Ketamine:
Why now? How?
Where do we go from here?

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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

It Is Time to Address the Crisis in the Pharmacotherapy of Posttraumatic Stress Disorder: A Consensus Statement of the PTSD Psychopharmacology Working Group

Biological Psychiatry

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To the Editor:

There is an urgent need to address a critical lack of advancement in the psychopharmacologic treatment of posttraumatic stress disorder (PTSD).

Biol Psychiatry. 2017 Mar 14.

FDA-approved treatments: SSRIs

- Modest efficacy
  - About 10% difference in response vs placebo
  - Smaller effect size than psychotherapy
  - Unclear synergy with psychotherapy
- Slow:
  - Sertraline separates from placebo at 10 weeks
- Poorer outcomes in military/veteran populations?

Stein et al. Cochrane Database Syst Rev 2006 Friedman J Clin Psychiatry 2007, Hetrick et al. Cochrane Database Syst Rev 2010, Watts J Clin Psychiatry 2013,

PTSD Multicenter Trials Supported by the VA CSP

Biomarkers, Psychotherapy, Medication

- CSP 334: Psychophysiology biomarker (Heart rate)
- CSP 420: Group PE vs. Present-Centered Therapy
- CSP 494: Individual PE vs PCT
- **CSP 504: Risperidone**
- CSP 519: Smoking Cessation
- **CSP 563: Prazosin**
- CSP 575: Genomics of PTSD (Ongoing)
- CSP 591: PE vs. Cognitive Processing Therapy (Ongoing)

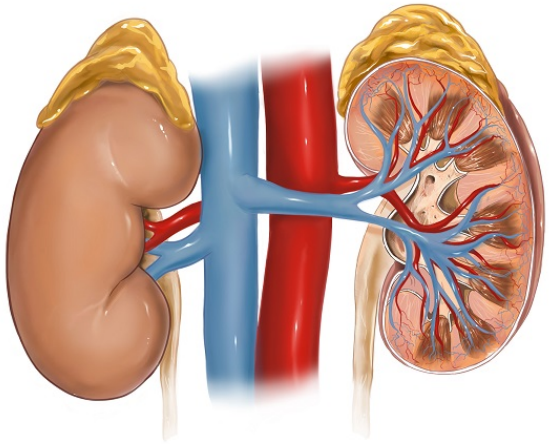
Keane et al. J Consult Clin Psychol 1998; Schnurr et al. Arch Gen Psychiatry 2003; Schnurr et al. J Gen Int Med 2013; McFall et al. JAMA 2010; Krystal et al. JAMA 2011

Outline

- Glutamate synaptic dysfunction and loss in PTSD
- Toward ketamine treatment for PTSD
- Where do we go from here?

Glutamate: The problem with cortisol

Adrenal Glands



Cortisol is harmful:
Chronic stress: persistent cortisol elevations

→ **Glial dysfunction** (Glutamate Synaptic Dysregulation)

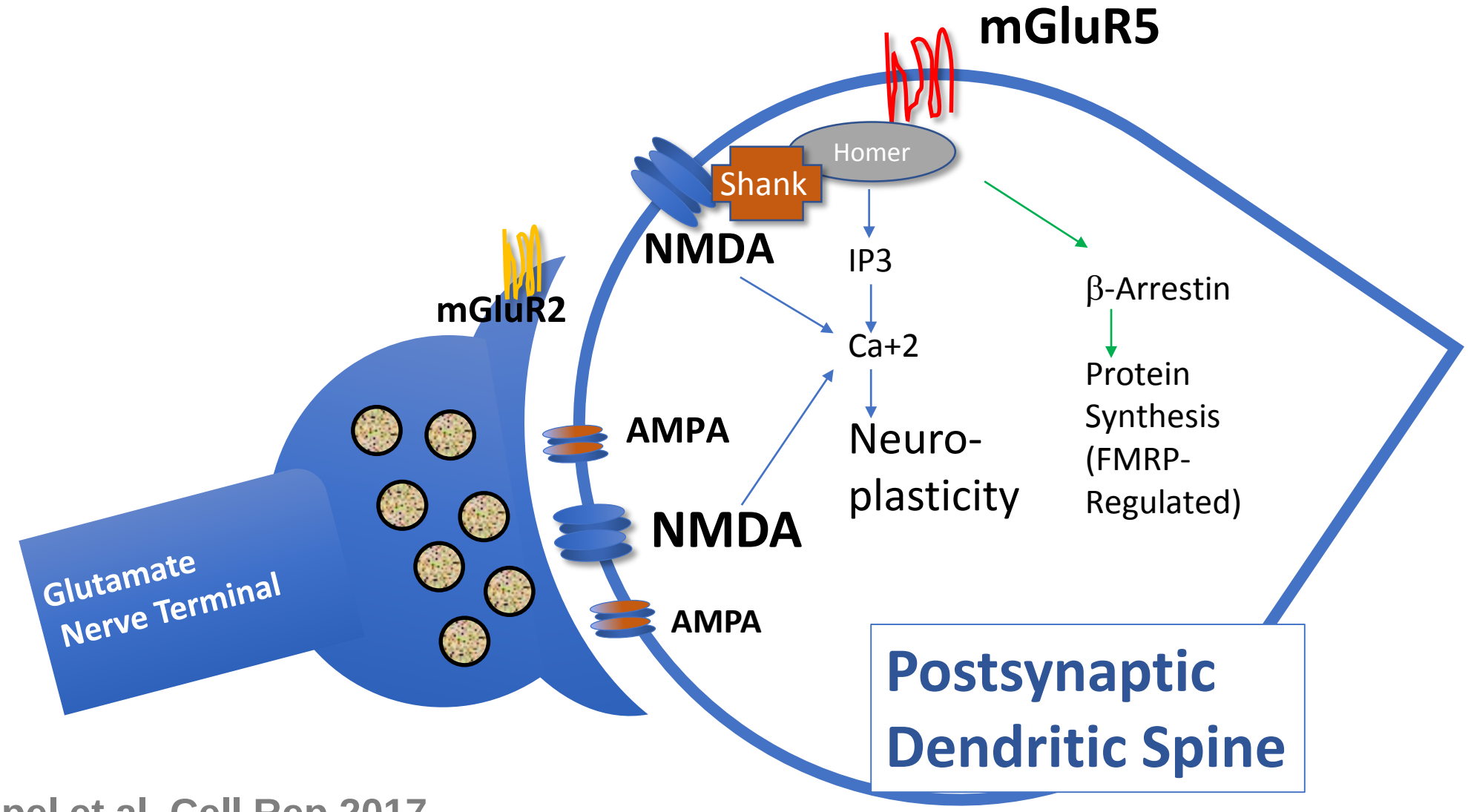
Synaptic Pruning

Cortisol is helpful:
PTSD: *inadequate* cortisol elevations relative to optimal stress response

→ **Aberrant GR signaling alters synaptic regulation**
-Glucocorticoid receptor
-FKBP5 (GR chaperone)
-SGK1

mGluR5: key modulator of neuroplasticity

mGluR=Metabotropic glutamate receptor



Stoppel et al. Cell Rep 2017

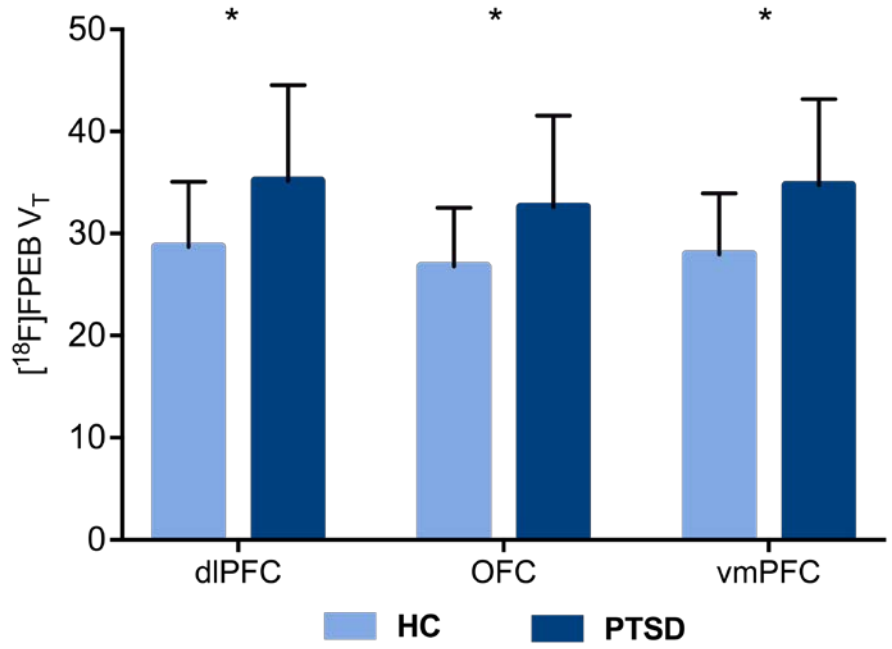
Glucocorticoid contribution to stress vulnerability via mGluR5?

- **Acute** stress (hypercortisolemia): downregulation of mGluR5 and docking protein, Homer 1b/c
  - Pattern similar to major depression
- **Chronic** mild stress upregulates mGluR5 protein
  - blocked by GR antagonist
- *Does PTSD look like acute stress (MDD) or CMS?*

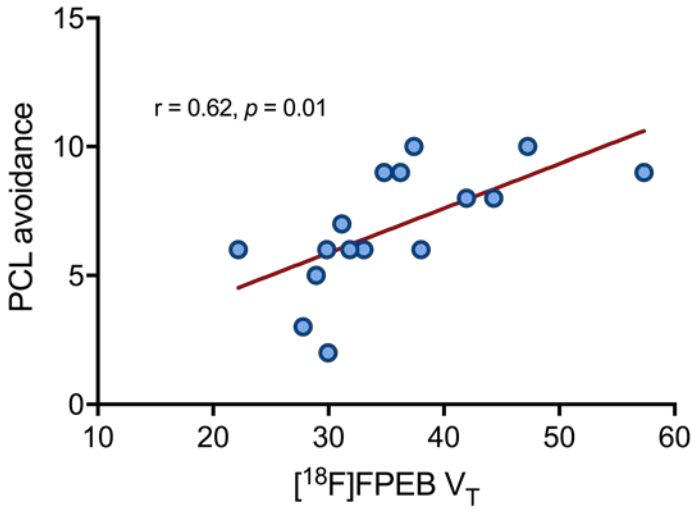
Deschwanden et al. Am J Psychiatry 2011; Wagner et al. J Neurosci 2013; Sun et al. Neuroscience 2017

mGluR5 upregulation in PTSD

mGluR5 Vt (receptor number) is increased In several brain regions in PTSD patients assessed with PET

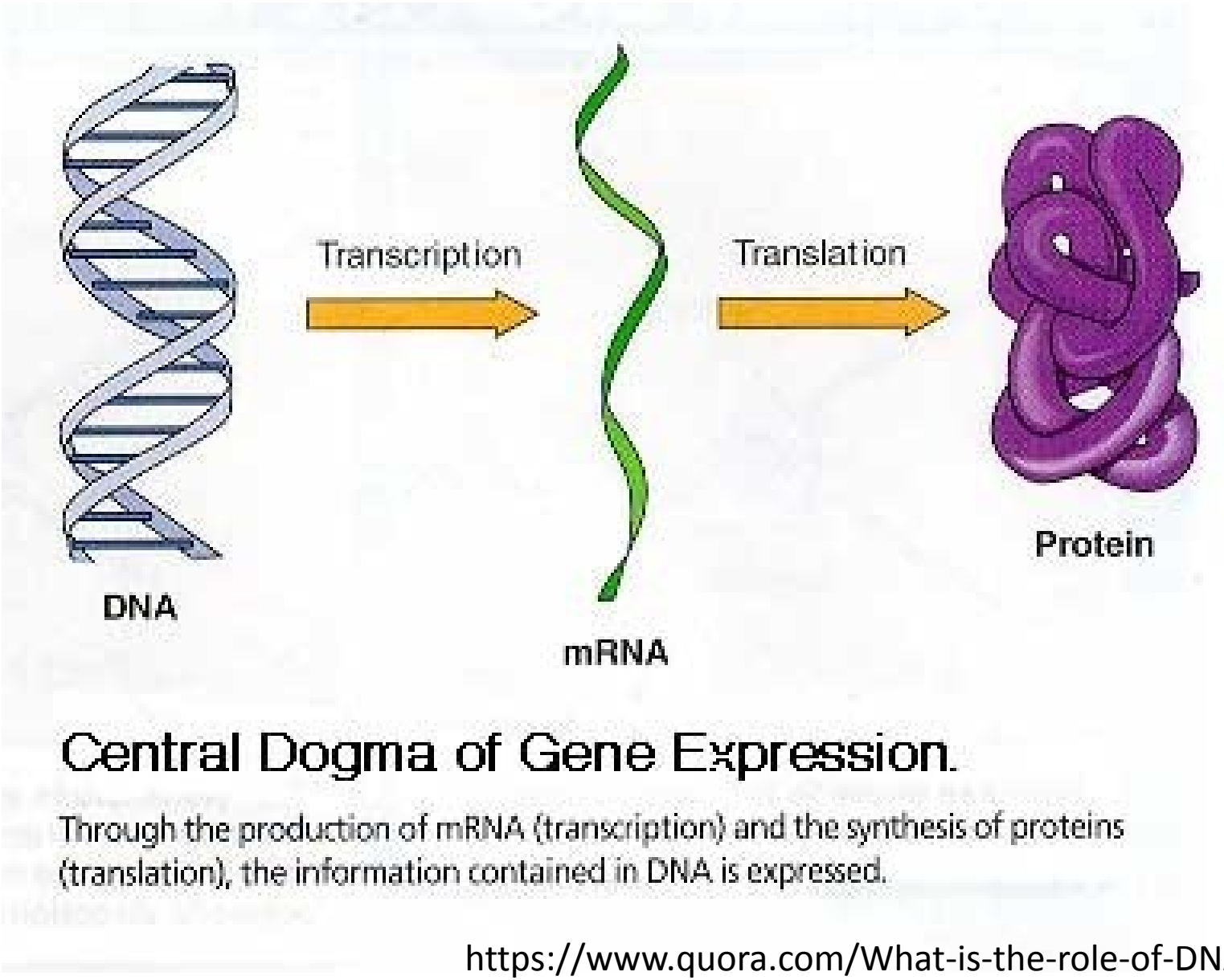


mGluR5 Vt in PFC correlates with severity of avoidance



S. Holmes et al. *Proc Natl Acad Sci* 2017

Measuring gene expression (mRNA level) to study cellular regulation

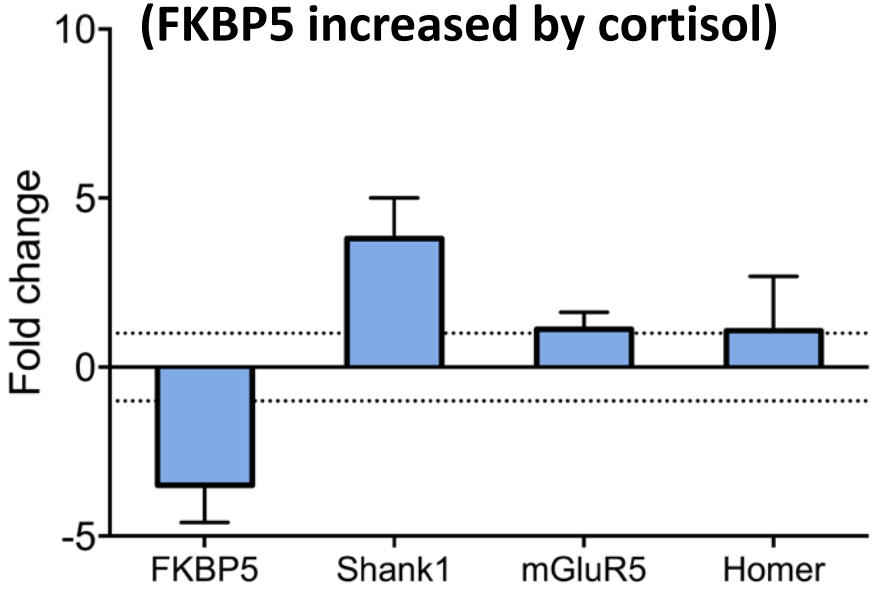


https://www.quora.com/What-is-the-role-of-DNA-in-protein-synthesis

PTSD: cortisol modulation of mGluR5 trafficking to synapse?

Post mortem PFC RNAseq: Shank1 but not mGluR5 is *increased*

and* FKBP5 is *decreased
(FKBP5 increased by cortisol)



S. Holmes et al. *Proc Natl Acad Sci 2017*

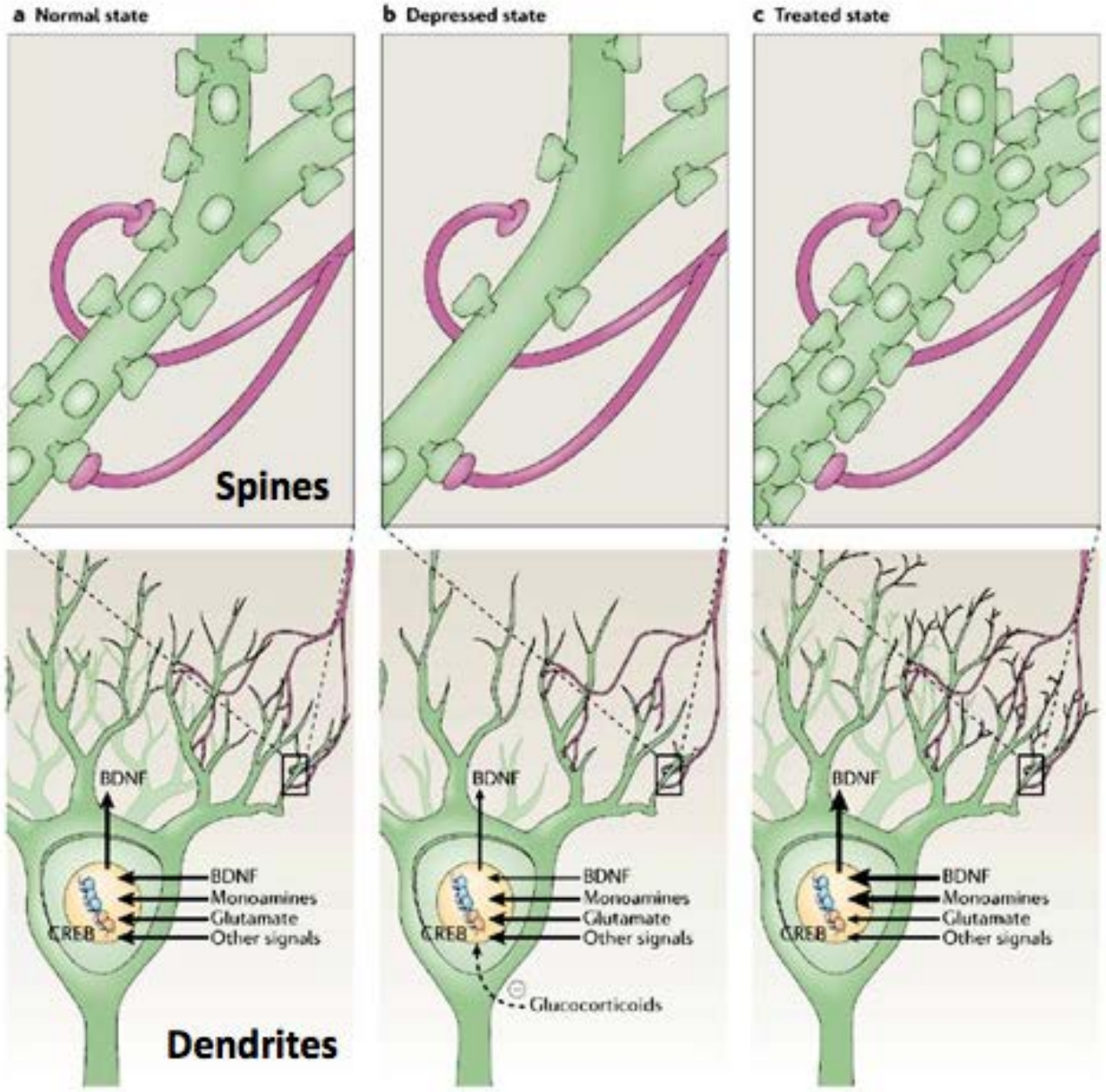
mGluR5 Summary

- mGluR5 upregulation in PTSD
- May arise from HPA alterations
- *Treatments to normalize mGluR5?*
  - *Glucocorticoid (prednisone) or GR antagonist (mefipristone)?*
  - *mGluR5 Negative Allosteric Modulators (NAMs)*
  - *Ketamine?*

High Cortisol
Low BDNF

Promote synaptic loss and dendritic atrophy

Reversed by antidepressant treatment

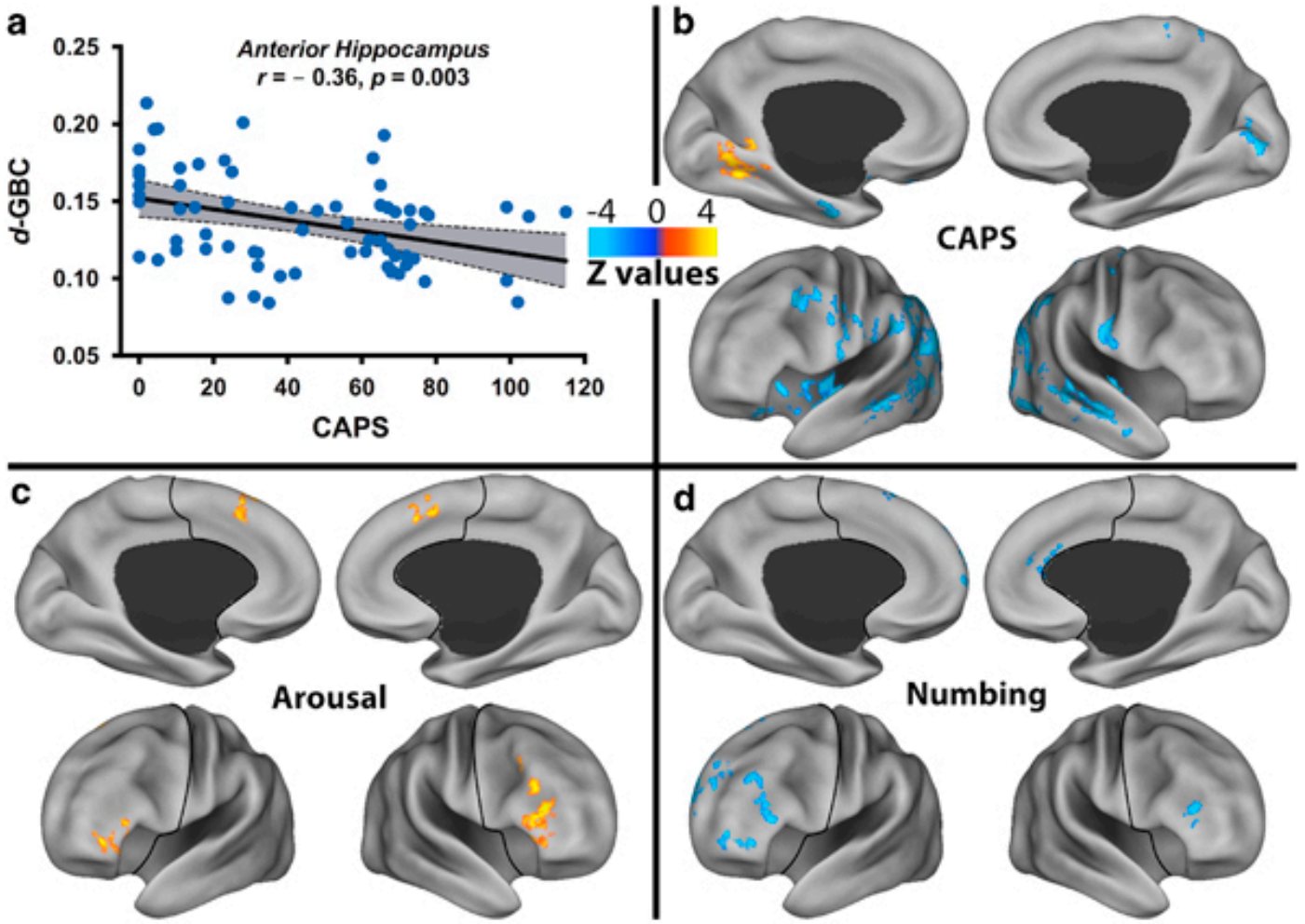


Berton *et al. Nat Rev Neurosci* 2006;7

A “connectionist” hypothesis

- Stress-induced loss of synaptic connectivity in PTSD impairs:
  - Adaptive executive deficits (memory, planning)
  - Executive control of emotion
  - Neuroplasticity
- Some treatments for PTSD may work by restoring connectivity:
  - Restore executive control of thought and emotion
  - Enhance plasticity (capacity to respond to treatment)

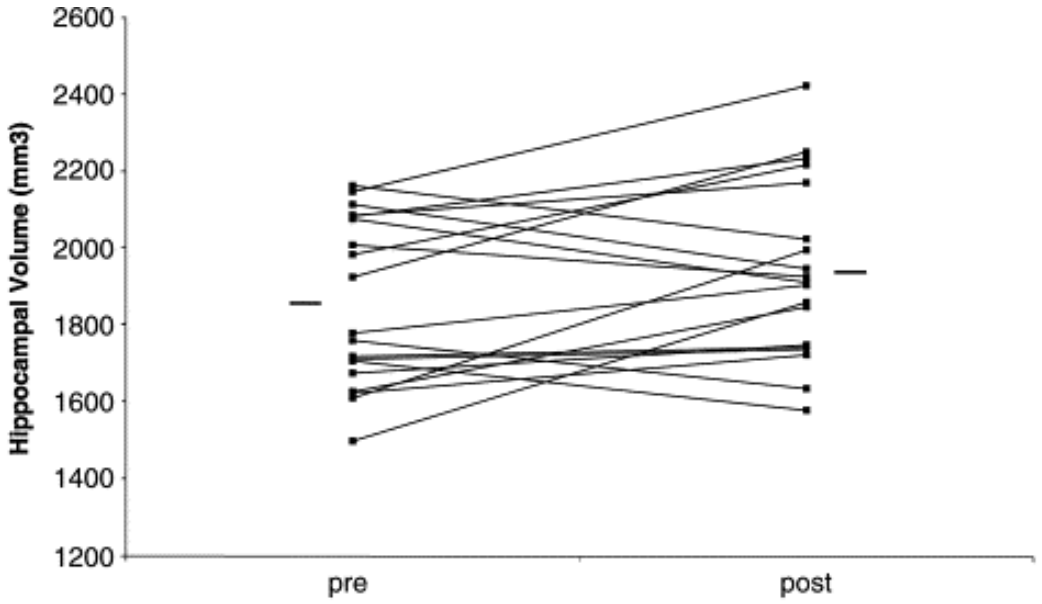
Supporting a connectionist hypothesis



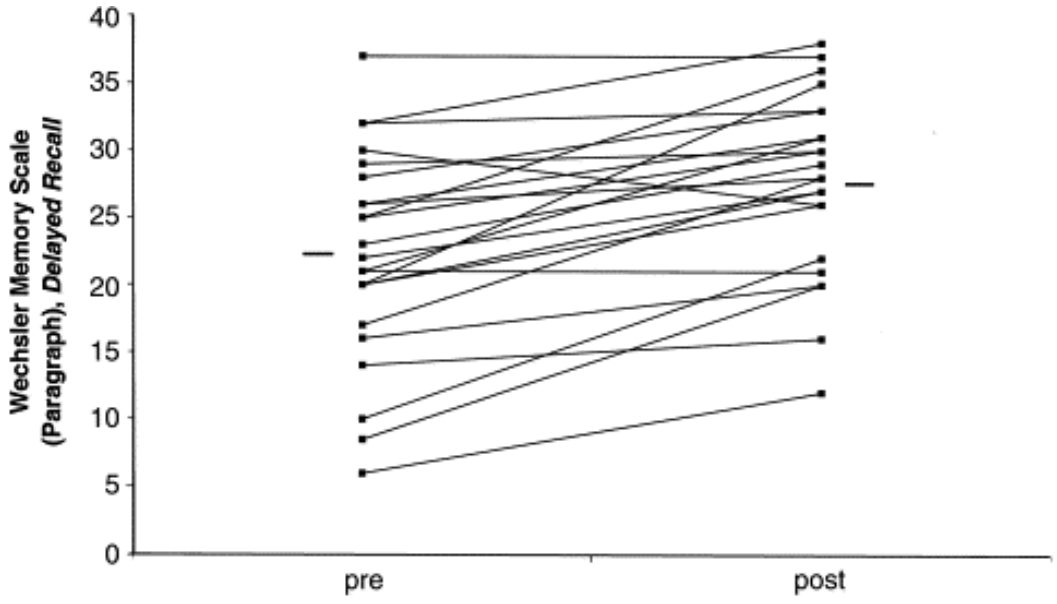
Abdallah et al. Transl Psychiatry 2017 (dGBC seed-based tractography)

Paroxetine (6 mo) increases hippocampal volume

Hippocampal Volume



Wechsler: Paragraph, Delayed Recall



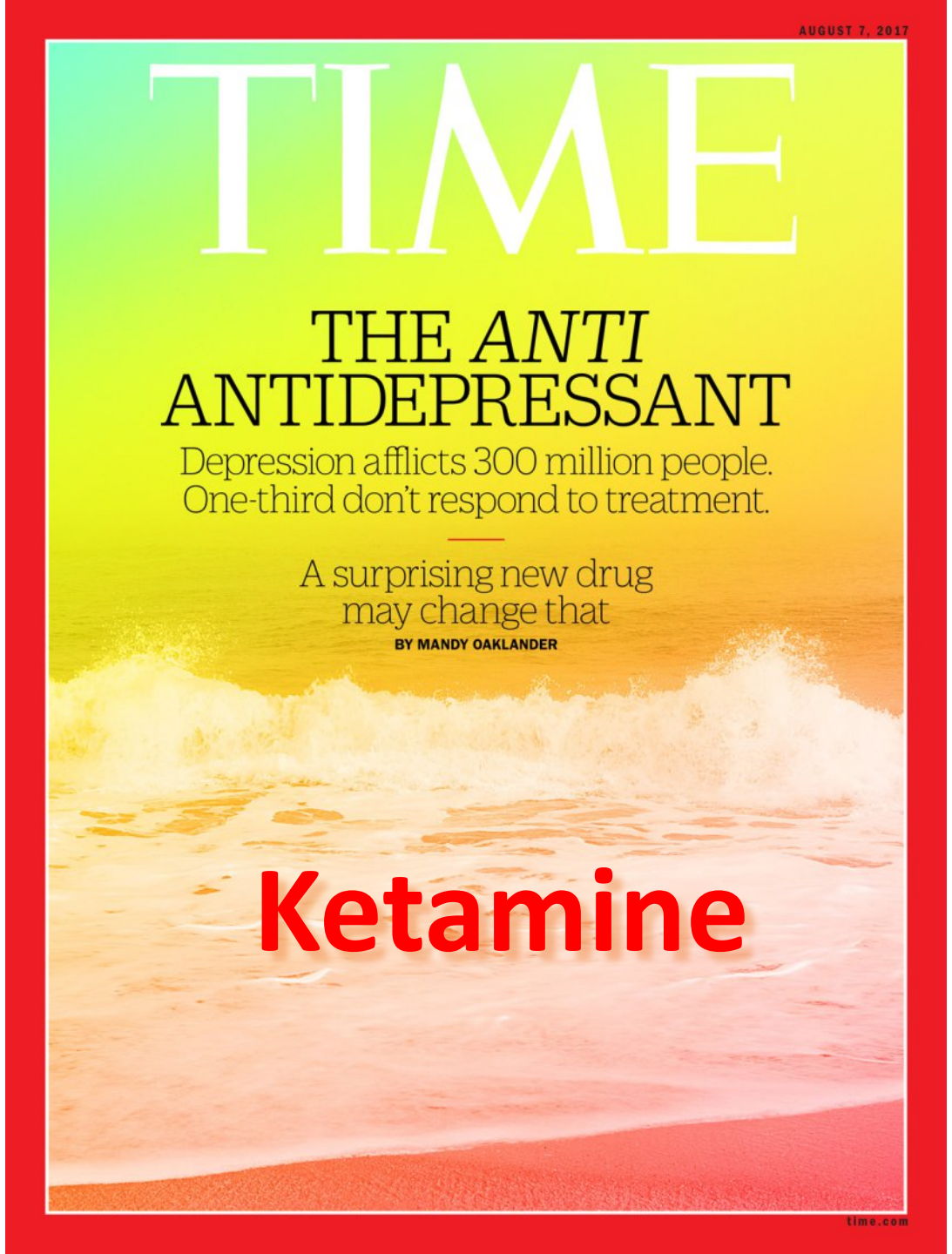
Vermetten et al. Biol Psychiatry 2003

Summary: A Connectionist hypothesis

- Stress reduces synaptic connectivity
- PTSD symptoms are associated with MRI changes
- Long-term antidepressant treatment improves connectivity
- *What if this could happen better and quicker?*

Outline

- Glutamate synaptic dysfunction and loss in PTSD
- Toward ketamine treatment for PTSD

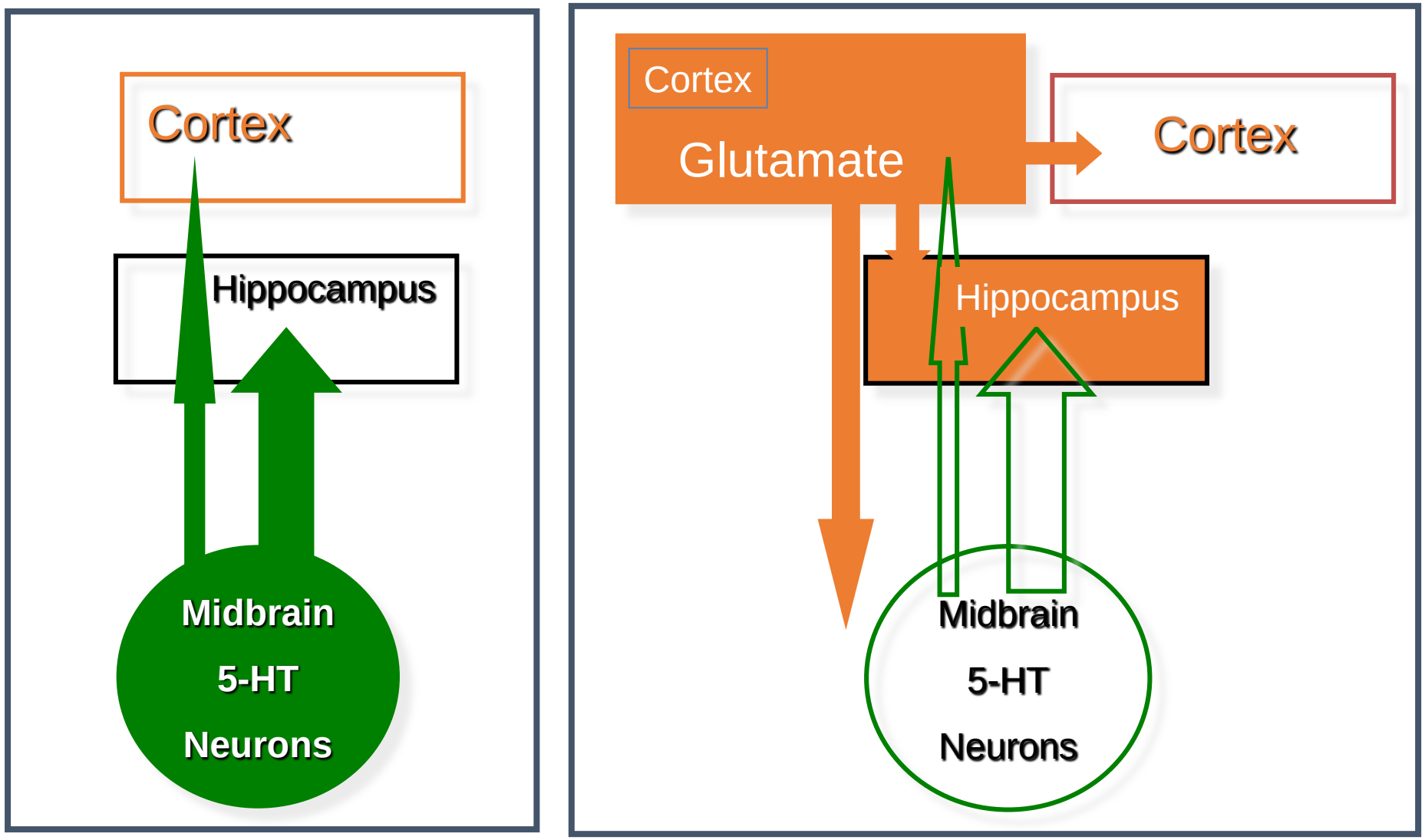

AUGUST 7, 2017
TIME
THE ANTI ANTIDEPRESSANT
Depression afflicts 300 million people. One-third don't respond to treatment.
A surprising new drug may change that
BY MANDY OAKLANDER
Ketamine
time.com

Is depression a product of monoamine depletion?

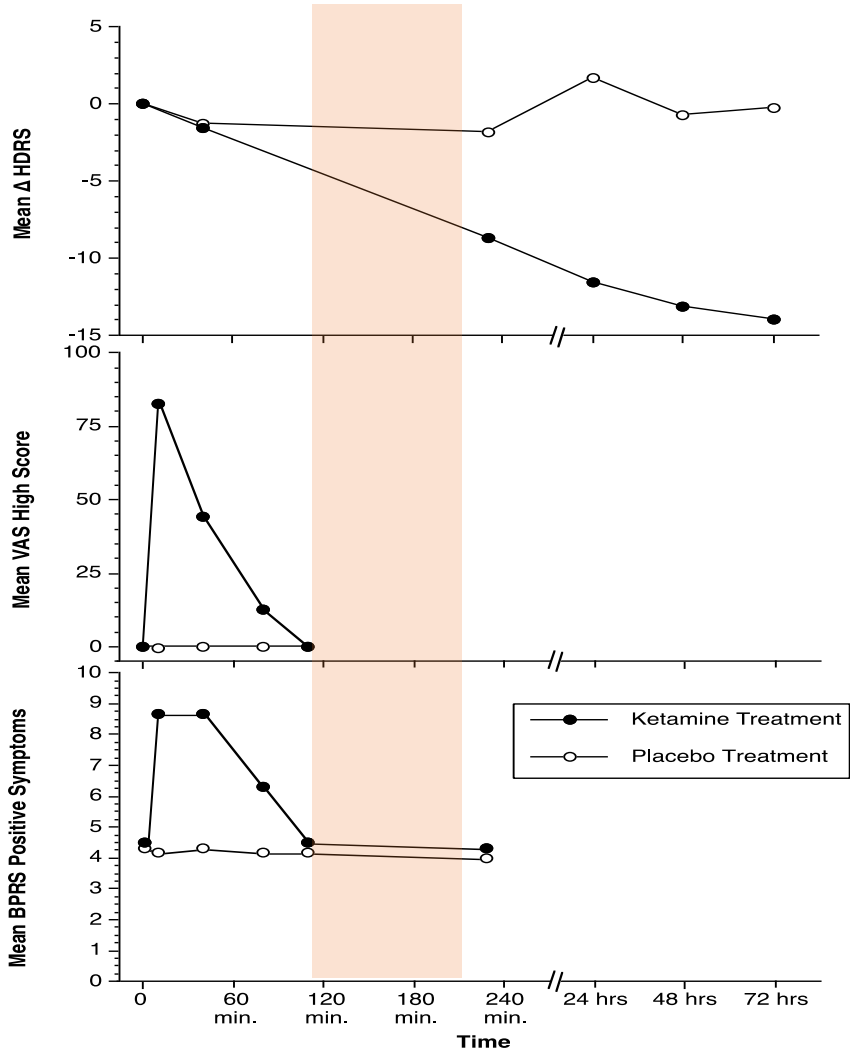
Technique	Amine	Depression?
Tryp Depl	5HT	No
AMPT	NE/DA	No
TD + AMPT	5HT/NE/DA	No

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

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



Rapid antidepressant effects of ketamine



Hamilton Depression Scale: p=.0001

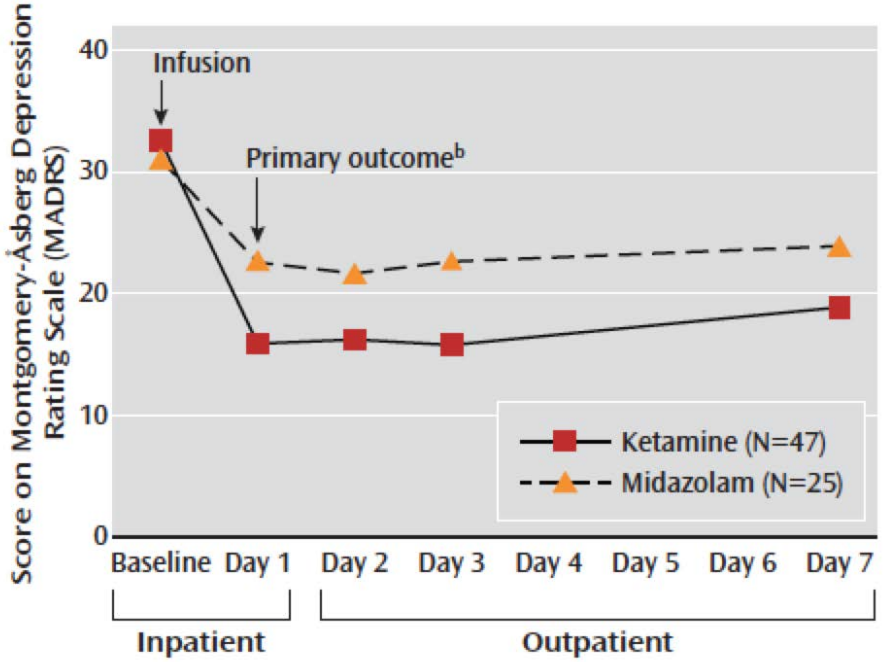
VAS, “High” P=.0001

BPRS, Positive Symptoms of Schizophrenia P=.007

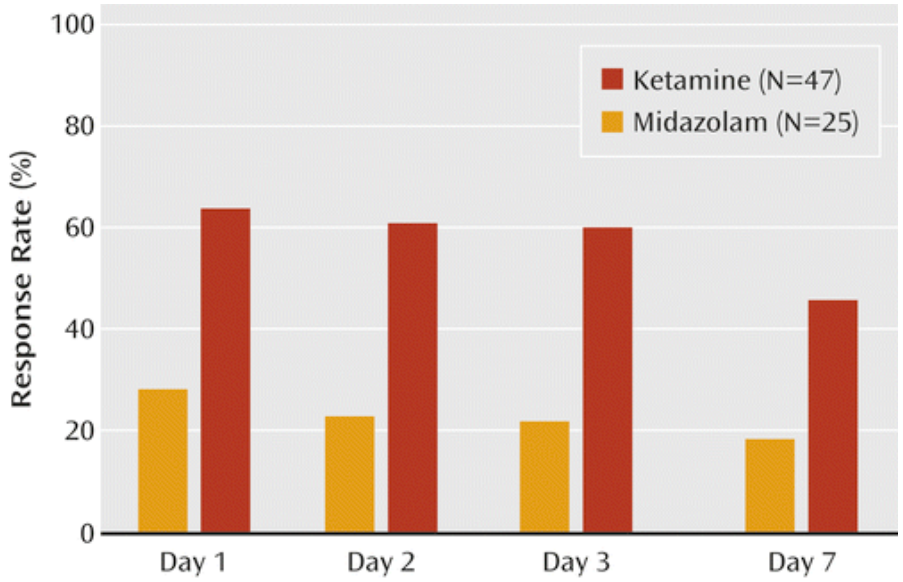
R. Berman Biol Psychiatry 2000

Specificity of ketamine effects: greater and more persistent than midazolam

Depression Severity: MADRAS

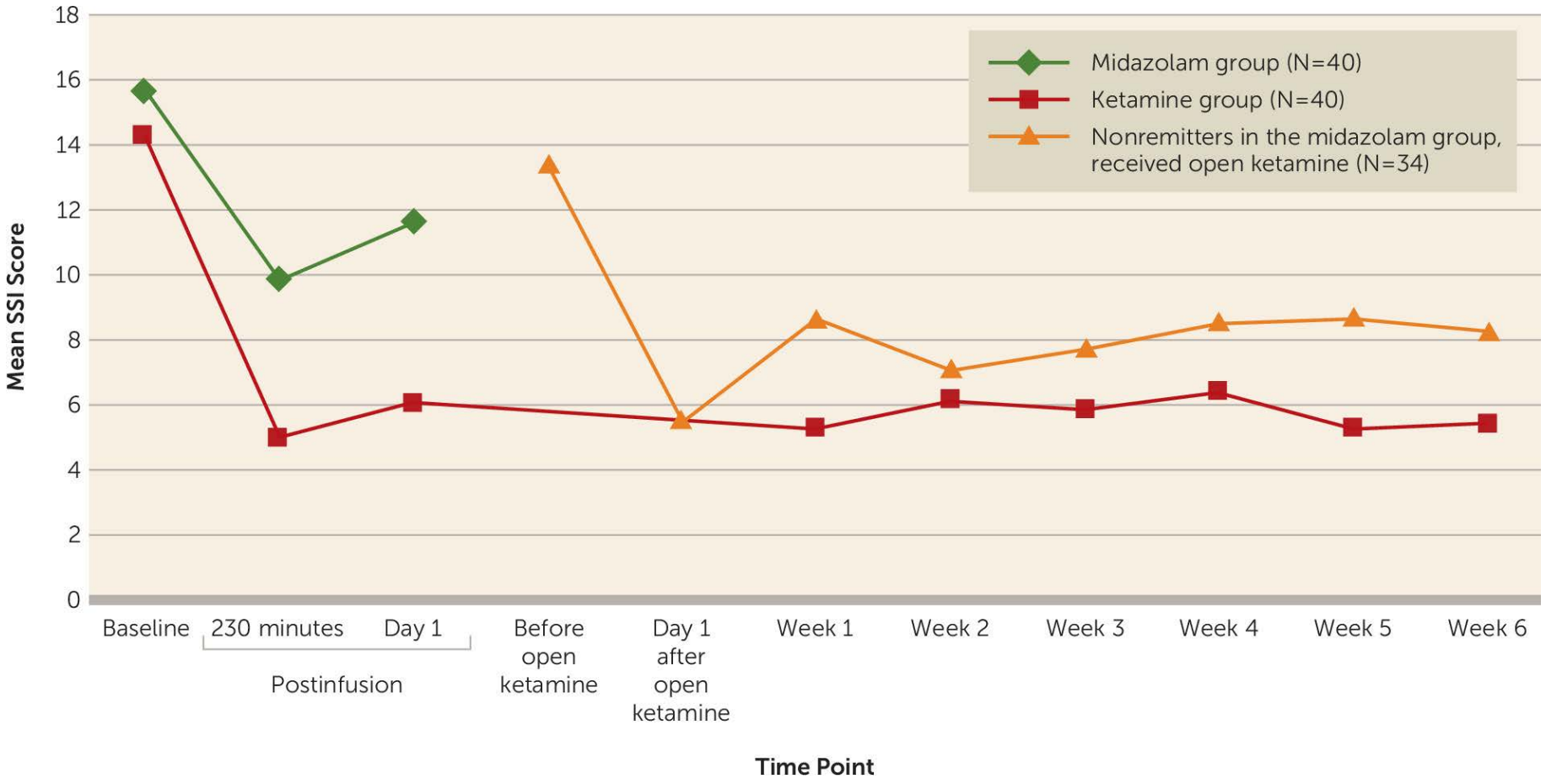


Response Rate: 50% Reduction



J.W Murrough AJP 2013

Ketamine reduces suicidal ideation



Grunebaum M et al. AJP 2017

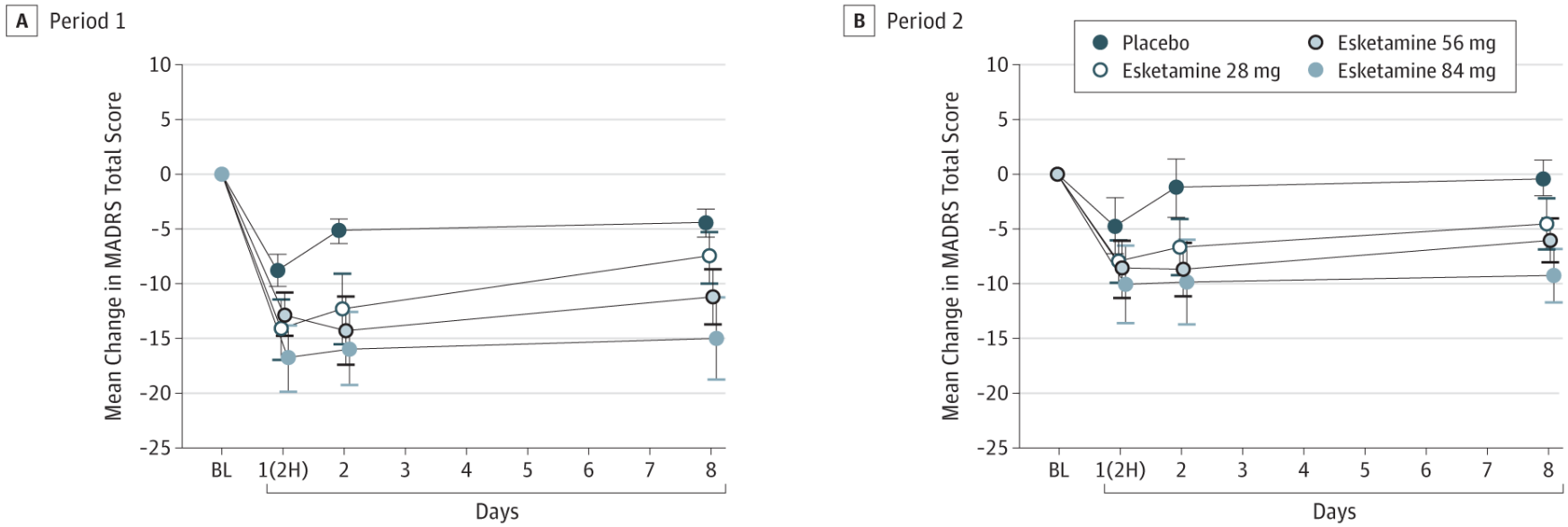
Other NMDA-R Modulators

- **S-ketamine (Johnson & Johnson, Phase III)**
- Repastinel (Glyx-13, Allergan)
- AZD6765 (unselective; AstraZeneca)
- D-cycloserine (glycine partial agonist)
- Nitrous oxide
- Dextromethorphan + qunidine (Nuedexta)

S-Ketamine shows dose-related efficacy

Initial Randomization

Placebo Non-Responders



No. of participants				
Placebo	33	33		33
Esketamine 28 mg	11	11		11
Esketamine 56 mg	11	11		11
Esketamine 84 mg	12	12		12

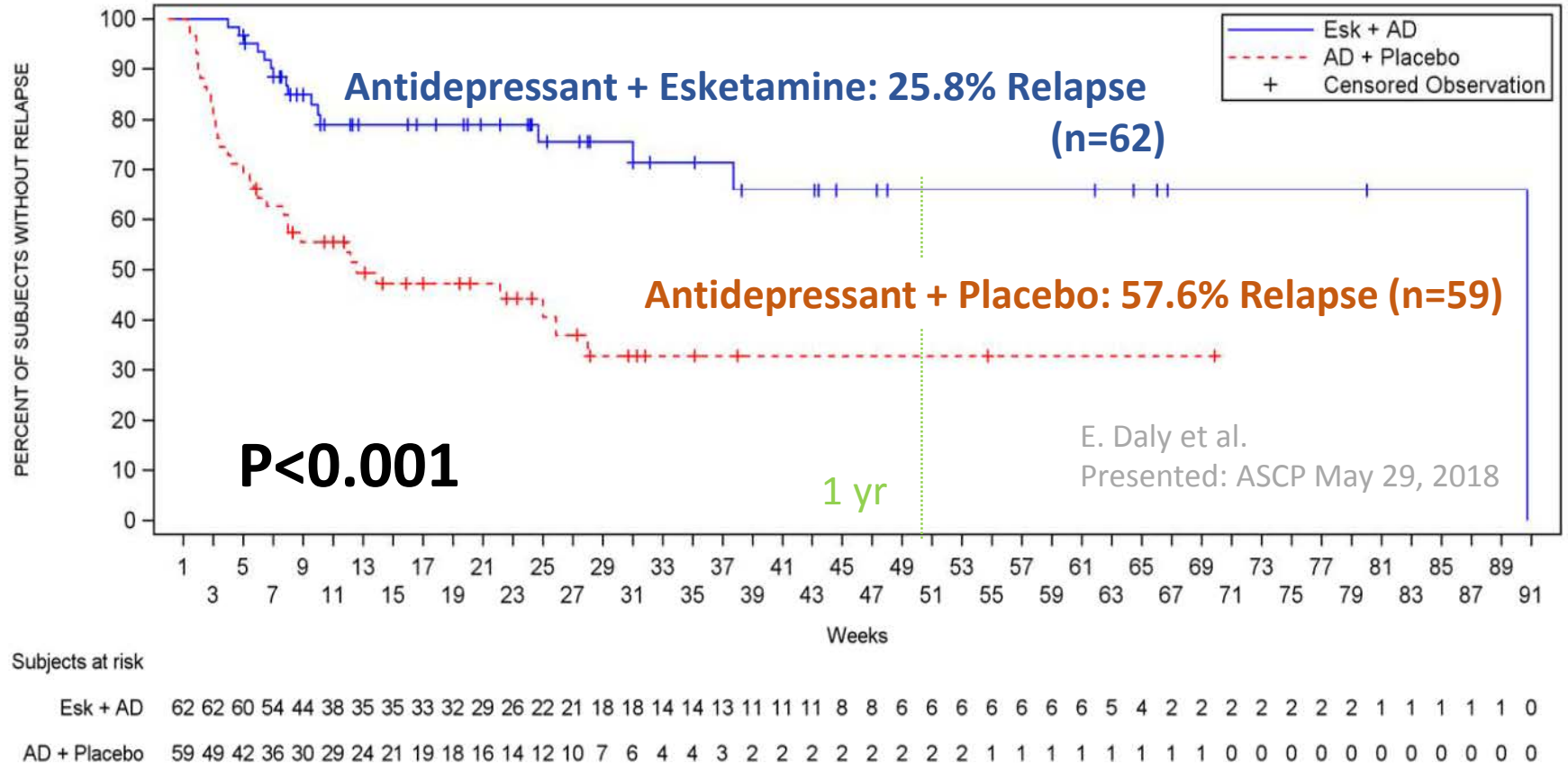
No. of participants				
Placebo	6	6		6
Esketamine 28 mg	8	8		8
Esketamine 56 mg	9	9		9
Esketamine 84 mg	5	5		5

Daly EJ et al. JAMA Psychiatry 2017

S-Ketamine robustly protects against relapse (OR=0.3) in TRD Responders to AD + Esketamine

Janssen Esketamine Study #3003

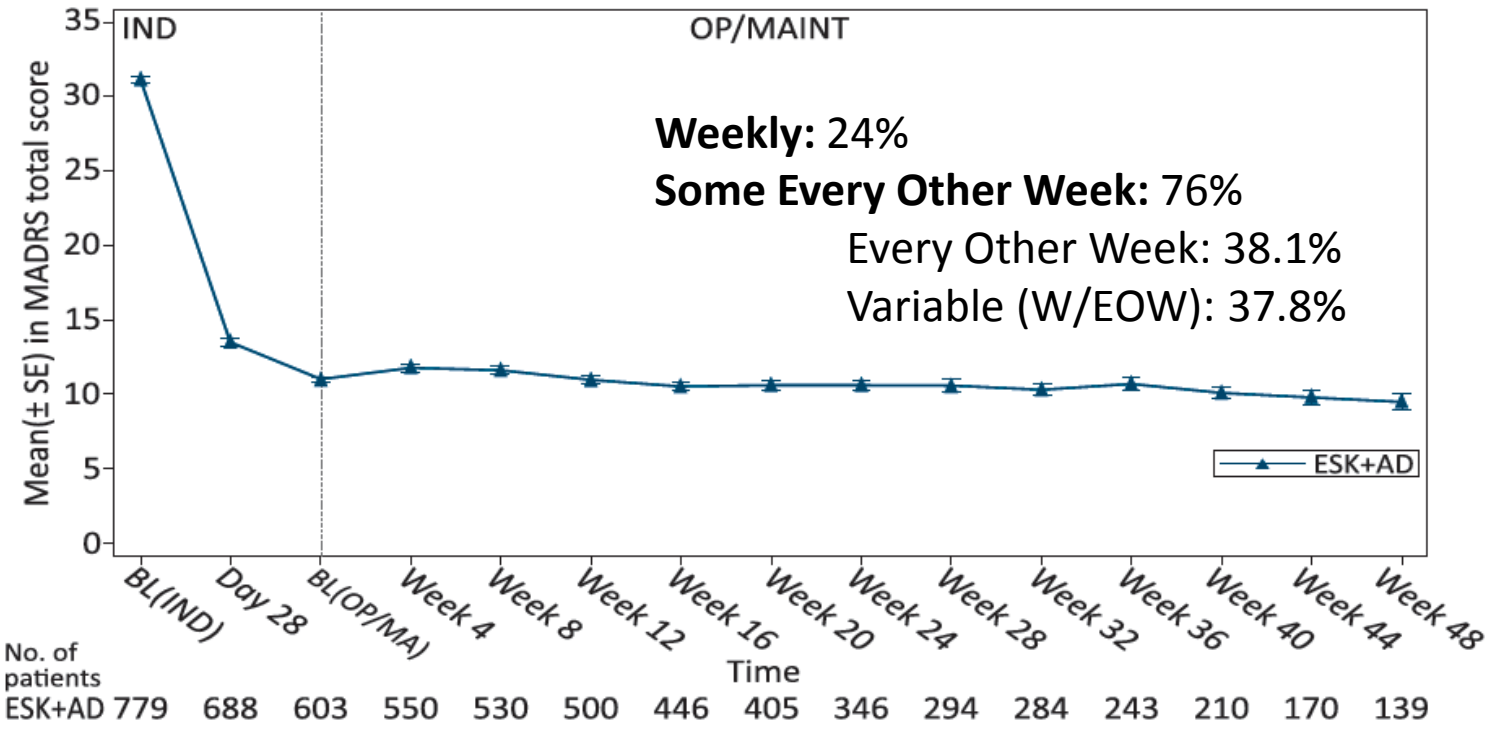
Cumulative Proportion of Subjects Who Remained Relapse Free; Maintenance Phase (Kaplan-Meier Estimates): *Stable Responders*



Long-term open label sustained efficacy (n=603)

Janssen Esketamine Sustain-2 Study

Figure 3: Mean (±SE) Montgomery-Asberg Depression Rating Scale total score over time (full analysis sets [IND and OP/MAINT]; observed case analysis)



Full analysis sets for IND and OP/MAINT: patients who received ≥1 dose of nasal spray study medication or oral antidepressant in the open-label IND and OP/MAINT phases, respectively. AD; oral antidepressant; ESK, esketamine; IND, induction phase; MADRS, Montgomery-Asberg Depression Rating Scale; OP/MAINT, optimization/maintenance phase; SE, standard error

E. Wajs et al. Presented: ASCP May 29, 2018

Long-term open label sustained safety (n=603)

Janssen Esketamine Sustain-2 Study

Table 3: Treatment-emergent adverse events(full analysis sets [IND and OP/MAINT] and all enrolled analysis set)			
	4-week IND phase (N=779)	48-week OP/MAINT phase (N=603)	IND and OP/MAINT phases (N=802)
	n (%)	n (%)	n (%)
Patients with ≥1 TEAEs	653 (83.8)	516 (85.6)	723 (90.1)
Patients with ≥1 SAEs	17 (2.2)	38 (6.3)	55 (6.9)
TEAEs leading to discontinuation of intranasal spray medication	53 (6.8)	23 (3.8)	76 (9.5)
TEAEs leading to discontinuation of oral AD	20 (2.6)	14 (2.3)	33 (4.1)
TEAEs leading to death	0	2 (0.3)	2 (0.2)

E. Wajs et al. Presented: ASCP May 29, 2018

Features

- **Safe:**
  - AE rate in 205 infusions = 1.95%
  - Psychosis/dissociation is transient manageable with support
  - Nausea managed with ondansetron pretreatment
  - Abuse liability with restricting to clinic administration
- **Effective in TRD and Suicidal ideation**
  - 75% response in clinics
  - Synergy with CBT (extending benefit)
  - ECT non-responders
  - Bipolar, Psychotic depression, Anxious, Comorbid pain
- **Sustained benefit:**
  - Biweekly-monthly administration
  - Clinical experience: >4 yr

Wan et al. J Clin Psychiatry 2014;Ibrahim et al. Prog Neuropsychopharm Biol Psych 2011; DiazGranados N et al. J Clin Psychiatry 2010; Lapidus KA et al. Biol Psych 2014; Irwin et al. Psychosomatics 2014; Wilkinson et al. AJP 2017; Wilkinson et al. Psychother Psychosom 2017

Treating depression in context of pain

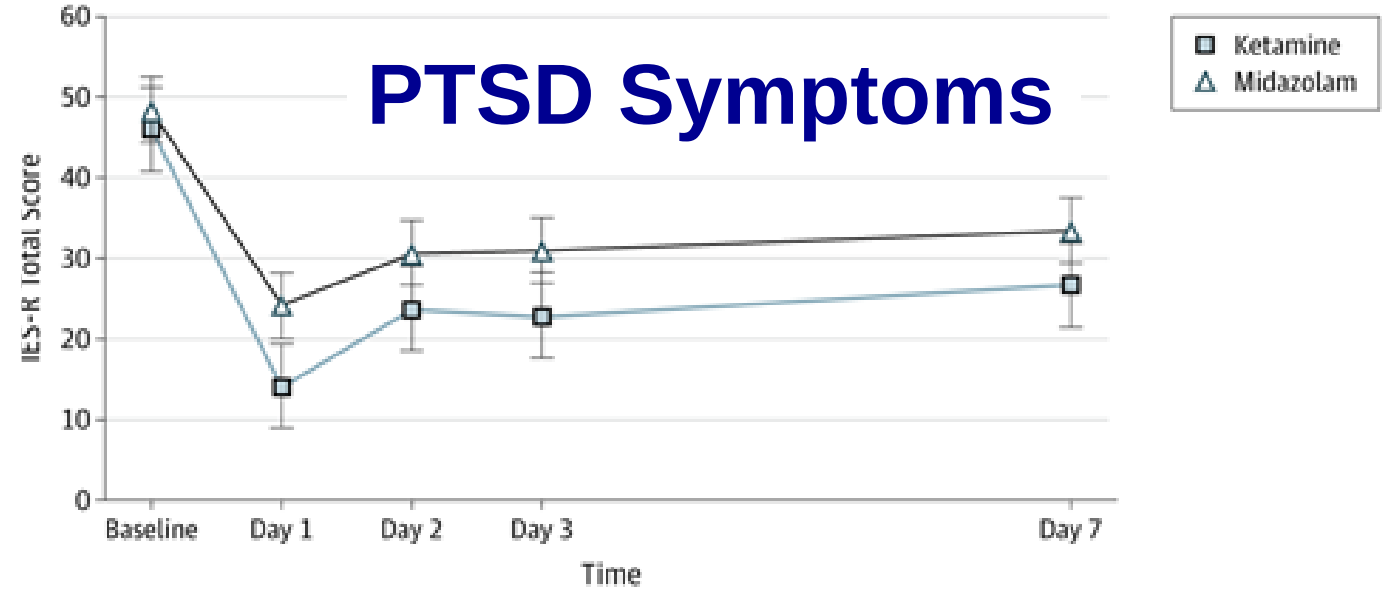
Ketamine for the Treatment of Depression in Patients Receiving Hospice Care: A Retrospective Medical Record Review of Thirty-One Cases

Psychosomatics 2014

Alana Iglewicz, M.D., Katherine Morrison, M.D., Richard A. Nelesen, Ph.D., Tingting Zhan, Ph.D., Boris Iglewicz, Ph.D., Nathan Fairman, M.D., M.P.H., Jeremy M. Hirst, M.D., Scott A. Irwin, M.D., Ph.D.

- Rapid improvement in depression and pain
- Ketamine is well-tolerated and safe
- Sustained by repeated dosing

PTSD
(n=41)



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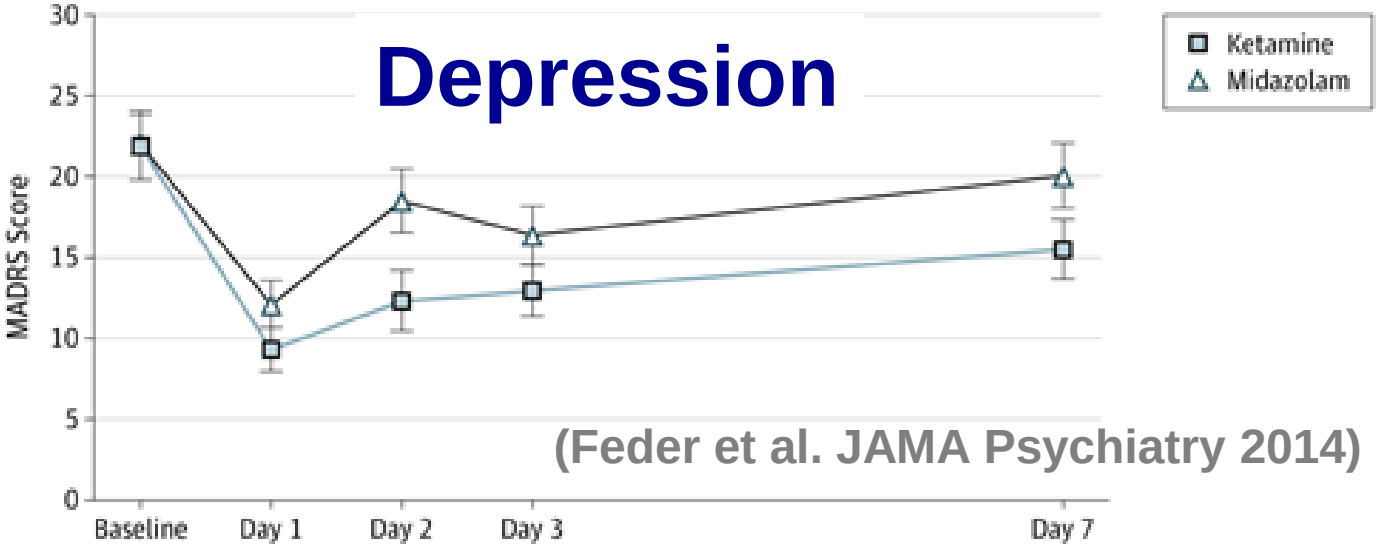
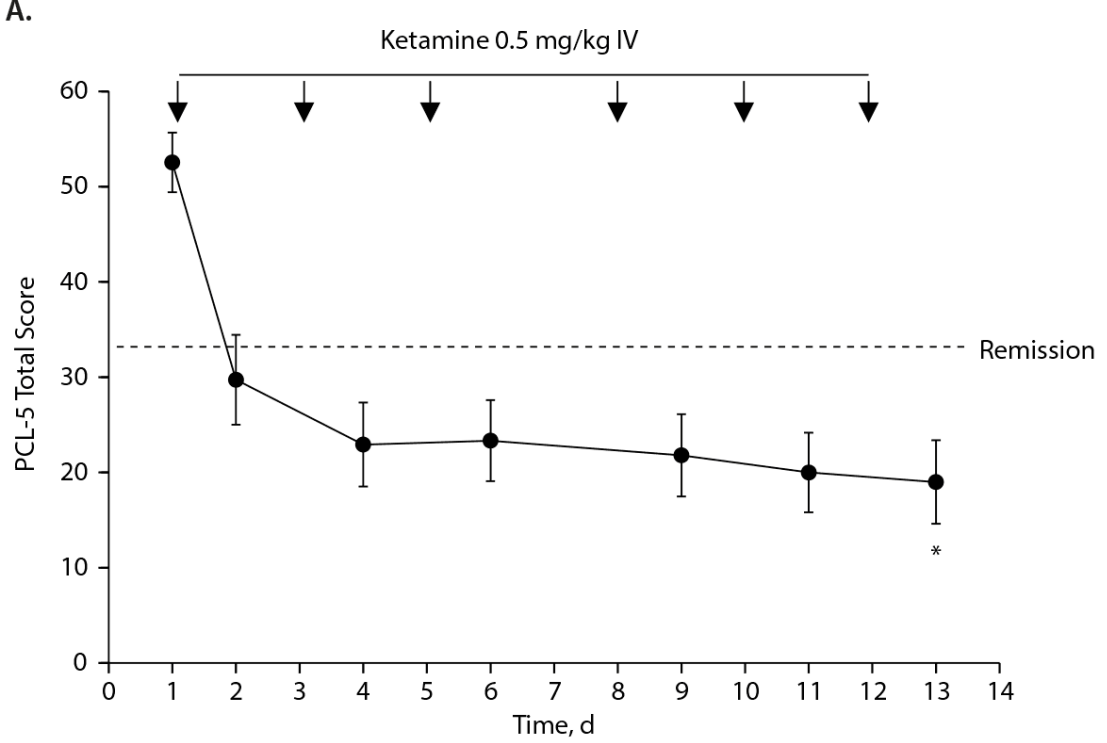
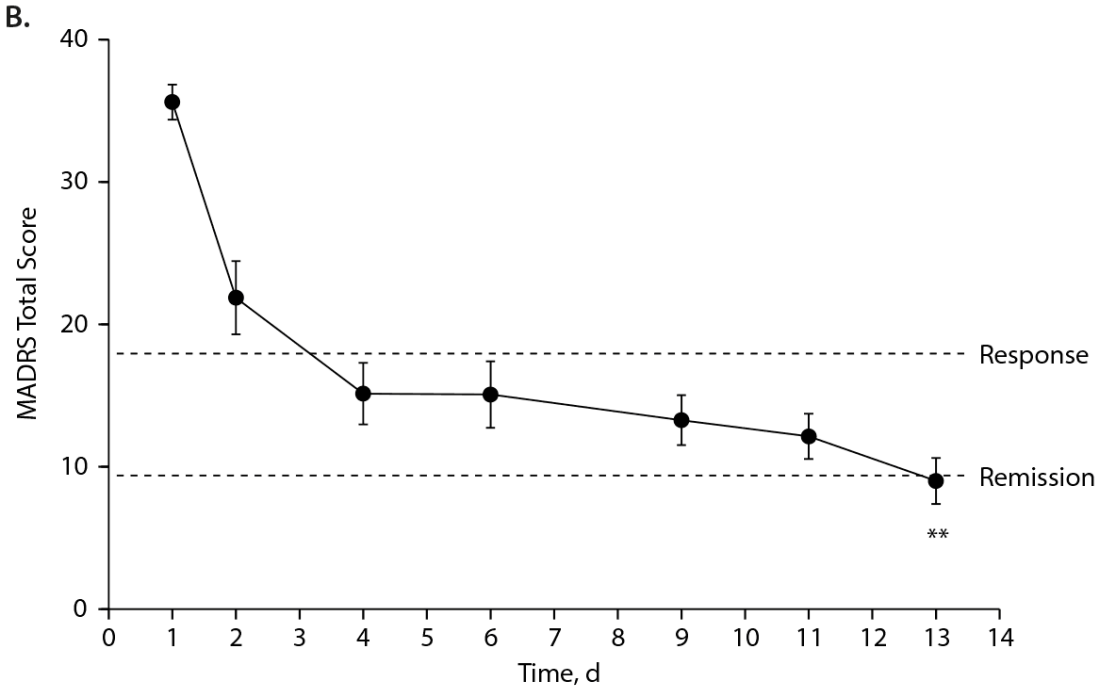


(Feder et al. JAMA Psychiatry 2014)

Ketamine PTSD Open Label Efficacy (n=15)

Abbott et al.
J Clin Psychiatry
2018





CAP Ketamine Study

- Team: (West Haven) C. Abdallah, L. Averill, J. Krystal, (San Antonio): A. López-Roca, J. Roache, S. Young, et al.
- PTSD (n=198) from VA and DoD
- Dose related safety and efficacy (0, 0.2, 0.5 mg/kg)
- Treatment: 4 weeks
- Durability of benefit: 4 weeks
- Banking of biosamples

New roles for ketamine in the treatment of PTSD

- **Rapid Remission:**
  - Crisis intervention/suicide prevention?
  - Mitigating/shortening hospitalization?
  - Prevent missed work days?
- **Treatment-resistant PTSD**

Outline

- Glutamate synaptic dysfunction and loss in PTSD
- Toward ketamine treatment for PTSD
- Where do we go from here?

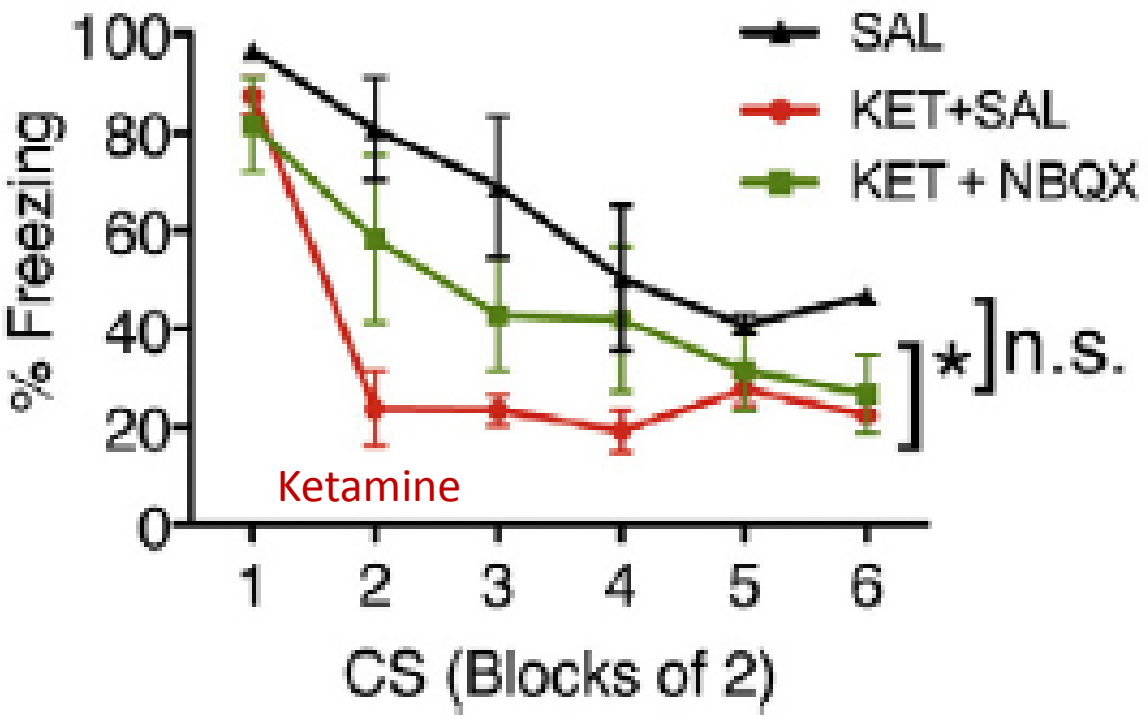
Key directions

- Optimize use of ketamine for PTSD
- Optimize ketamine (alternatives)

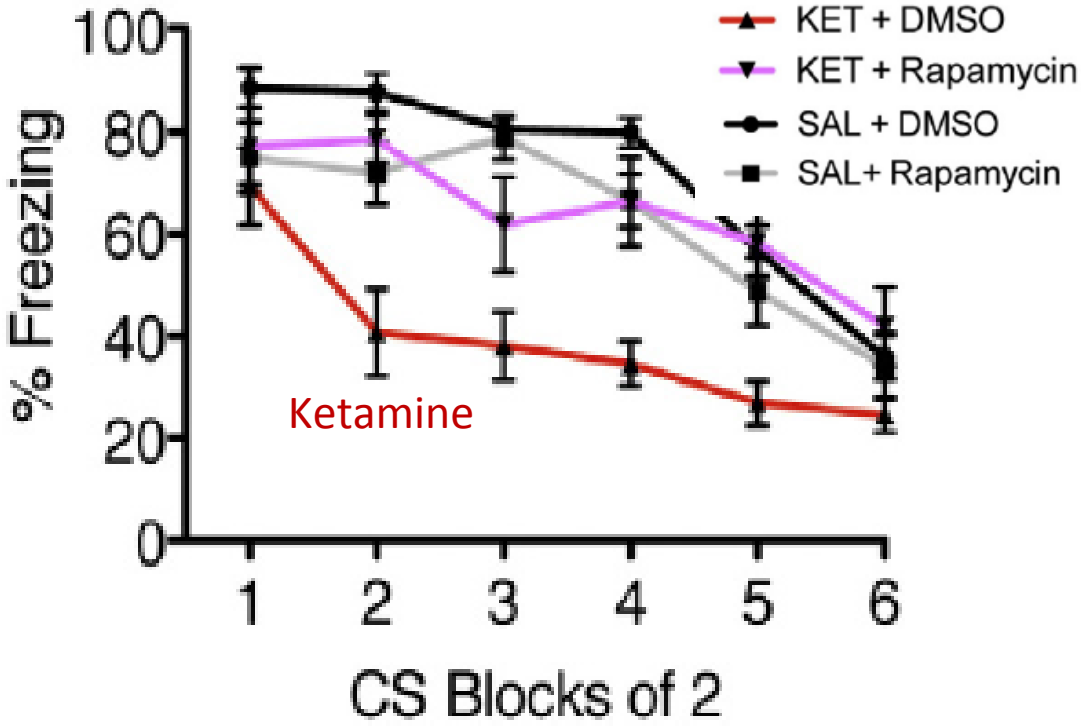
Ketamine accelerates fear extinction: combine with PE or CPT?

Girgenti et al. Neurobiology of Disease 2017

Effect is Dependent on AMPA-R



Effect is Dependent on mTOR

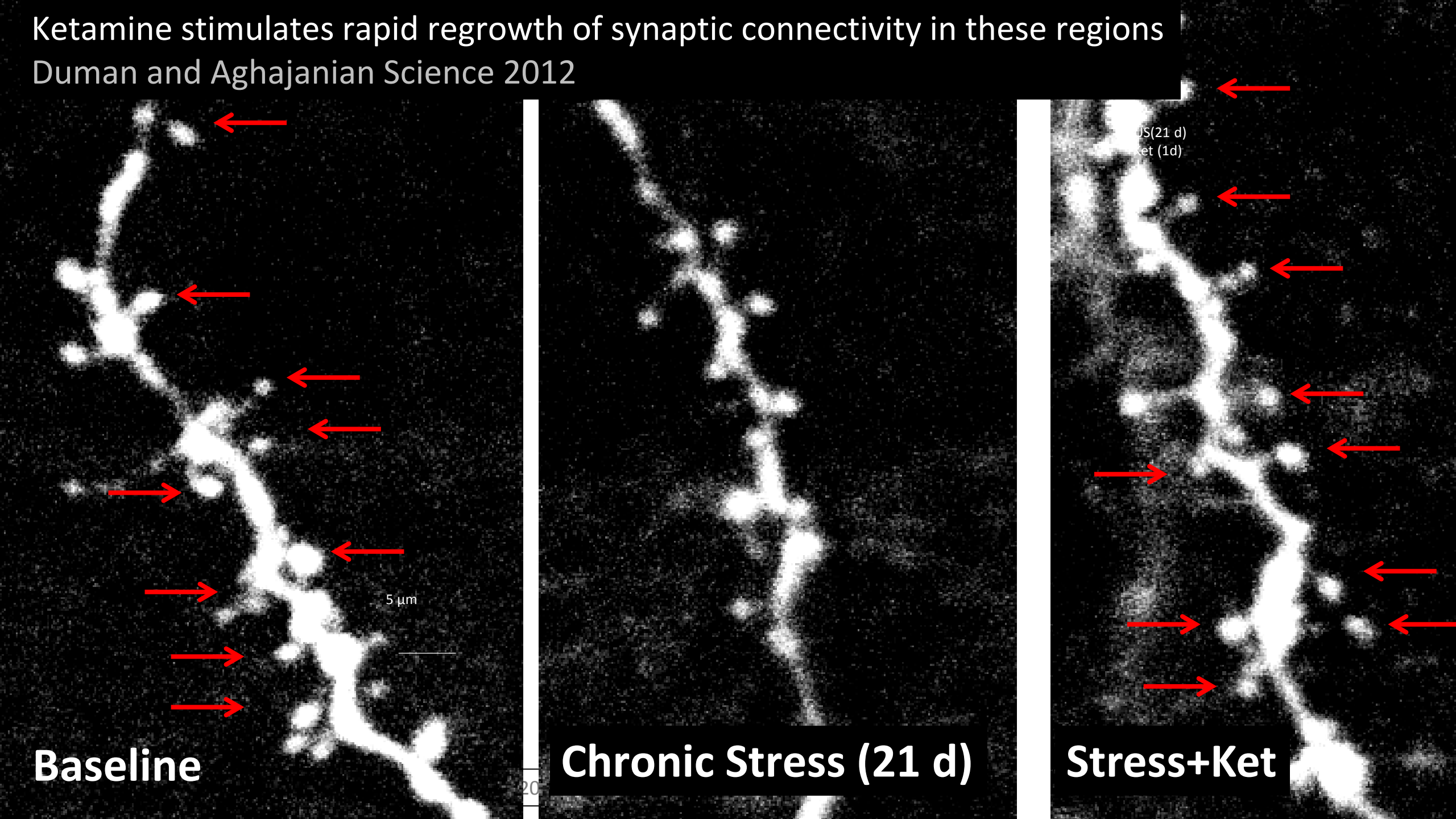


Key directions

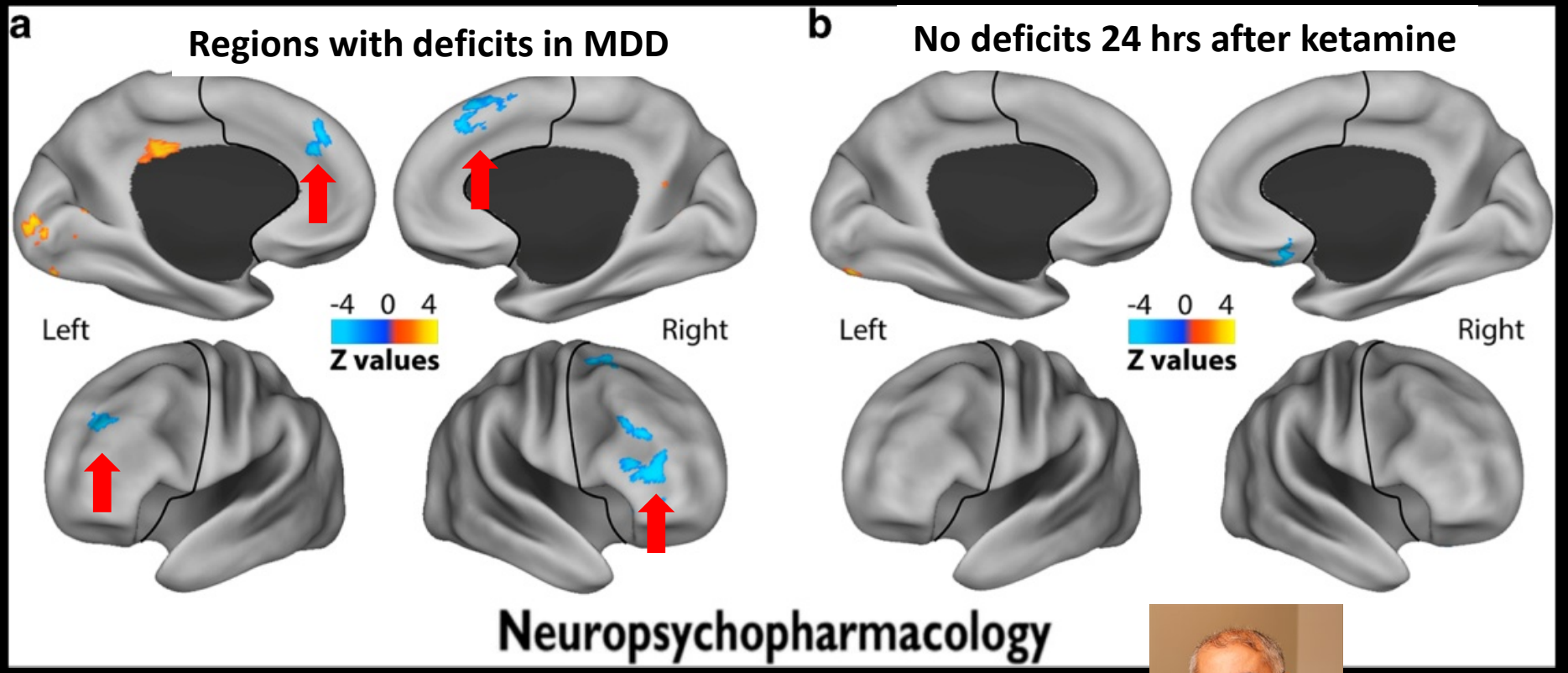
- Optimize use of ketamine for PTSD
- Optimize ketamine (alternatives)
  - Need to understand how it works

Ketamine stimulates rapid regrowth of synaptic connectivity in these regions

Duman and Aghajanian Science 2012



amine stimulates rapid restoration of functional connectiv epressed patients

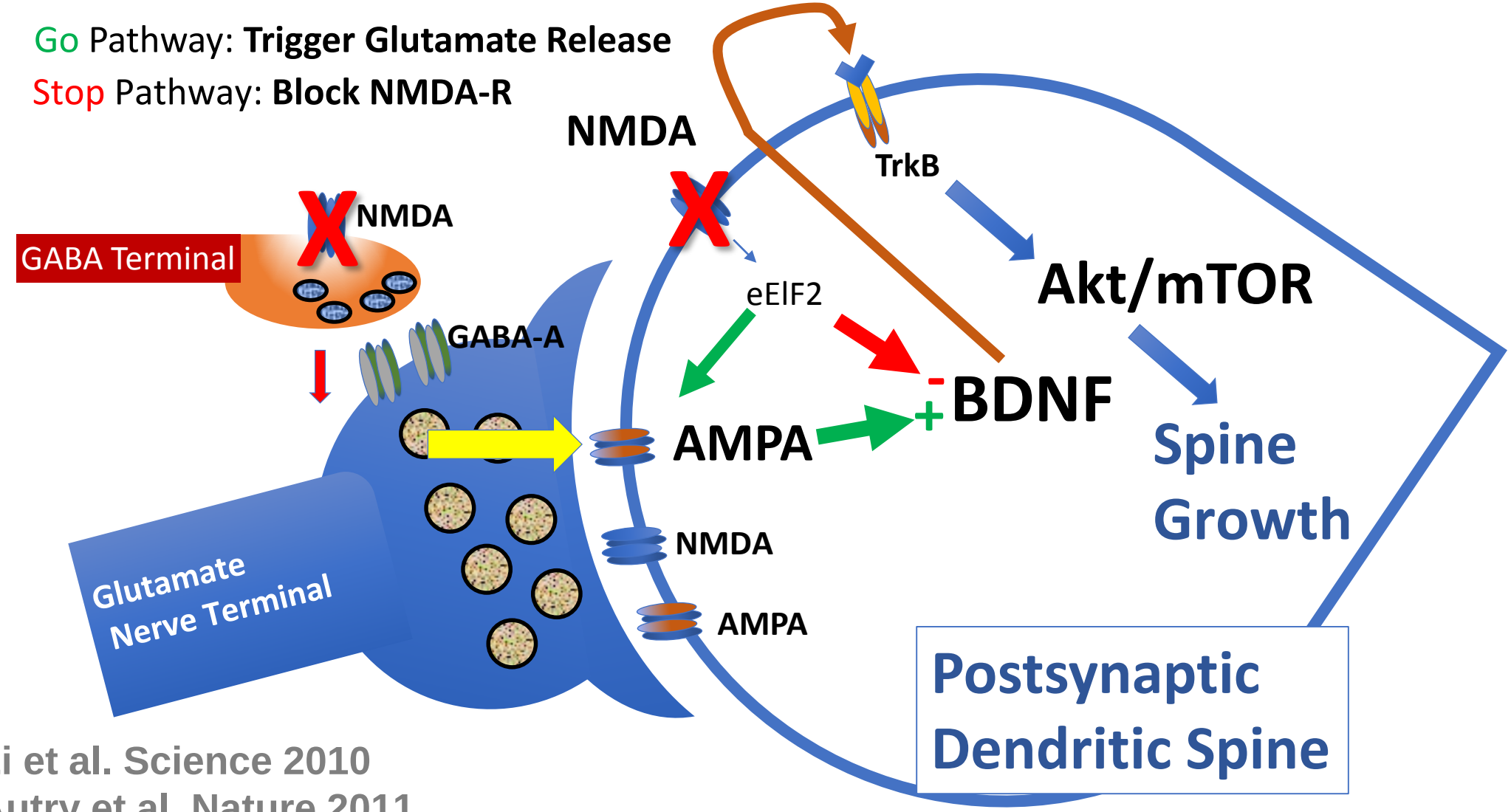


Chadi Abdallah C et al. NPP 2016

Hypotheses Regarding Ketamine Efficacy

Go Pathway: **Trigger Glutamate Release**

Stop Pathway: **Block NMDA-R**

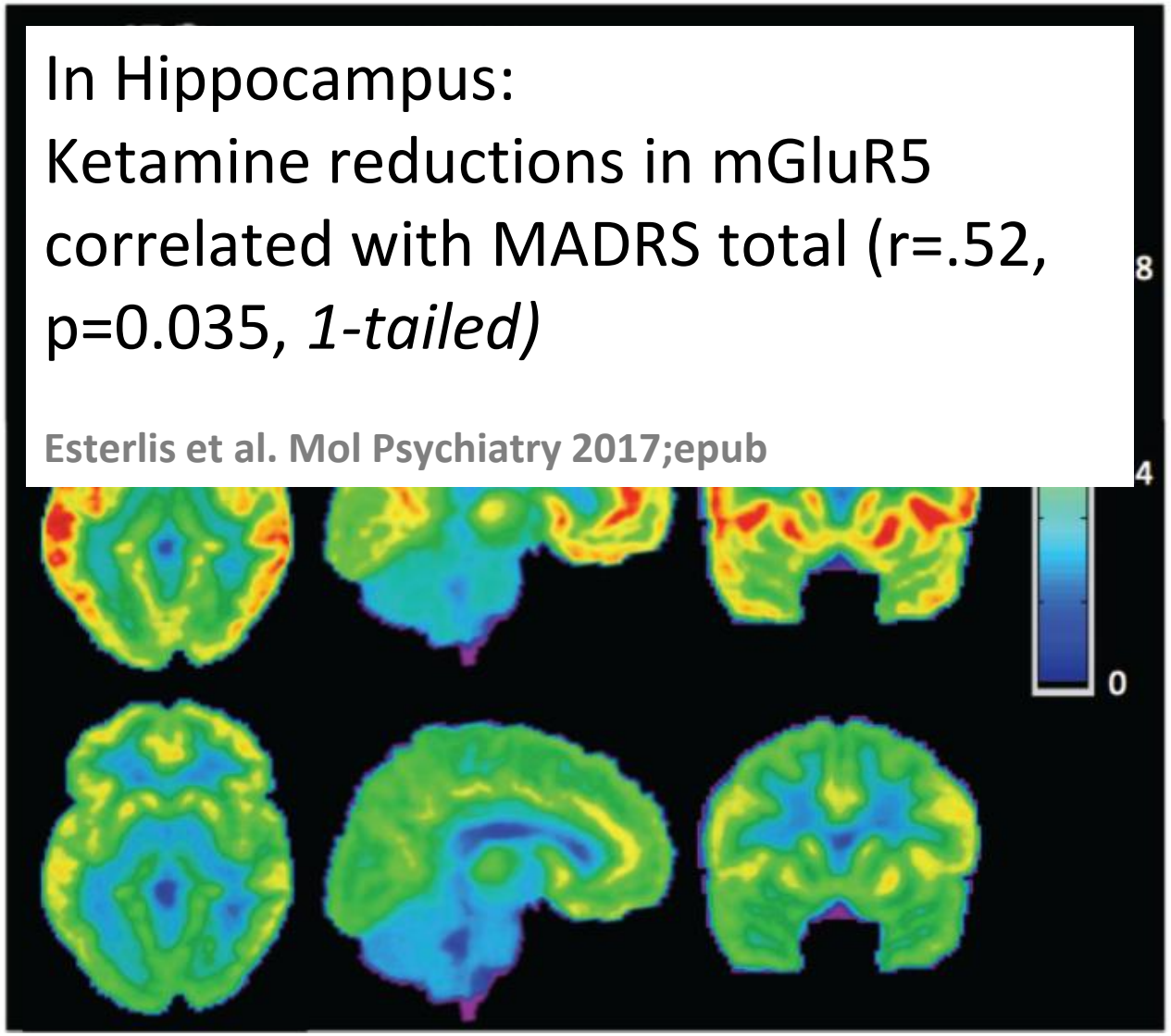


Li et al. Science 2010

Autry et al. Nature 2011

Ketamine efficacy related to mGluR5 normalization?

mGluR5 NAMs?



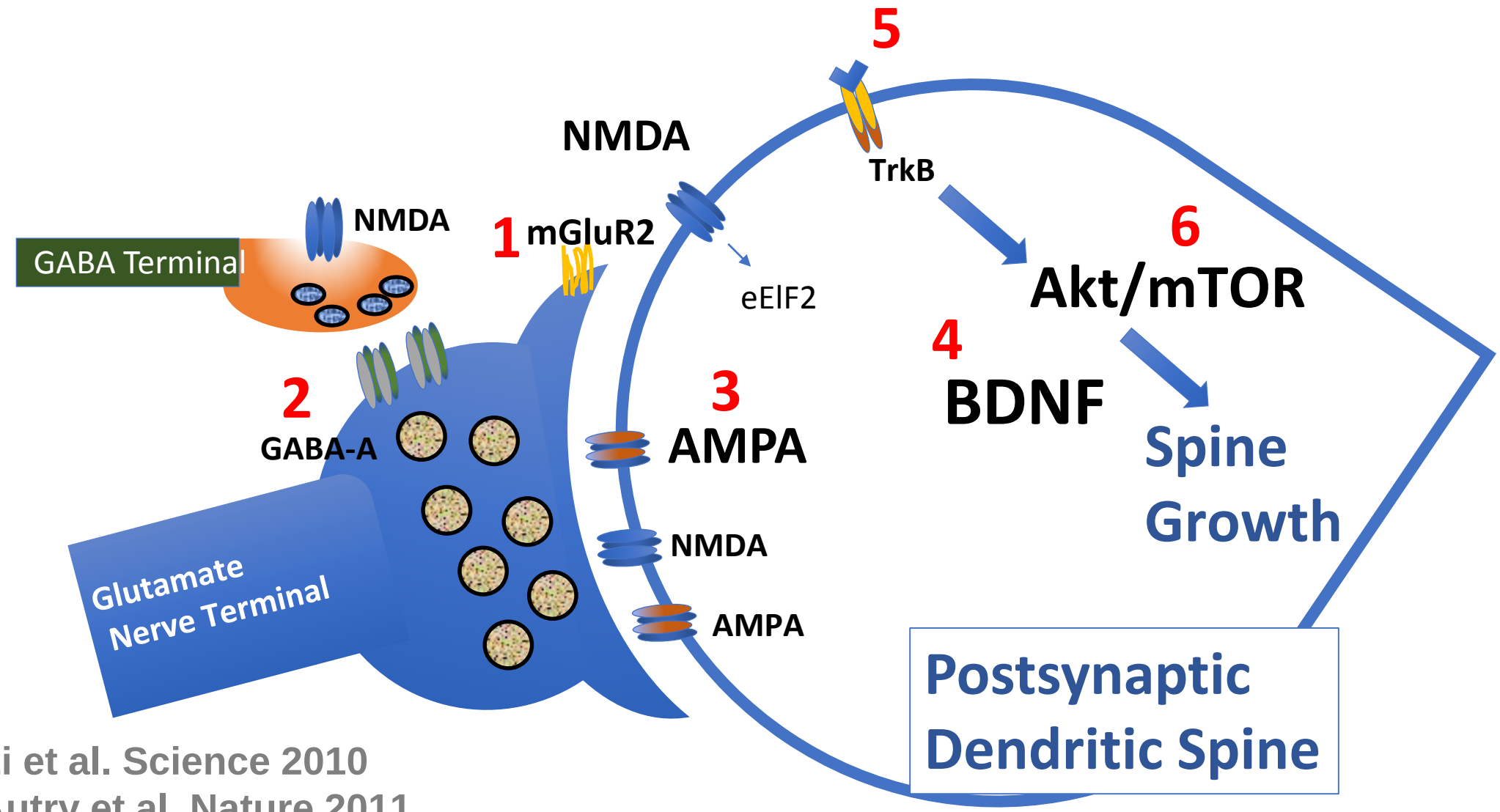
In Hippocampus:
Ketamine reductions in mGluR5 correlated with MADRS total (r=.52, p=0.035, *1-tailed)*

Esterlis et al. Mol Psychiatry 2017;epub

DeLorenzo et al. Biol Psychiatry 2015

Healthy Subjects N=10

Novel Non-NMDA Candidate Antidepressant Targets



Li et al. Science 2010
Autry et al. Nature 2011

Summary: A new opportunity

- The promise:
  - Rapid action
  - Anti-suicidal
  - Treatment-resistant
  - Promote fear extinction
- Tip of the iceburg: novel mechanisms
  - PTSD
  - Treatment