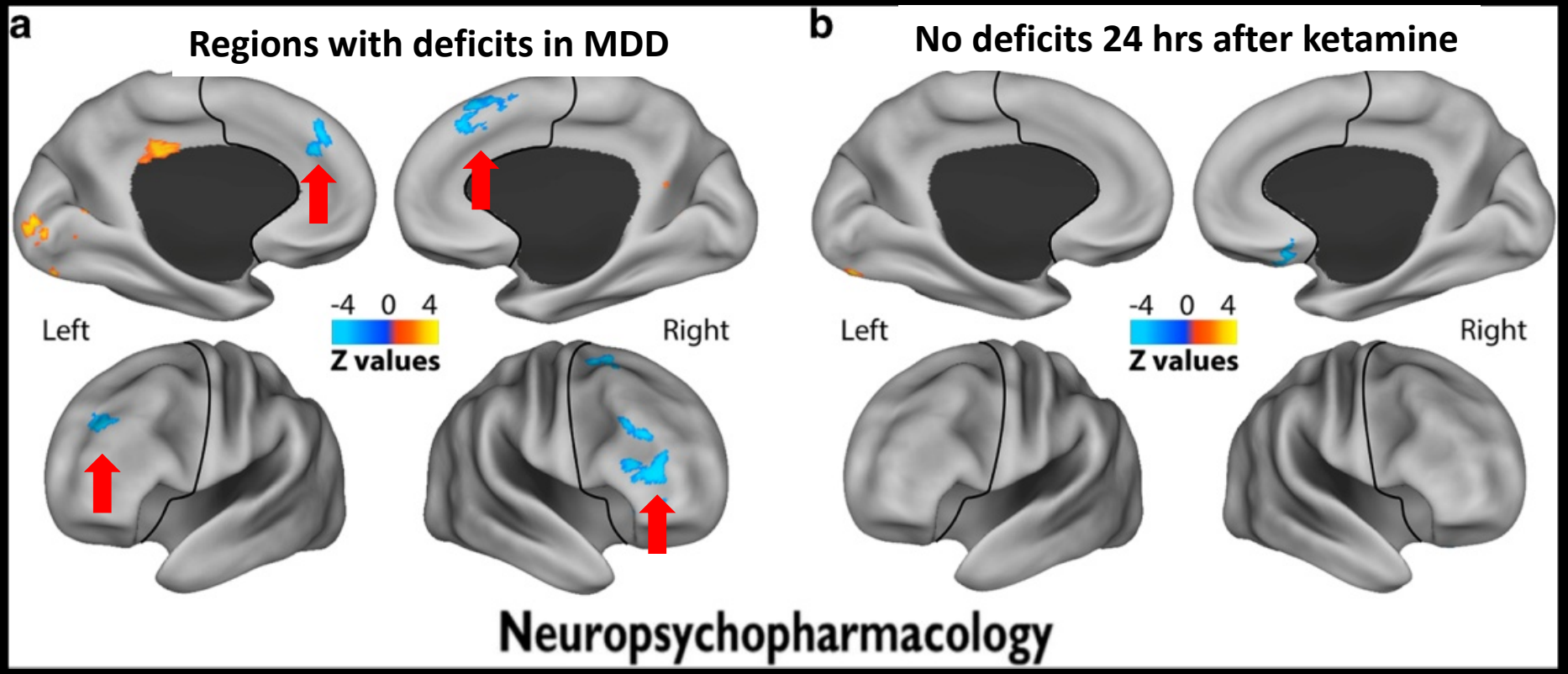


Dissociation: associated with synaptic increases but antidepressant response only in “synaptic deficit” patients



Holmes et al. in review 2021

Ketamine stimulates rapid restoration of functional connectivity in depressed patients



Chadi Abdallah C et al. NPP 2016

Could behavioral interventions increase efficacy?

- During ketamine: Reduced neuroplasticity
  - Ketamine powerfully interferes with learning (Krystal)
  - Retards rate of extinction in animals when given after learning (Scavio, Clifton)
  - **Ketamine appears to interfere with reconsolidation** of alcohol memories in AUD (Das) and trauma memories in PTSD (Duek)
- 24 Hours after ketamine: Increased neuroplasticity
  - In animals: **ketamine increases fear extinction rate** (Girgenti)

Krystal et al. AGP 1994, Psychopharm 1998, Psychopharm 1999; Scavio et al. Behav Neurosci 1992; Clifton et al. J Psychopharm 2018; Das et al. Nature Comm 2019; Duek et al. in review 2021; Girgenti et al. Neurobiol Dis 2017

Outline

- How do we think R/S-ketamine (Ketamine) and S-ketamine (Esketamine) work?
- **What other drugs are implicated? (R-ketamine, 2R,6R-HNK, etc.)**

Other R-ketamine and S-ketamine targets only engaged at anesthetic doses of R/S-ketamine (>5x)

Table III. Affinity of ketamine enantiomers for various receptors[30]

Receptor	K_i (μmol/L)	
	S-(+)-ketamine	*R*-(−)-ketamine
NMDA	0.9[a]	2.5[a]
Opioid μ	28.6[a]	83.8
Opioid κ	23.7[a]	60.0
Opioid δ	205.0	286.0
Opioid σ	131.0	19.0[a]
Muscarinic acetylcholine	125.0	91.0
Dopamine transporter	46.9[a]	390.0
Noradrenaline (norepinephrine) transporter	64.8	68.9
Serotonin transporter	156.0	148.0

a High affinity for the site.

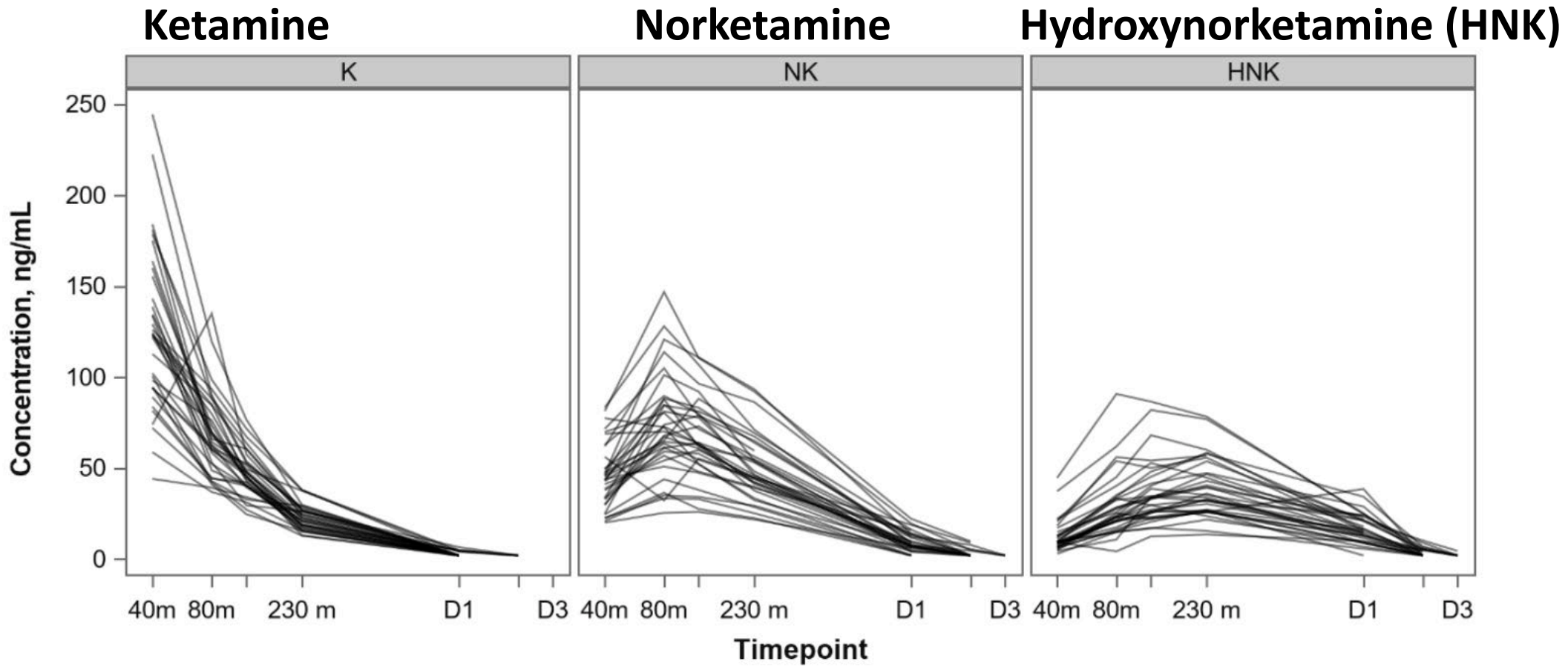
K_i = inhibition constant.

Wolf K, Wistock AR CNS Drugs 2006

Some candidate RADs

- Increased dendritic excitability:
  - Muscarinic antagonists (scopolamine)
  - 5HT2A agonists (psychedelics)
  - GABA-A partial inverse agonists
  - AMPAkine
- Increased glutamate release
  - mGluR2 antagonists (HNK?)
  - 5HT2A agonists (psychedelics)
- Pro-BDNF/TrkB signaling
- Enhance mTORC1 (Navitor)

Plasma HNK levels peak with emergence of antidepressant effects



Farmer et al. NPP 200, fig S4; n=34

But HNK levels are associated with poorer clinical response at days 3 and 7 after ketamine

- **Ketamine** plasma levels (AUC, Cmax) **positively** correlated with antidepressant effect at post-ketamine day 11
- **2R,6R HNK** plasma levels **negatively** correlated with antidepressant effect at post-ketamine days 3 and 7
- **HNK** plasma levels did not mediate ketamine antidepressant effects

Farmer et al. NPP 2020; n=34

Summary: Ketamine MOA

- Ketamine blockade of NMDA-R most likely target
- Two key hypotheses:
  - Increased glutamate release: AMPA-R and mTORC1 dependent
  - Blockade of postsynaptic GluN2B-NMDA-R: eELF2/eELF2K
- Induction via enhanced synaptic function
- Maintenance via enhance synaptic structures
- Numerous potential novel mechanisms implicated

Dissociation: a sign of adequate target engagement or contributor to treatment efficacy?

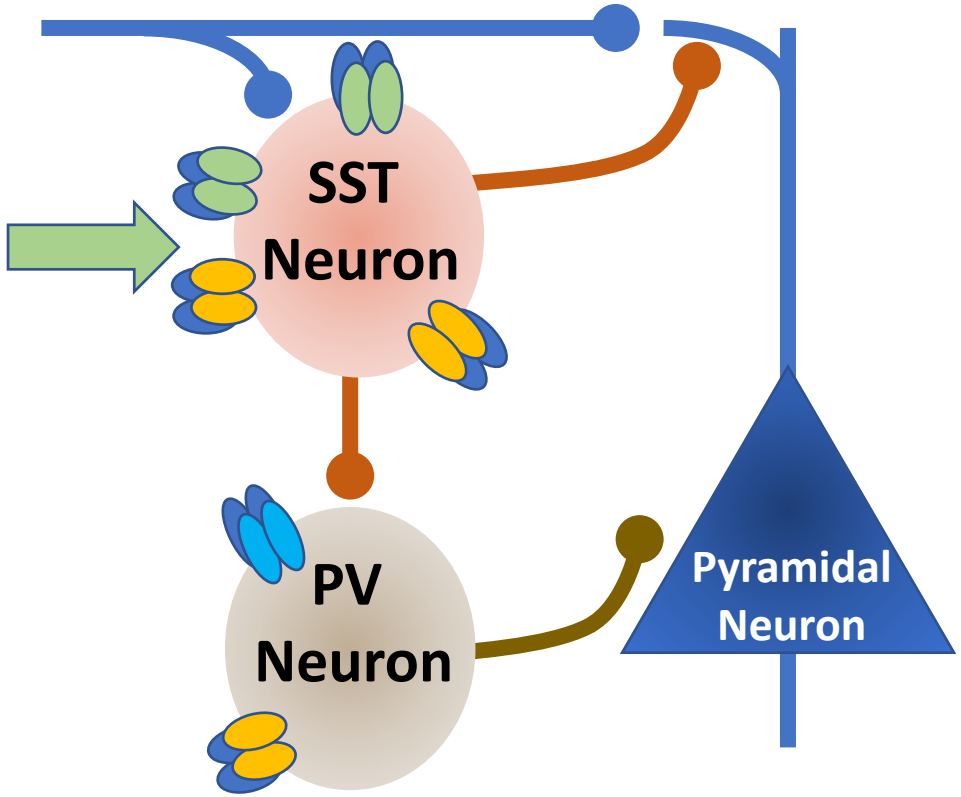
- Ketamine:
  - Dissociation/psychosis with NMDA-R occupancy in HS (Stone)
  - Associated with efficacy across TRD studies (Ballard and Zarate)
  - Associated with synaptic increases and efficacy in TRD w/ synaptic deficits, but not efficacy w/o synaptic deficits (Holmes)
  - Increasing dissociation not increase efficacy (Fava) and some patients respond with minimal dissociation (Singh et al.)
- Other NMDA-R antagonists without dissociative effects at tested doses have not succeeded in clinical trials

Stone et al. Psychopharm 2008, Ballard and Zarate Nature Comm 2020, Holmes et al. in review 2021, Fava et al. Mol Psychiatry 2020, Singh et al. Biol Psychiatry 2016,

Deficits in SST neurons after US in animals and in depression and PTSD may increase role for PV neurons – GluN2D/2B

Healthy: SST more ketamine sensitive than PV?

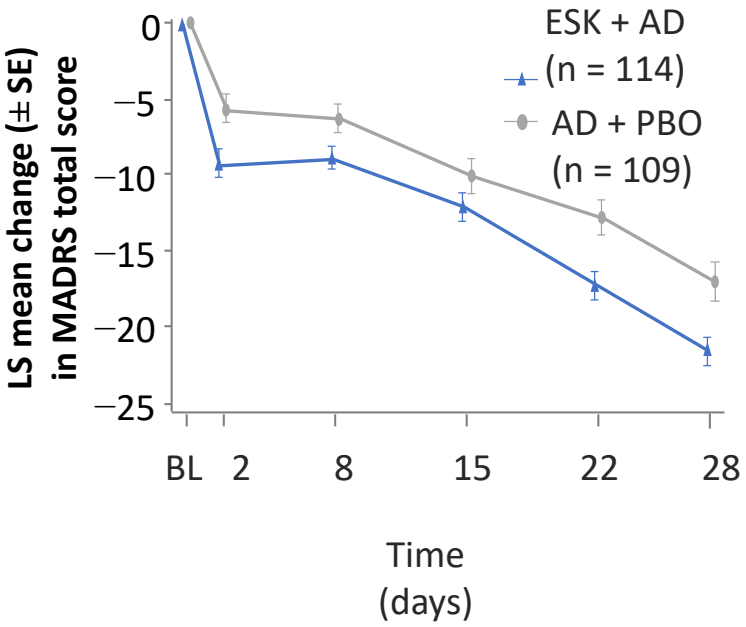
GluN2C and NMDA/AMPA ratio



Khlestova et al. J Neurosci 2016, Krystal et al. Biol Psychiatry 2017, Fee et al. Biol Psychiatry 2017, Maccaferri and Dingledine JN 2002, Hull et al. JN 2009, Rotaru et al. JN 2011, Banasr et al. Chronic Stress 2017, Fee et al. IJNPP 2021, Ren et al. Biol Psychiatry 2016

Little knowledge about time-dependent ketamine effects at longer scale: Why doesn't ketamine *cure* depression?

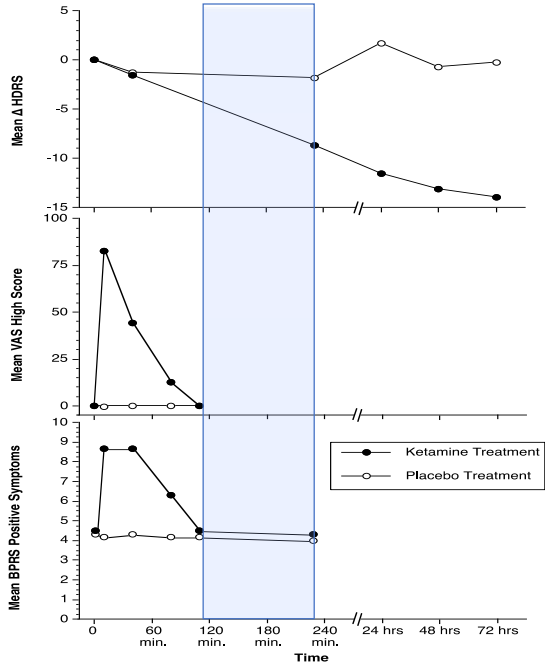
Cumulative effects with
repeated treatment (Esketamine)



Popova V, et al. Poster presented at ASCP 2018; no. W30; "Hypothetical patient"; Abdallah et al. NPP 2020

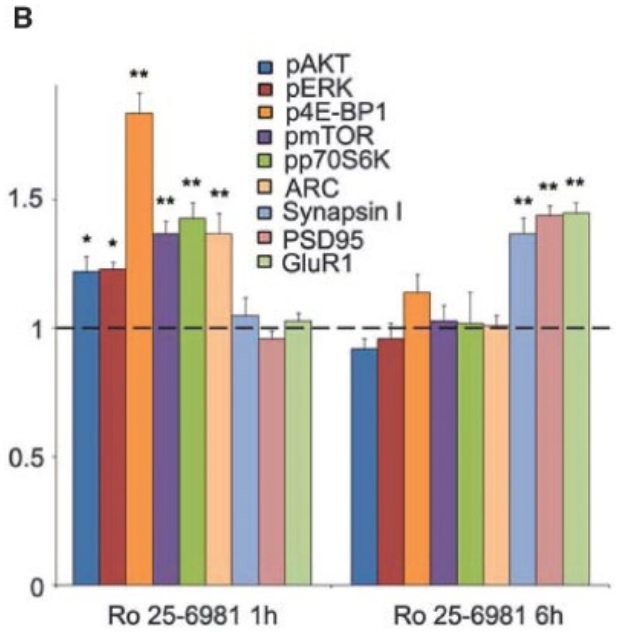
Antidepressant effect is distinct from the symptoms of acute intoxication

Time gap between intoxication and mood changes in patients (n=7)



R. Berman et al. Biol Psychiatry 2000

In animals:
Acute (1hr): neural activation
Delayed (6 hr): new synapses



Li et al. Science 2010