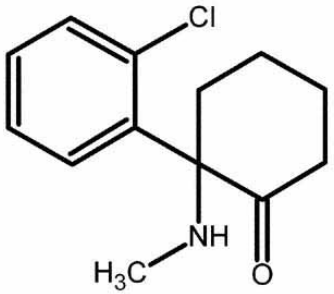
Rapid Acting Antidepressants:

Opportunities and Mechanisms

John H. Krystal, M.D.

Yale University



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BRAIN & BEHAVIOR RESEARCH FOUNDATION
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NIH National Center for Advancing Translational Sciences

NIH National Institute on Alcohol Abuse and Alcoholism

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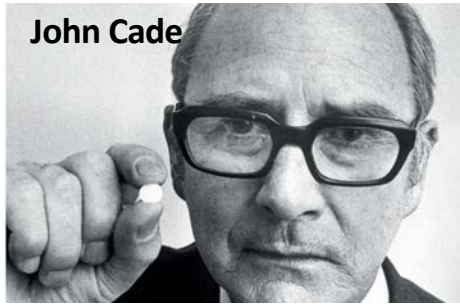
BioHaven Medical Sciences, Terran, Cadent, Blackthorn, Spring

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

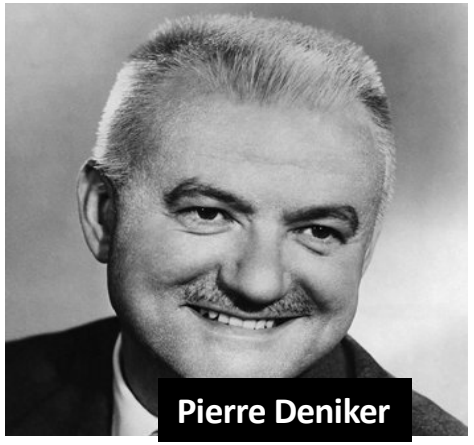
Antidepressants: Early Triumphs

Lithium



1949

”Antipsychotic” D2/-5HT2 Antagonism

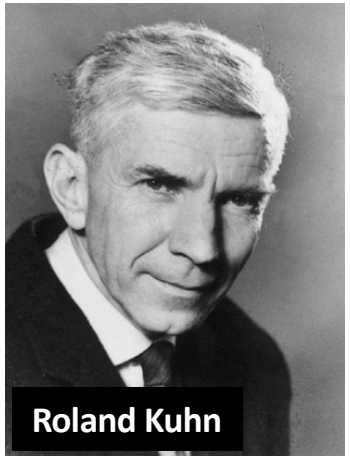


1953

MAO Inhibition

1957

Serotonin-Norepinephrine Reuptake Inhibitors



1957

Health

In biggest advance for depression in years, FDA approves novel treatment for hardest cases

The nasal spray works in a new way and is based on an old anesthetic, ketamine, that has been used as a party drug.

The U.S. Food and Drug Administration approved a nasal spray, esketamine, to treat depression. (Jacquelyn Martin/AP)

By **Carolyn Y. Johnson** and **Laurie McGinley**
March 5

The Food and Drug Administration approved a novel antidepressant late Tuesday for people with depression that does not respond to other treatments — the first in decades to work in a completely new way in the brain.

The Washington Post
Democracy Dies in Darkness

Outline

- The problem with antidepressants
- Why ketamine?
- From mechanisms to new treatments

Depression is worse than we thought

- **More common:** ~7% (narrow definition) but up to 20% (broad definition)
- **More disabling:** leading cause of disability in adults in U.S.
- **More lethal:**
  - Contributor to rising suicide rate
  - Shortens life by 10 years on average

Anxiety and Depression Association of America, Global Burden of Disease Study, Lancet; U.S. Substance Abuse and Mental Health Administration data; Lawrence et al. BMJ 2013

Antidepressants are less effective than we hoped

- **Too few:** 30% remission initially
- **Too incremental:** 30% non-reponse at 1 year
- **Too slow:** 2 months to remission
- **Too unstable:** ¾ of treatment resistant patients (step 3 and 4) relapse within 1 year

NIMH STAR*D Trial: Gaynes et al. Gen Hosp Psychiatry 2008; Rush et al. CNS Drugs 2009

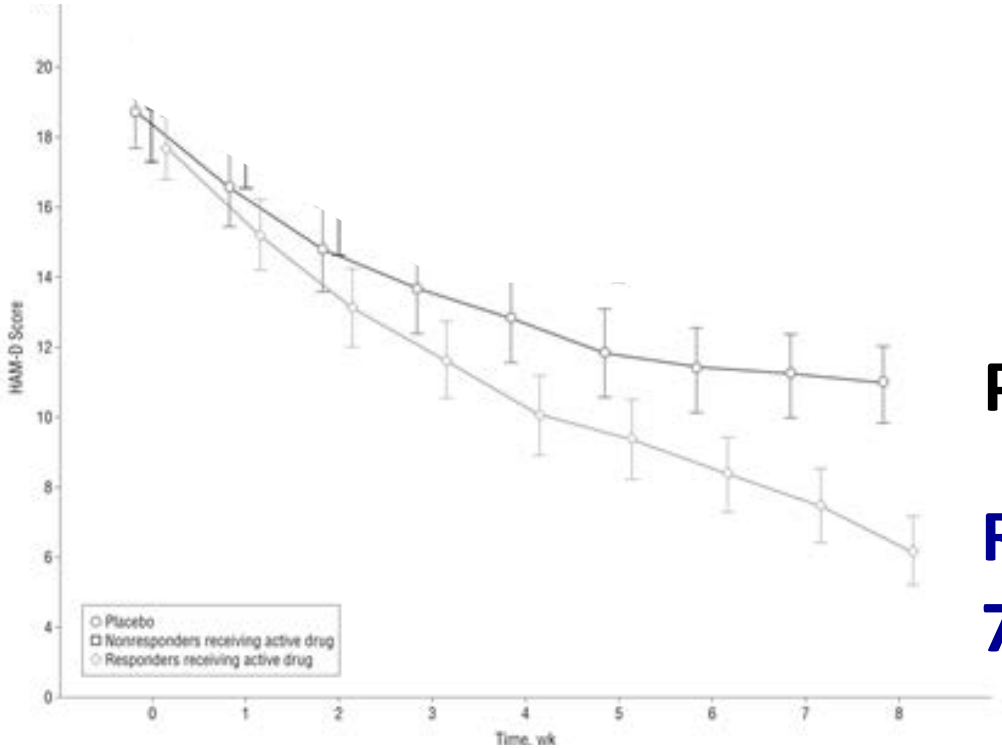
ORIGINAL ARTICLE

Trajectories of Depression Severity in Clinical Trials of Duloxetine

2011;68:1227

Insights Into Antidepressant and Placebo Responses

Ralitza Gueorguieva, PhD; Craig Mallinckrodt, PhD; John H. Krystal, MD



PLACEBO

RESPONDER

76.3%

Outline

- The problem with antidepressants
- **Why ketamine?**

Serotonin and norepinephrine focus based on drugs

Technique	Amine	Which one?
TRYP Depletion	5HT	SSRI
AMPT	NE/DA	NRI
TD + AMPT	5HT/NE/DA	Both

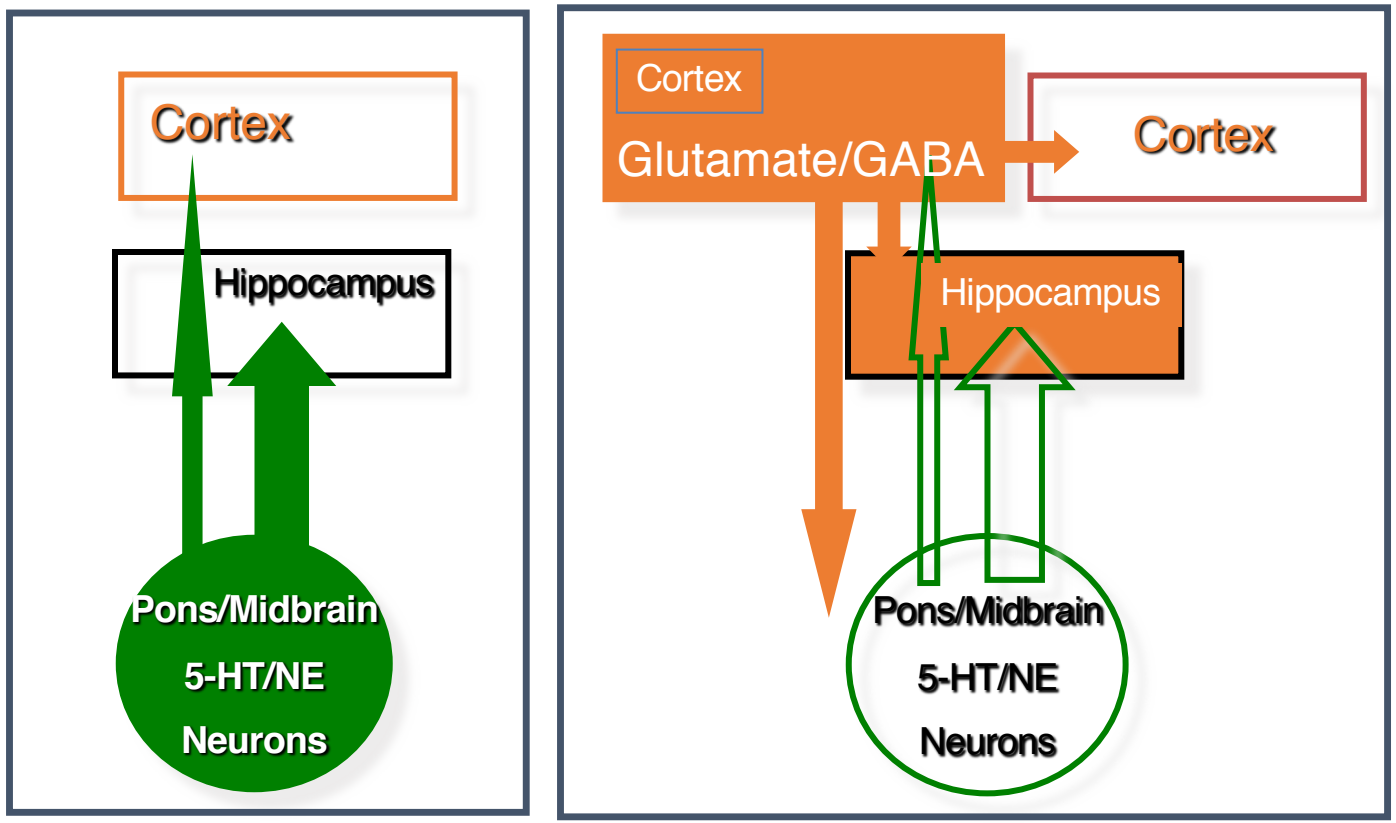
Heninger et al. Pharmacopsychiatry 1996

Serotonin and norepinephrine cannot explain depression

Technique	Amine	Depression?
TRYP Depletion	5HT	No
AMPT	NE/DA	No
TD + AMPT	5HT/NE/DA	No

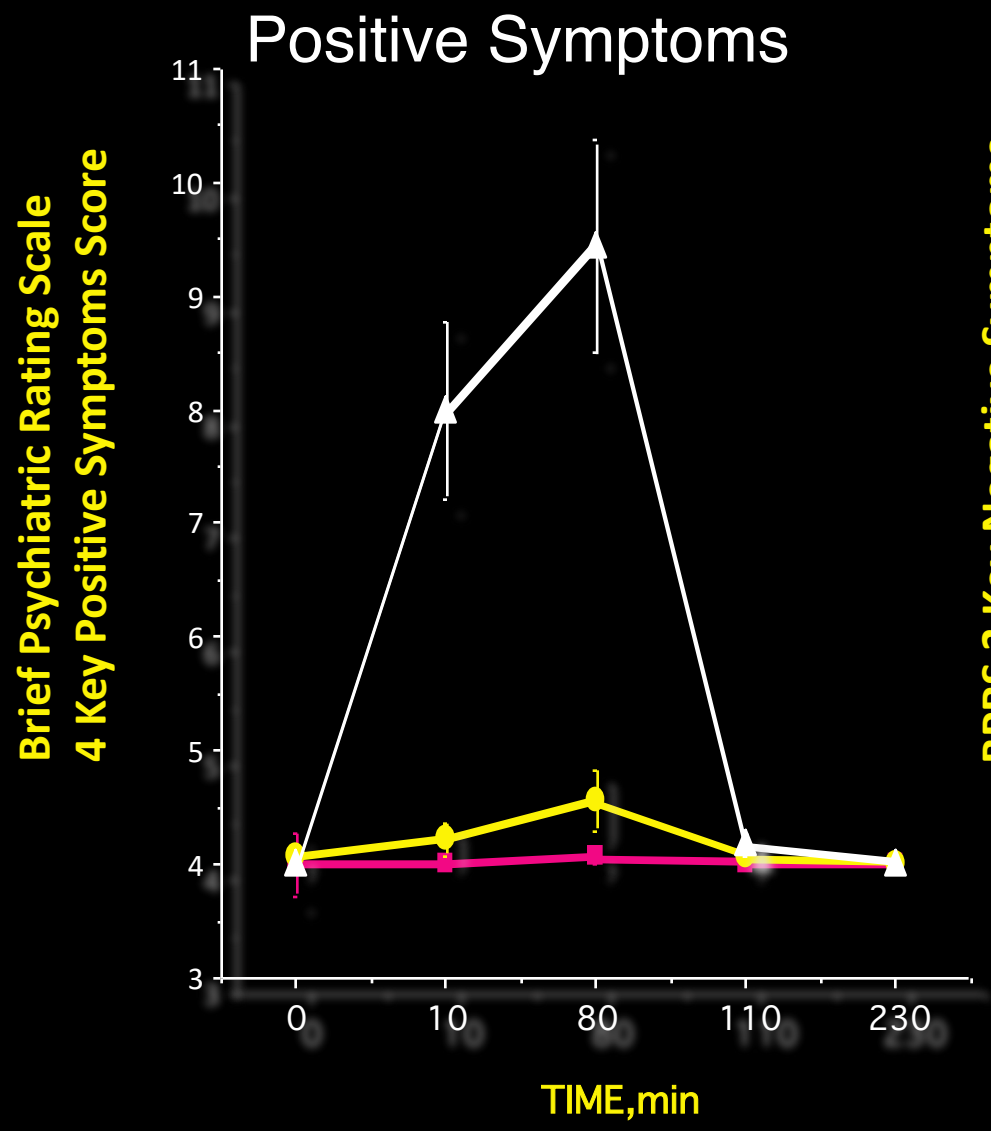
Moreno et al. Biol Psychiatry 1997; Salomon et al. Biol Psychiatry 1997;

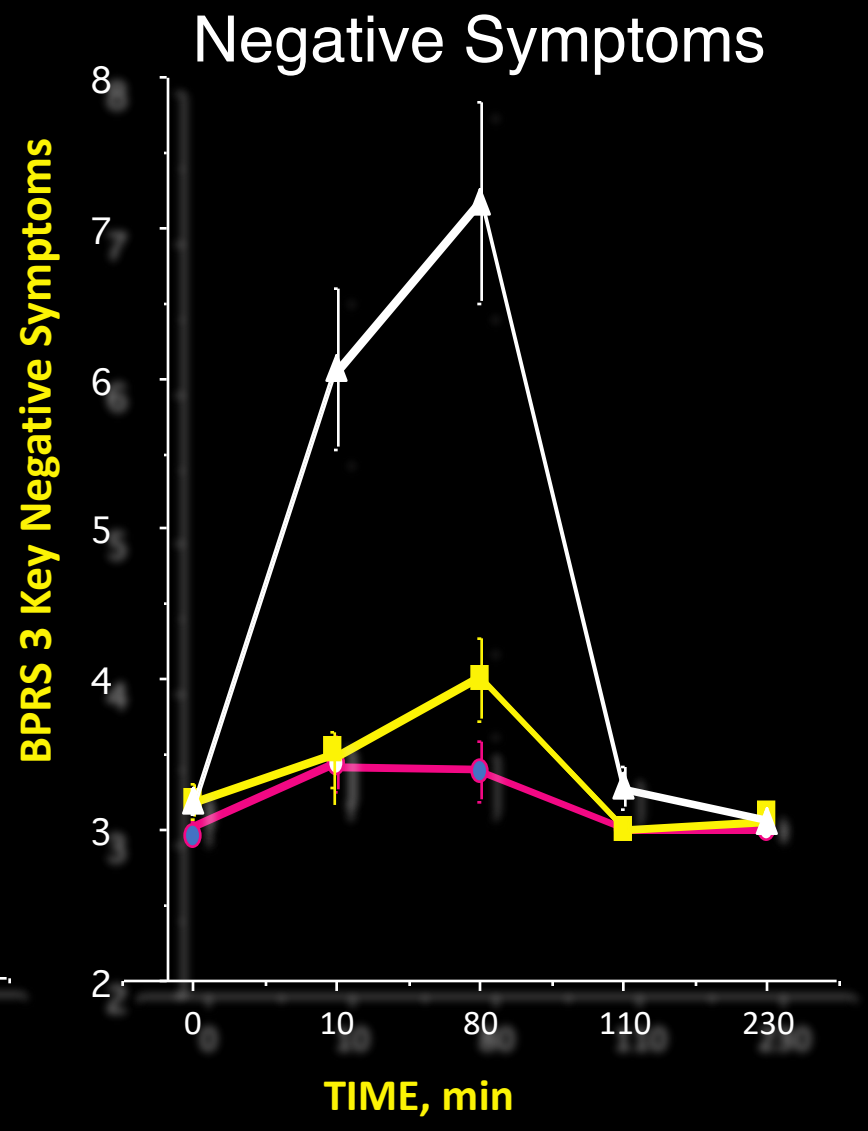
A shift from serotonin/midbrain to glutamate and cortico-limbic circuits



Ketamine Produces BPRS Positive and Negative Symptoms in Healthy Subjects

Krystal et al. Arch Gen Psychiatry 1994 (n=18)



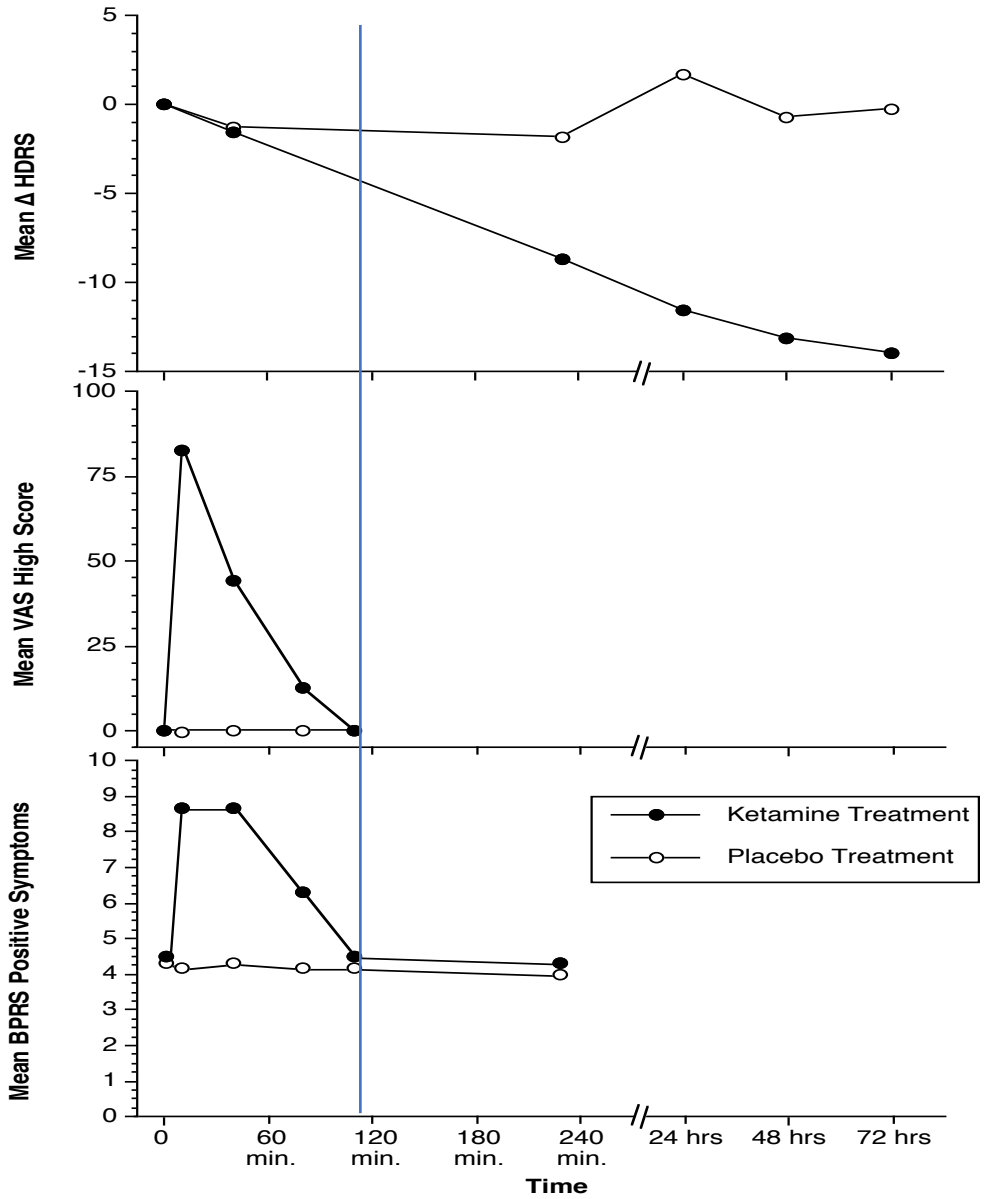


Placebo

0.1 mg/kg

0.5 mg/kg

Antidepressant effects of ketamine



Hamilton Depression Scale: p=.0001

VAS, “High” P=.0001

BPRS, Positive Symptoms of Schizophrenia P=.007

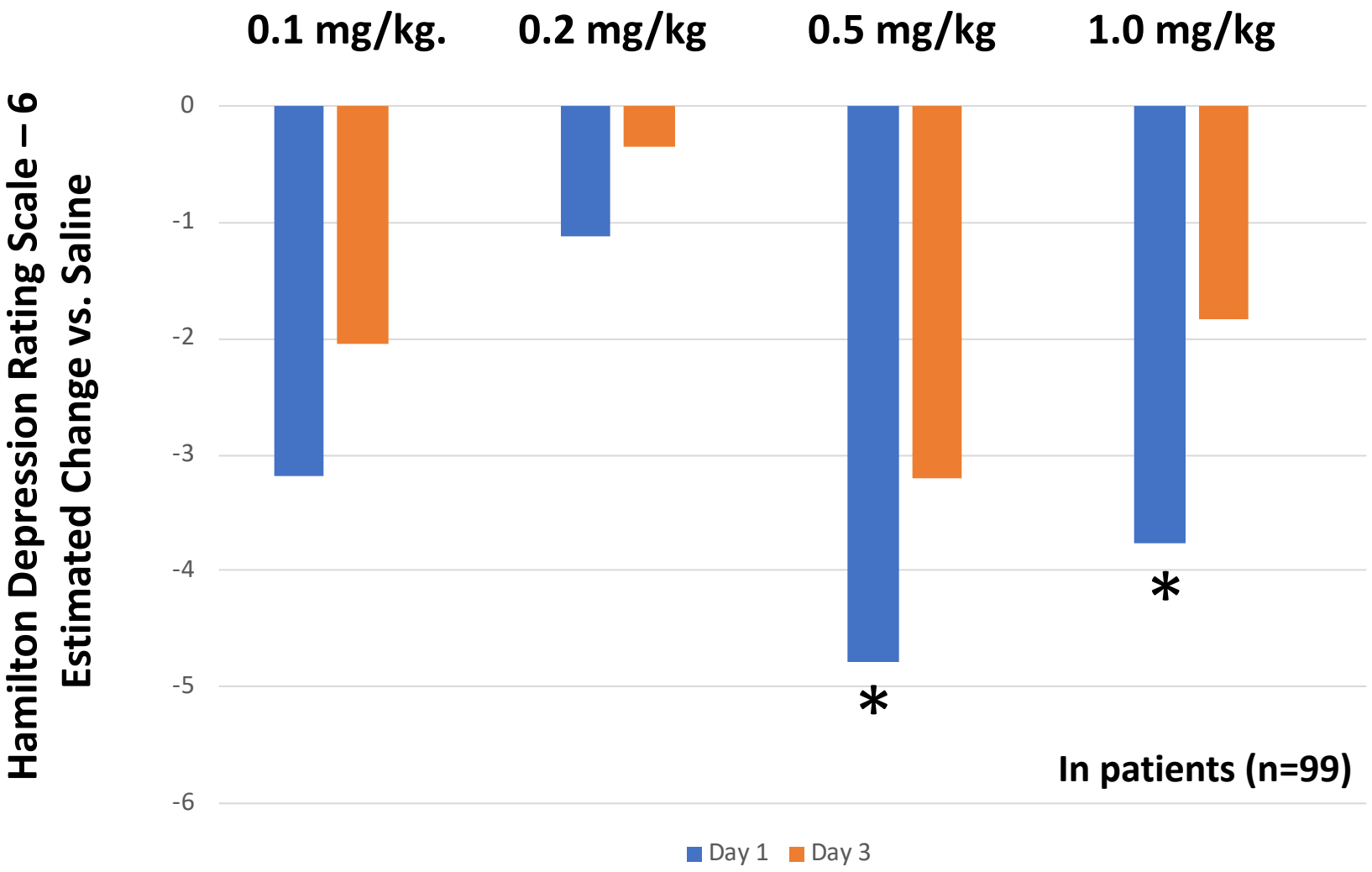
R. Berman et al. Biol Psychiatry 2000

YALE-NE
Psychiatric H

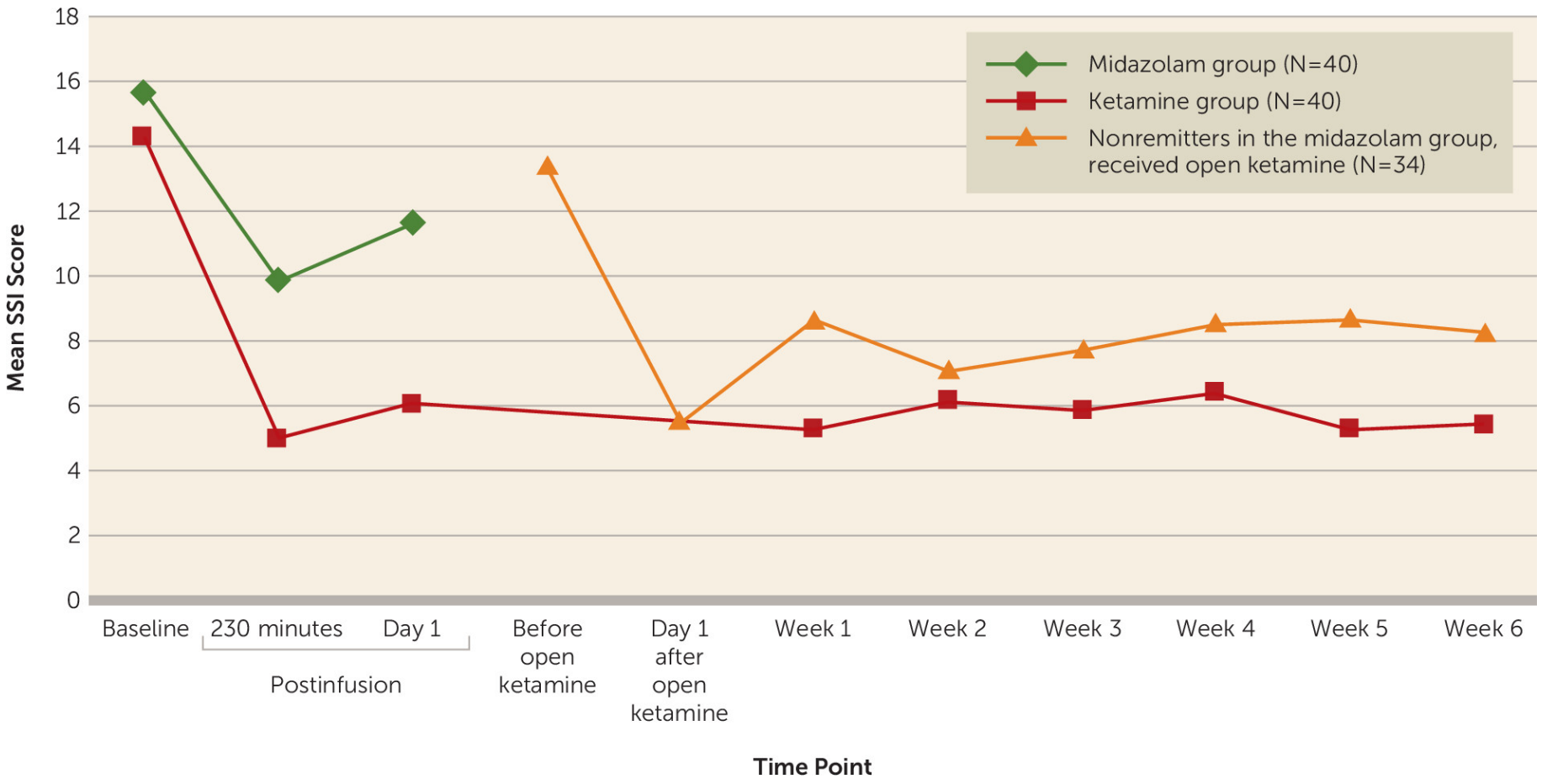
Dose-Related Ketamine Efficacy

Fava et al. Mol Psychiatry 2018

More dissociation≠More efficacy



Ketamine reduces suicidal ideation

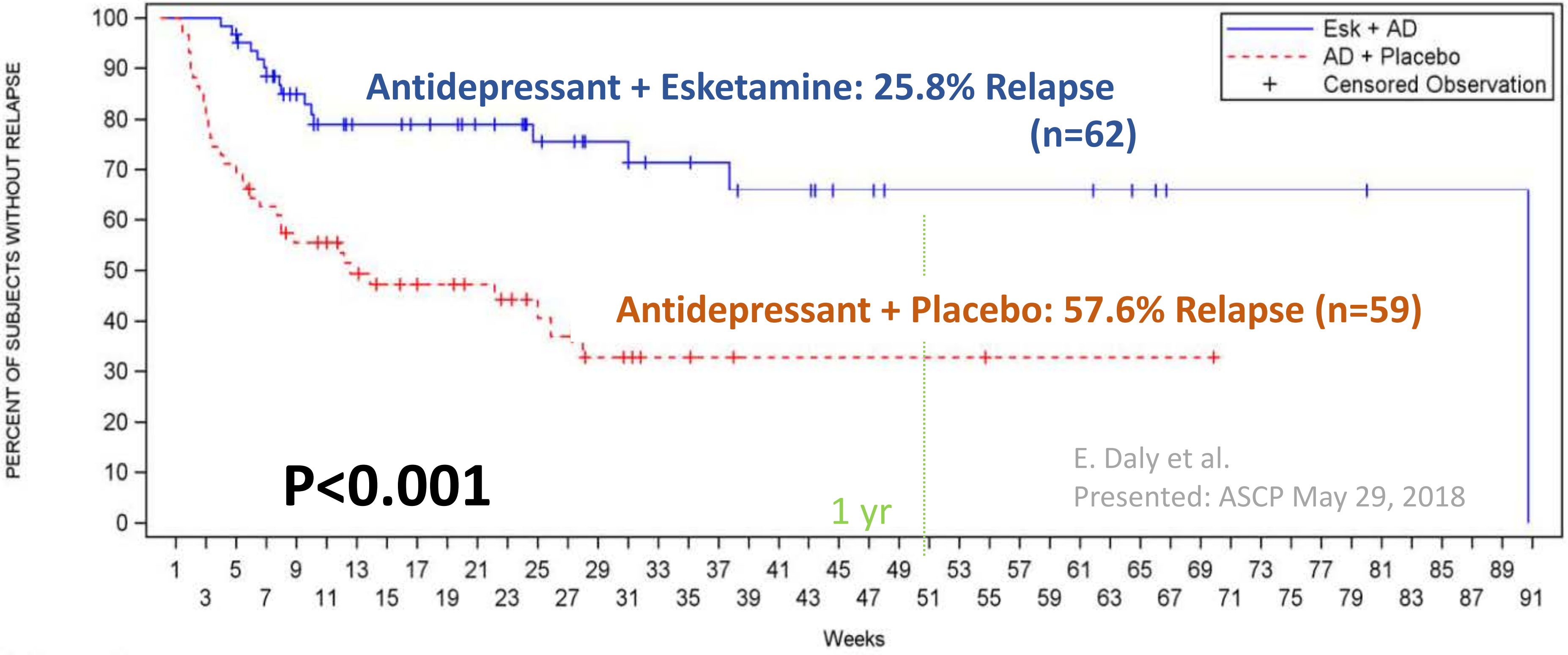


Grunebaum M et al. AJP 2017

Esketamine protects against relapse (OR=0.3) in TRD Responders

Janssen Esketamine Study #3003 (JAMA Psychiatry 2019)

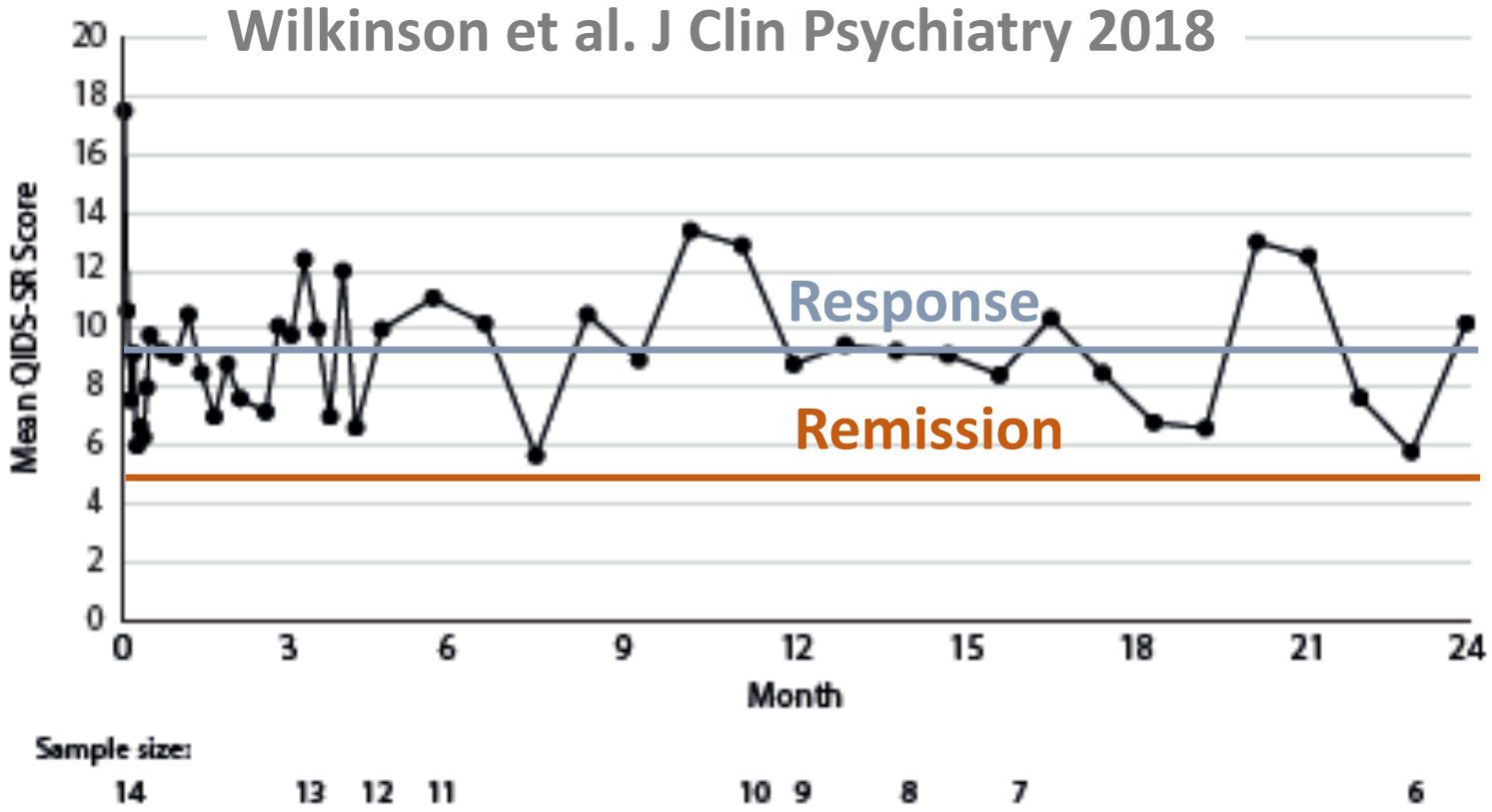
Cumulative Proportion of Subjects Who Remained Relapse Free; Maintenance Phase (Kaplan-Meier Estimates): *Stable Responders*



Subjects at risk

Esk + AD	62	62	60	54	44	38	35	35	33	32	29	26	22	21	18	18	14	14	13	11	11	11	8	8	6	6	6	6	6	6	6	5	4	2	2	2	2	2	2	2	1	1	1	1	1	0
AD + Placebo	59	49	42	36	30	29	24	21	19	18	16	14	12	10	7	6	4	4	3	2	2	2	2	2	2	2	2	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0

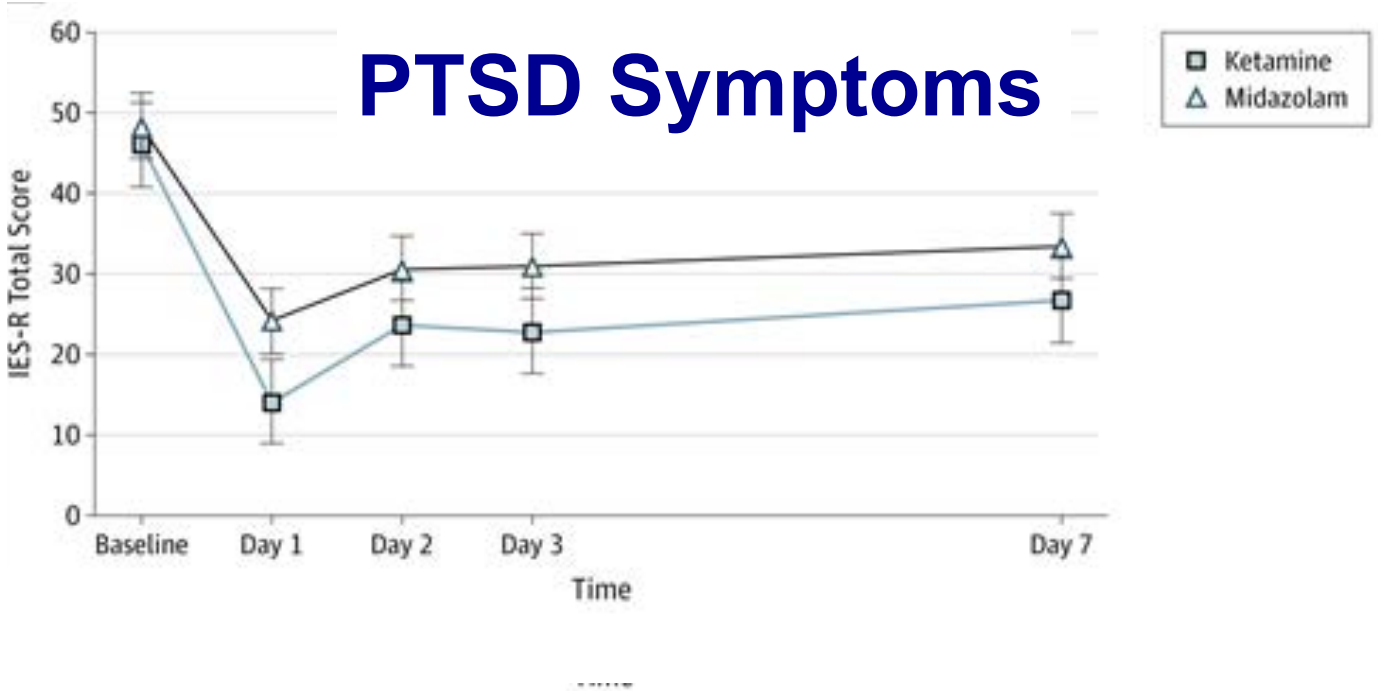
Effective treatment with ketamine has its ups and downs over 2 yr (n=14)



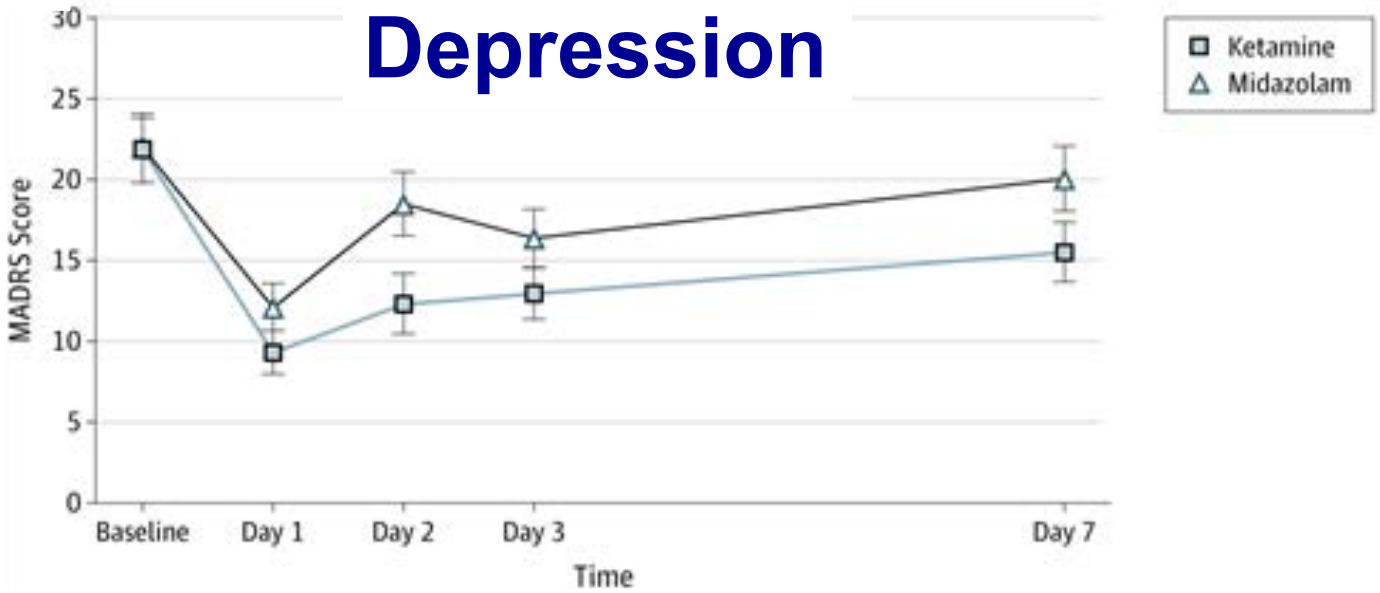
[a]The sample size decreases over time, reflecting that patients are at different stages of continuation/maintenance therapy and not reflecting patient dropout. Data for 1 of the patients were previously published in a case report.[27]

Abbreviation: QIDS-SR = Quick Inventory of Depressive Symptomatology-Self Report.

PTSD
(n=41)



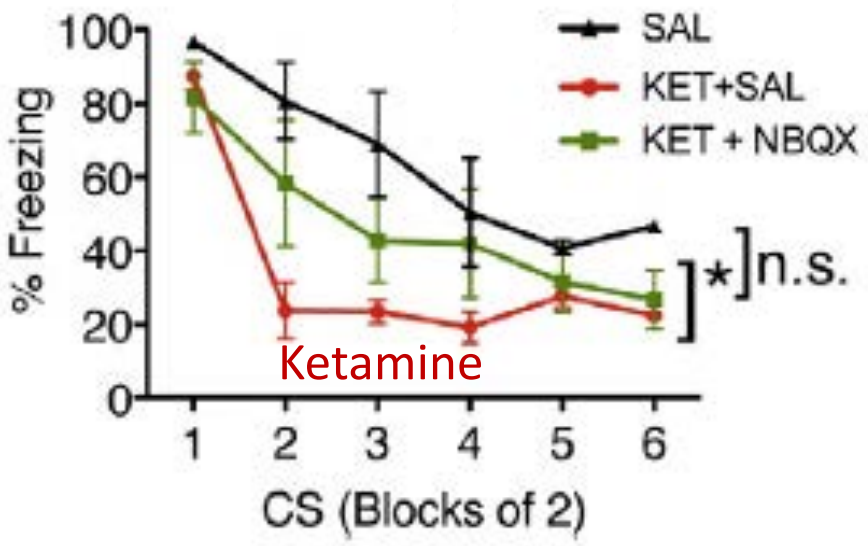
Feder et al.
JAMA Psychiatry
2014



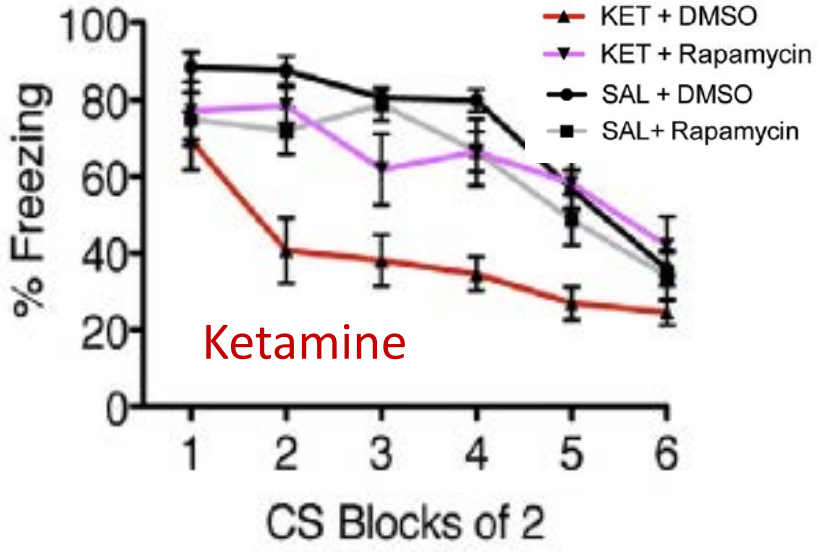
Ketamine accelerates fear extinction: Combine with PE or CPT?

Girgenti et al. Neurobiology of Disease 2017

Effect is Dependent on AMPA-R



Effect is Dependent on mTOR



New hope?

- Rapid relief – acute settings/severe symptoms
- Treatment-resistant symptoms
- Protection against relapse

Outline

- The problem with antidepressants
- Why ketamine?
- **From mechanisms to new treatments**

AUGUST 7, 2017

TIME

THE *ANTI* ANTIDEPRESSANT

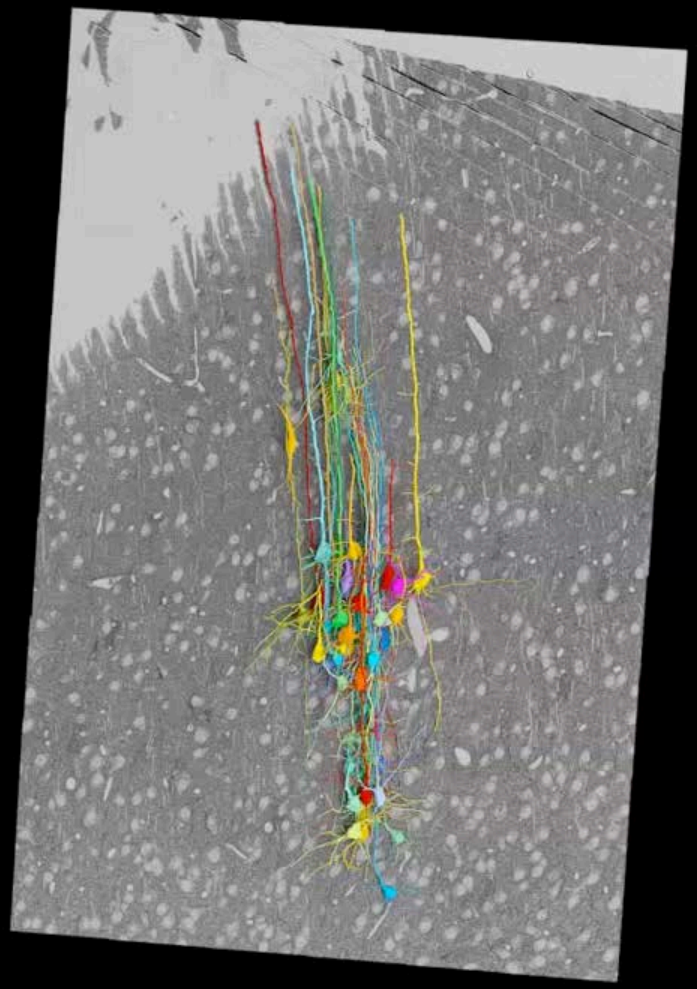
Depression afflicts 300 million people. One-third don't respond to treatment.

A surprising new drug may change that

BY MANDY OAKLANDER

time.com

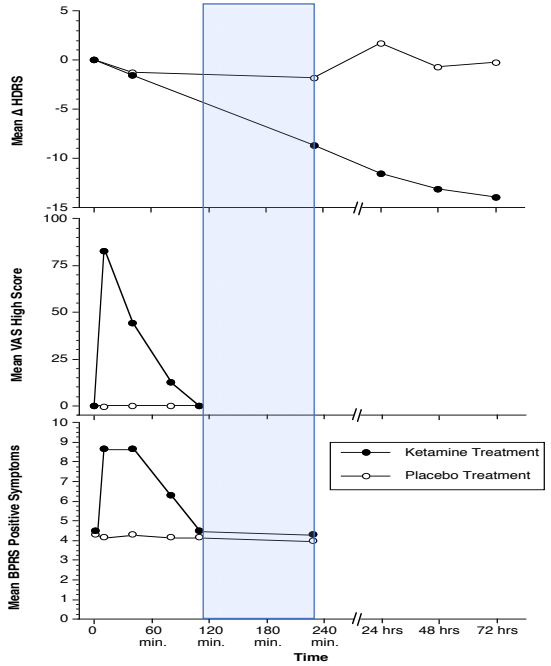
Glutamate?



Jeff Lichtman
Harvard University
From Kasthuri et al. Cell 2015

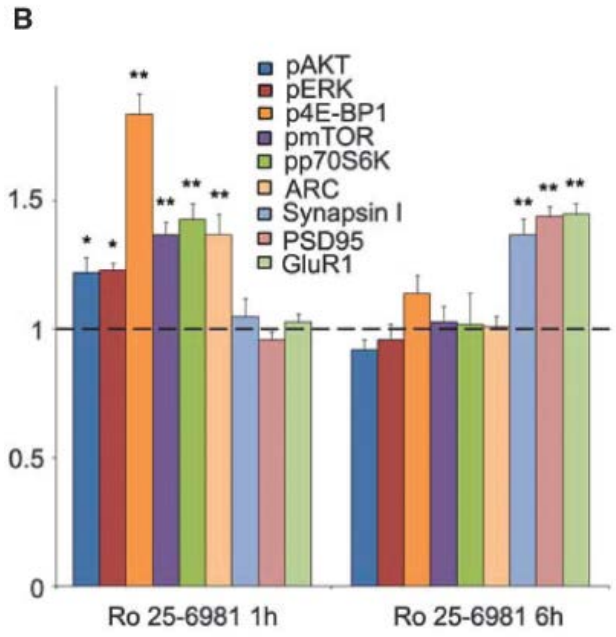
Antidepressant effect is distinct from the symptoms of acute intoxication

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



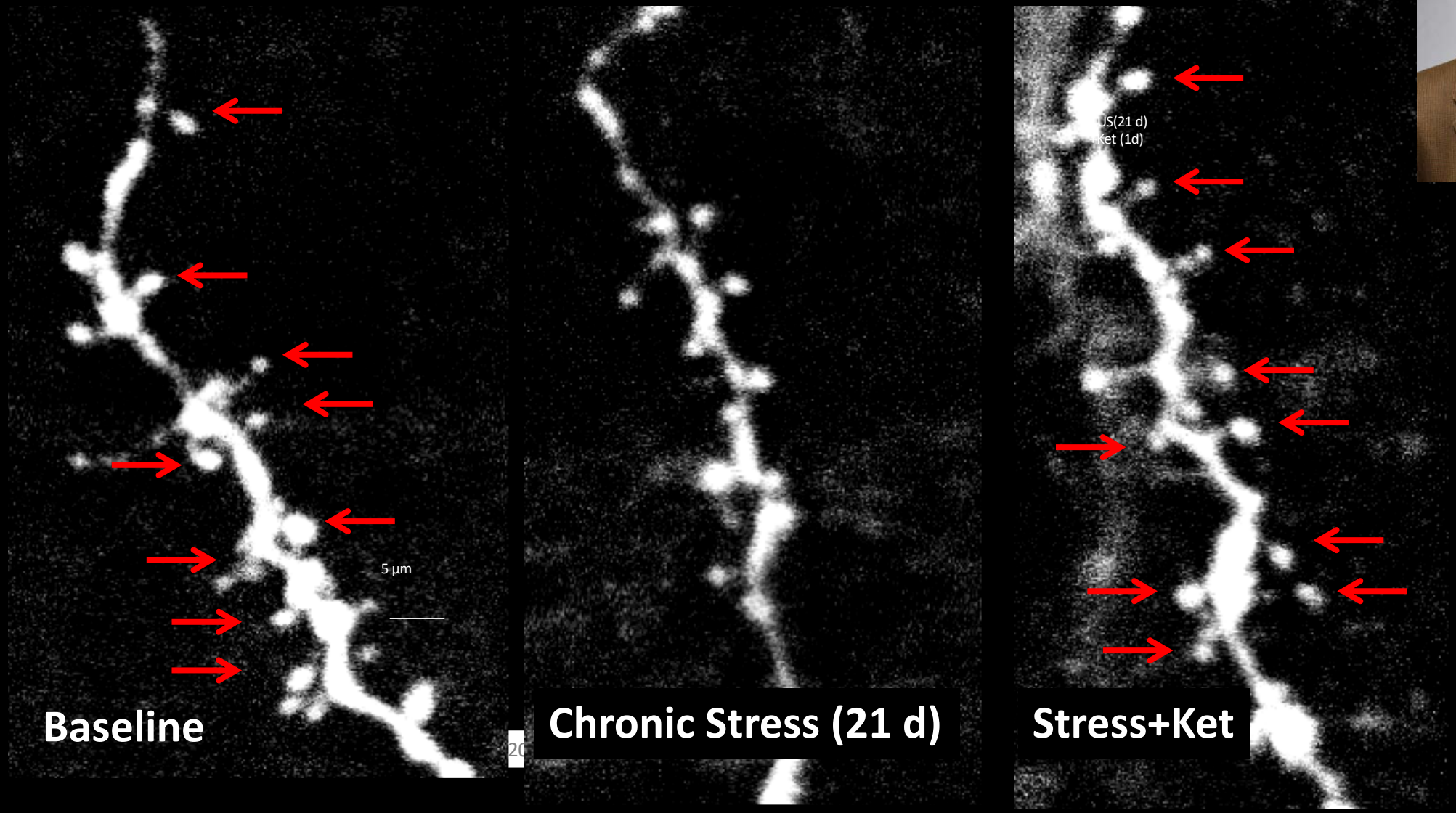
R. Berman et al. Biol Psychiatry 2000

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



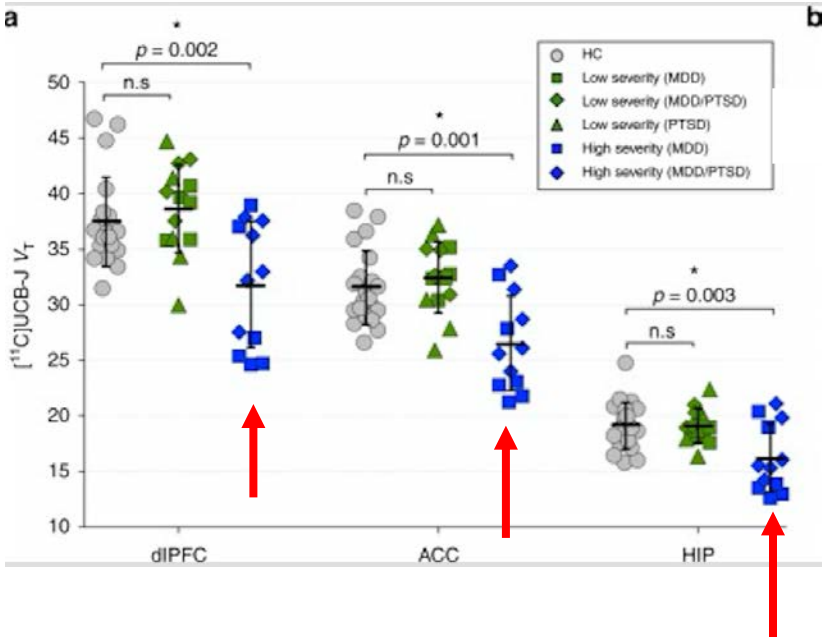
Li et al. Science 2010

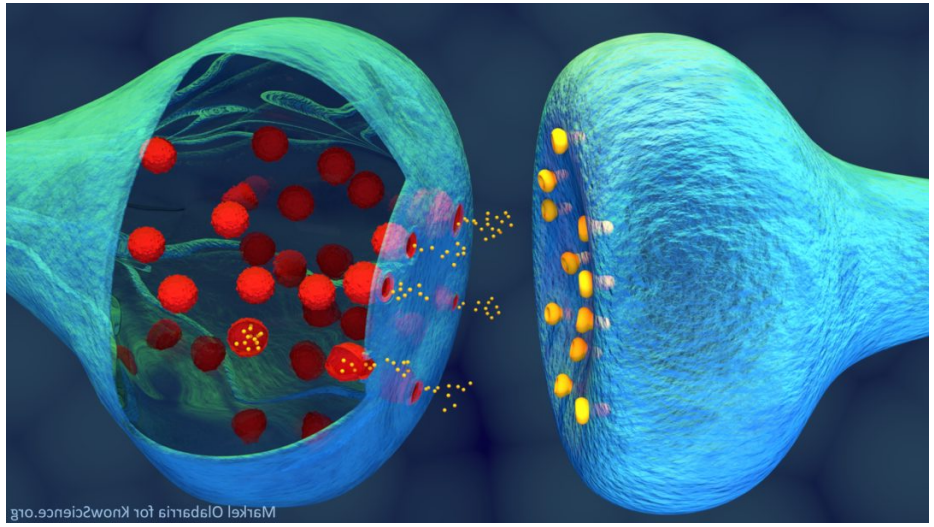
Ketamine stimulates rapid regrowth of synaptic connectivity in these regions
Duman and Aghajanian Science 2012



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

Reduced 11C-UCB-J associated with severe depression



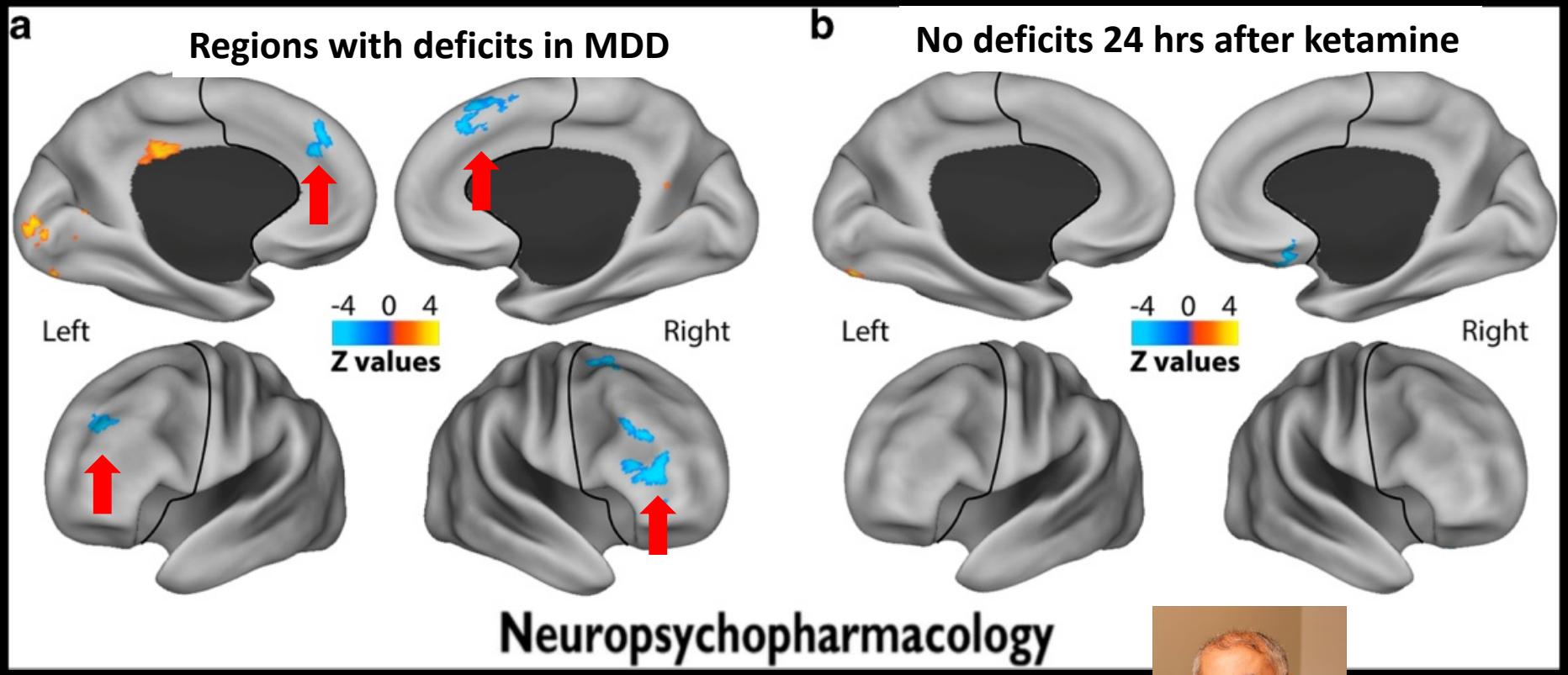


I. Esterlis

S. Holmes

Holmes et al. Nature Communcations 2019

Ketamine stimulates rapid restoration of functional connectivity in depressed patients

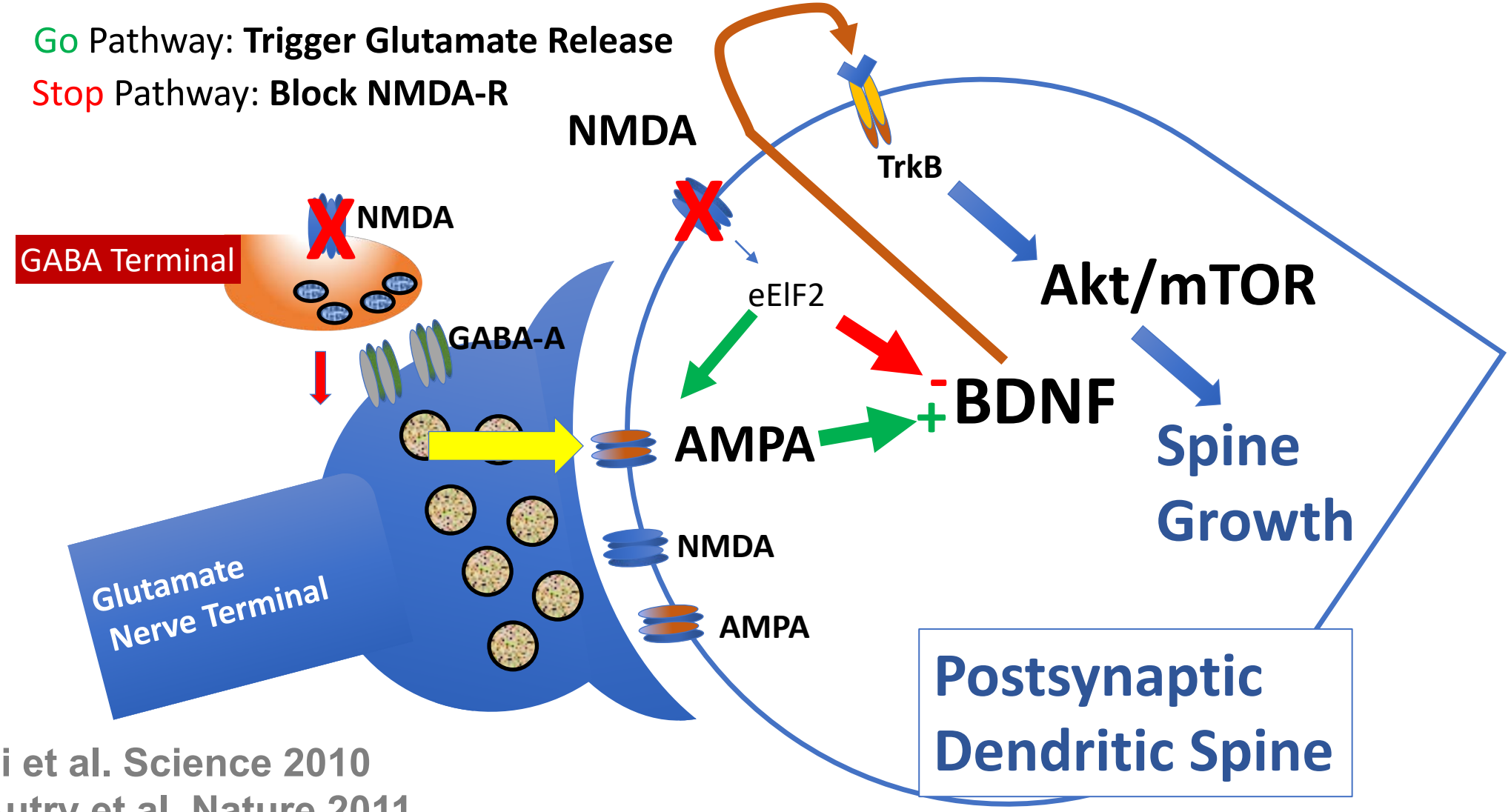


Chadi Abdallah C et al. NPP 2016

Hypotheses Regarding Ketamine Efficacy

Go Pathway: **Trigger Glutamate Release**

Stop Pathway: **Block NMDA-R**



Li et al. Science 2010

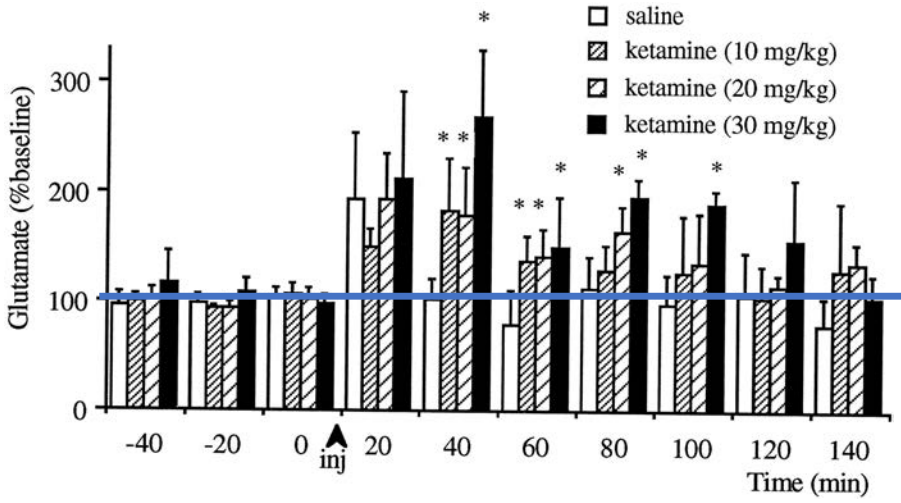
Autry et al. Nature 2011

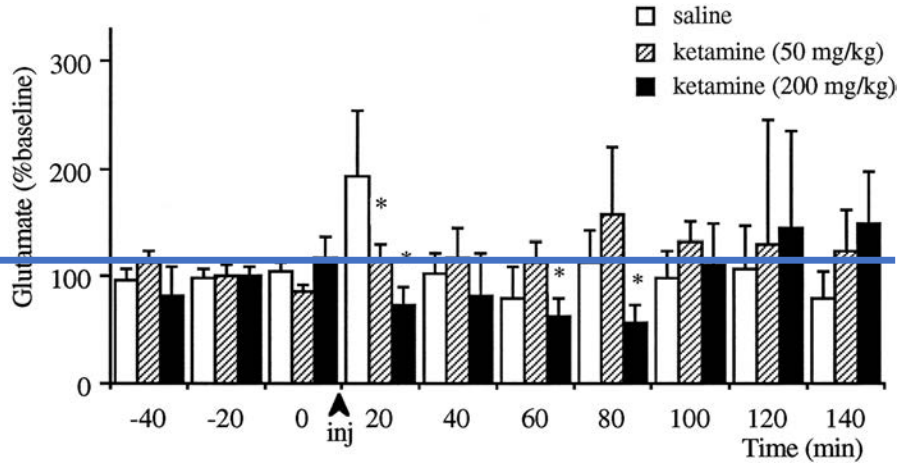
Ketamine and glutamate release – inverted-U:

Low doses increase, high doses decrease (Moghaddam et al. J Neurosci 1997)

Dose-related increases up to 10-30 mg/kg

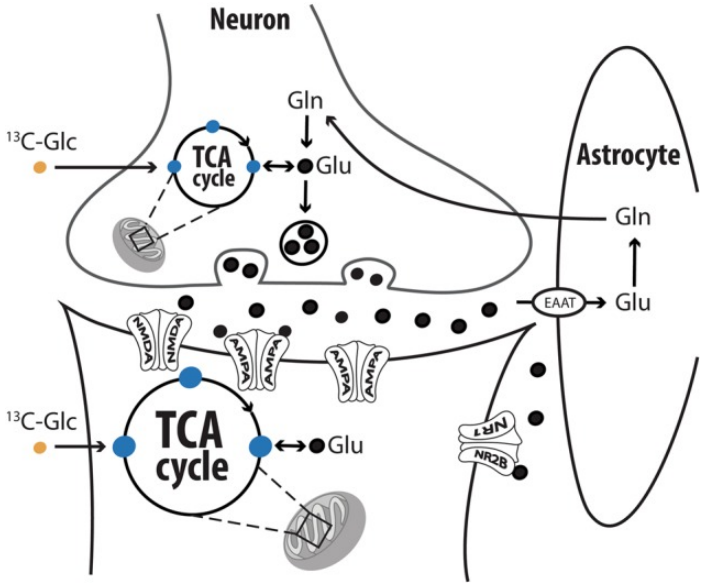
50 mg/kg-no change
200 mg/kg-decrease



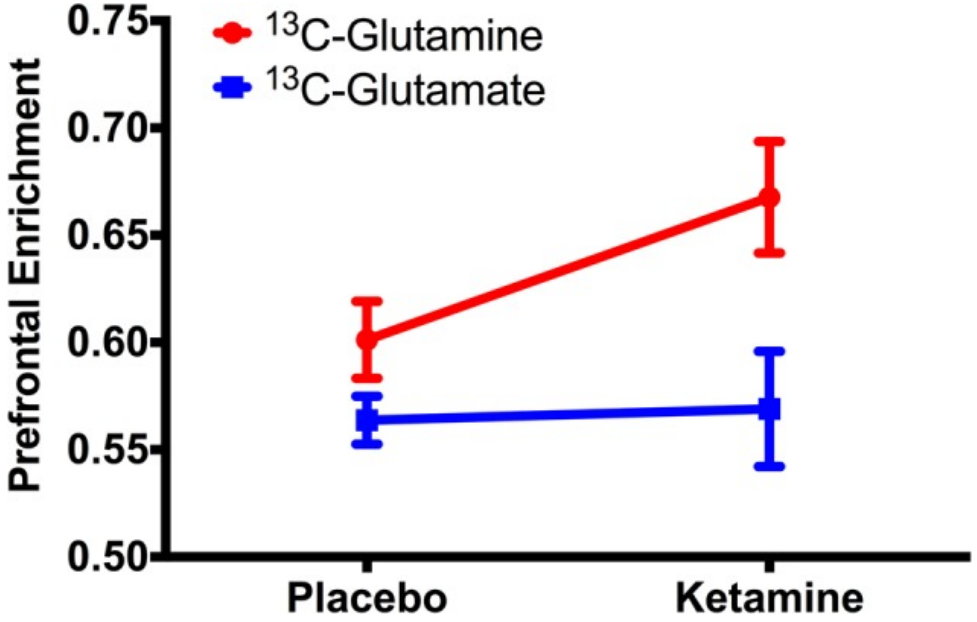


Ketamine increases glutamate release (13C-glutamine enrichment) in frontal cortex

Rate of conversion of glutamate to glutamate estimates glutamate release



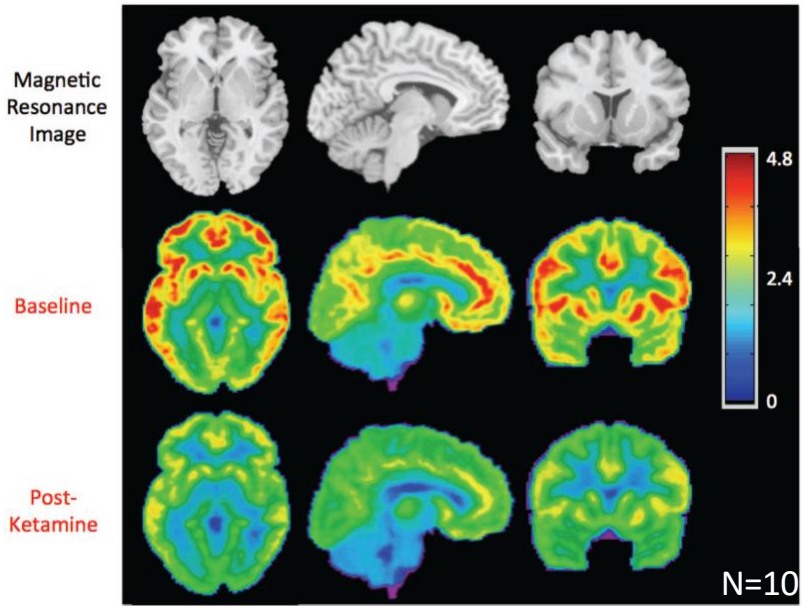
Increase in glutamate release (Glu-Gln) without metabolism increase (Glu)



Abdallah et al. NPP 2019

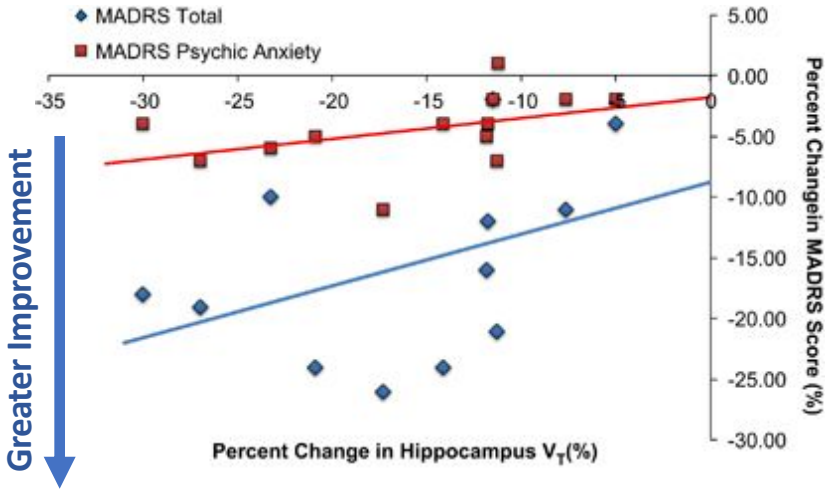
Ketamine efficacy related to mGluR5 normalization?

Ketamine causes rapid and sustained reduction in mGluR5 availability: displacement/internalization



DeLorenzo et al. Biol Psychiatry 2015

Degree of displacement/internalization predicts Clinical response in depression



Greater mGluR5 displacement/internalization

Esterlis et al. Mol Psychiatry 2018

Other implicated mechanisms

- **Other network effects:**
  - Blockade of habenula burst firing
  - Indirect endogenous opiate effect?
- **Anti-inflammatory effects:**
  - Kynurenine pathway vs anti-cytokine
  - Inflammatory “subtypes of depression?
- **Epigenetic effects:**
  - Resilience promoting
- **Neuroplasticity promoting**
  - Enhancing cognitive/behavioral therapies

Allen et al. J Psychiatry Res 2018; Tan et al. Biol Pharm Bull 2017; Bagot et al. Biol Psychiatry 2017; Girgenti et al. Neurobiol Dis 2017; Yang et al. Nature 2018

New medications?

- **Ketamine derivatives**
  - R-ketamine
  - HNK
- **Other NMDA-R antagonists**
- **AMPAkines**
- **mGluR2 antagonists**
- **BDNF facilitators**
- **mTORC1 facilitators**

Summary

- New clinical opportunities: rapid effectiveness for treatment-resistant symptoms
- New mechanisms of action sheds light on brain mechanisms of depression and its treatment
- New classes of medications?