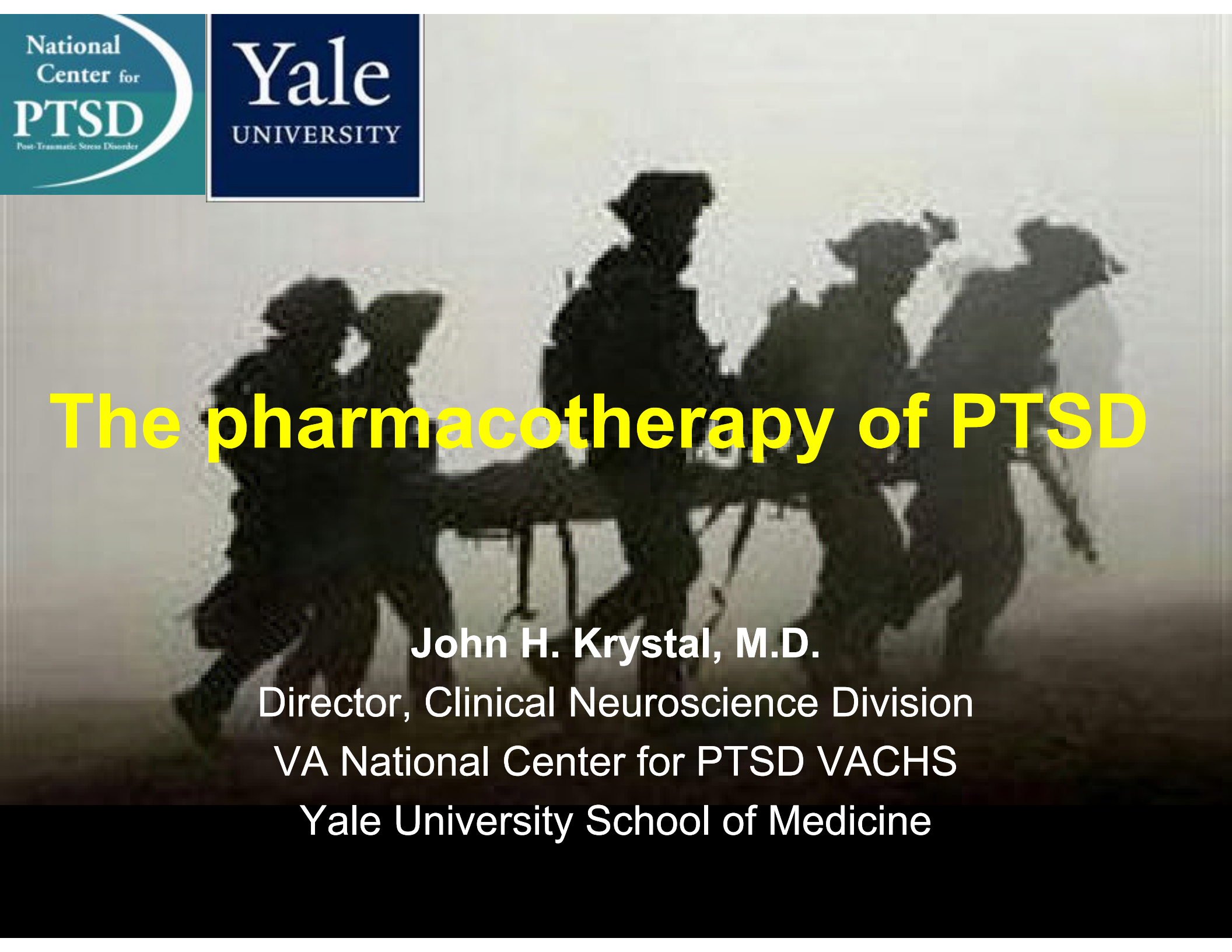


The pharmacotherapy of PTSD

John H. Krystal, M.D.
Director, Clinical Neuroscience Division
VA National Center for PTSD VACHS
Yale University School of Medicine

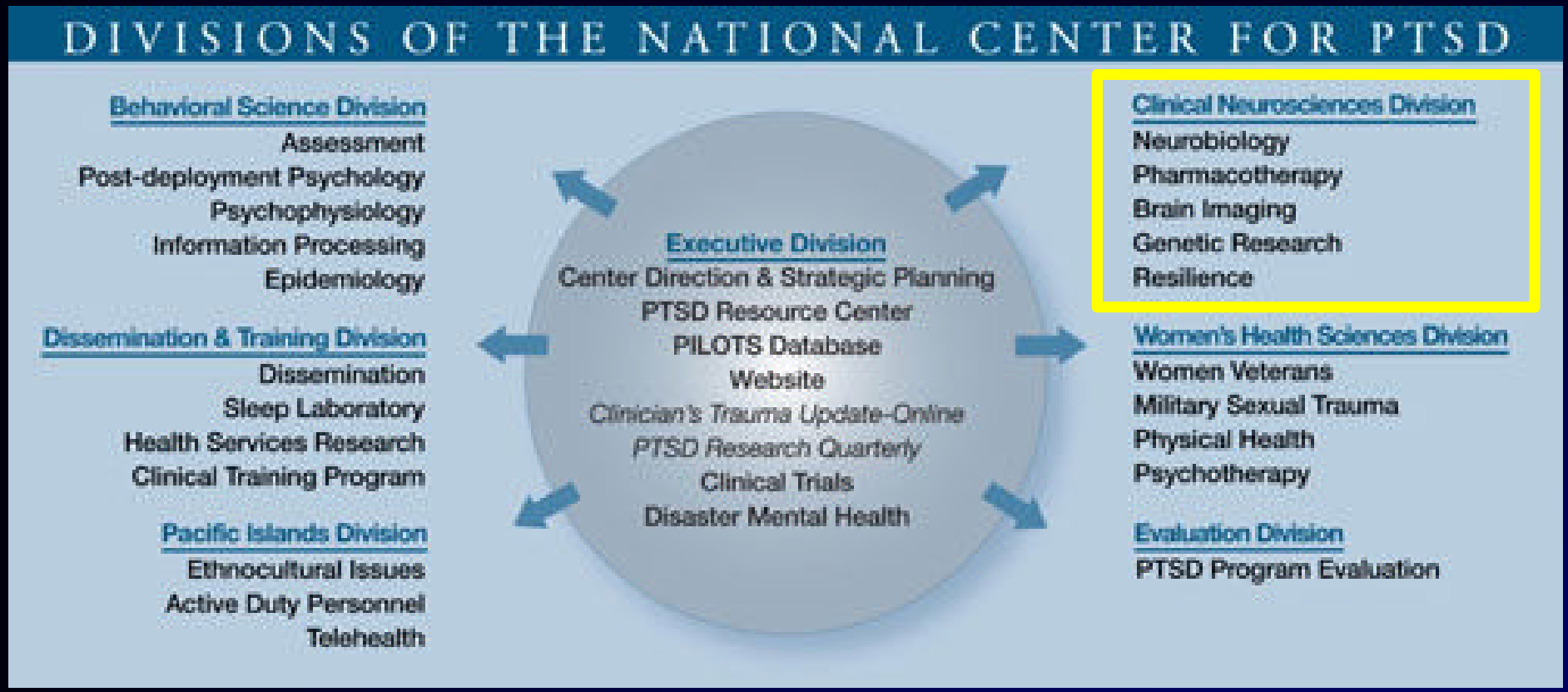
Financial Disclosure

Scientific Consultation 2 yrs: (all <10K/yr) Medivation, Sunovion, Takeda, Teva. Abbott, Bristol-Myers Squibb, Eisai, Eli Lilly and Co., Forest, Lohocla, Mnemosyne, Naurex, Pfizer, Shire

Research Contracts: Pfizer, AstraZeneca

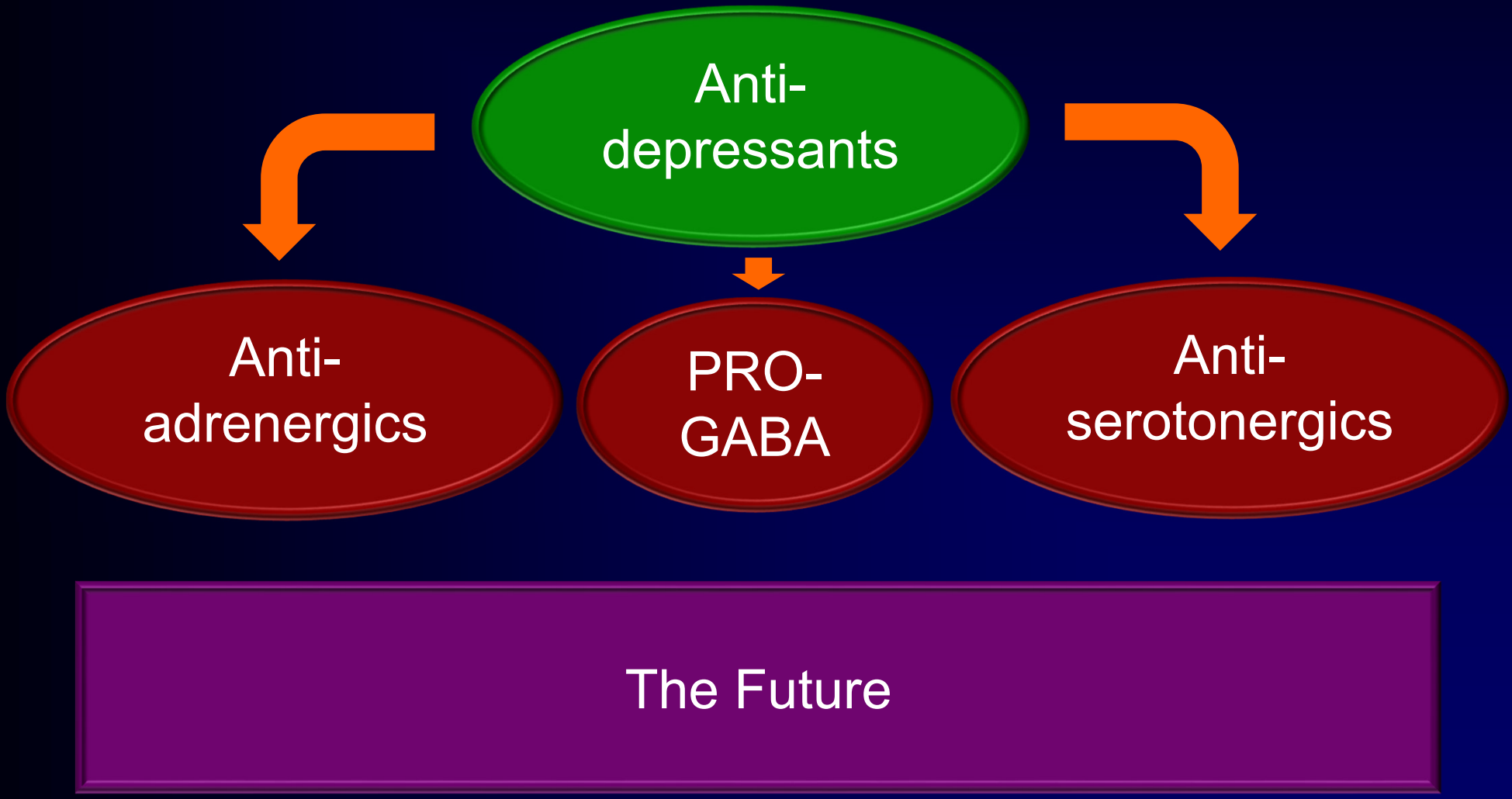
Patents: I am a co-sponsor of two pending patents: 1) glutamatergic agents for psychiatric disorders (depression, OCD) 2) antidepressant effects of oral ketamine.

Clinical Neuroscience Division, VA National Center for PTSD



Opinions expressed are my own and do
not represent NCPTSD, DVA, or U.S. Government

The pharmacotherapy of PTSD



Antidepressants superior to placebo (Frank et al. AJP 1988)

A Randomized Clinical Trial of Phenelzine and Imipramine for Posttraumatic Stress Disorder

Julia B. Frank, M.D., Thomas R. Kosten, M.D.,
Earl L. Giller, Jr., M.D., Ph.D., and Elisheva Dan, P.A.

Several studies (1–5) have used antidepressants to treat more than 60 patients with posttraumatic stress disorder (PTSD) and found that tricyclic antidepressants and monoamine oxidase (MAO) inhibitors are helpful in 67%–82% of cases. Here we report the preliminary results of what we believe to be the first placebo-controlled, double-blind clinical trial of both types of antidepressants in the treatment of PTSD.

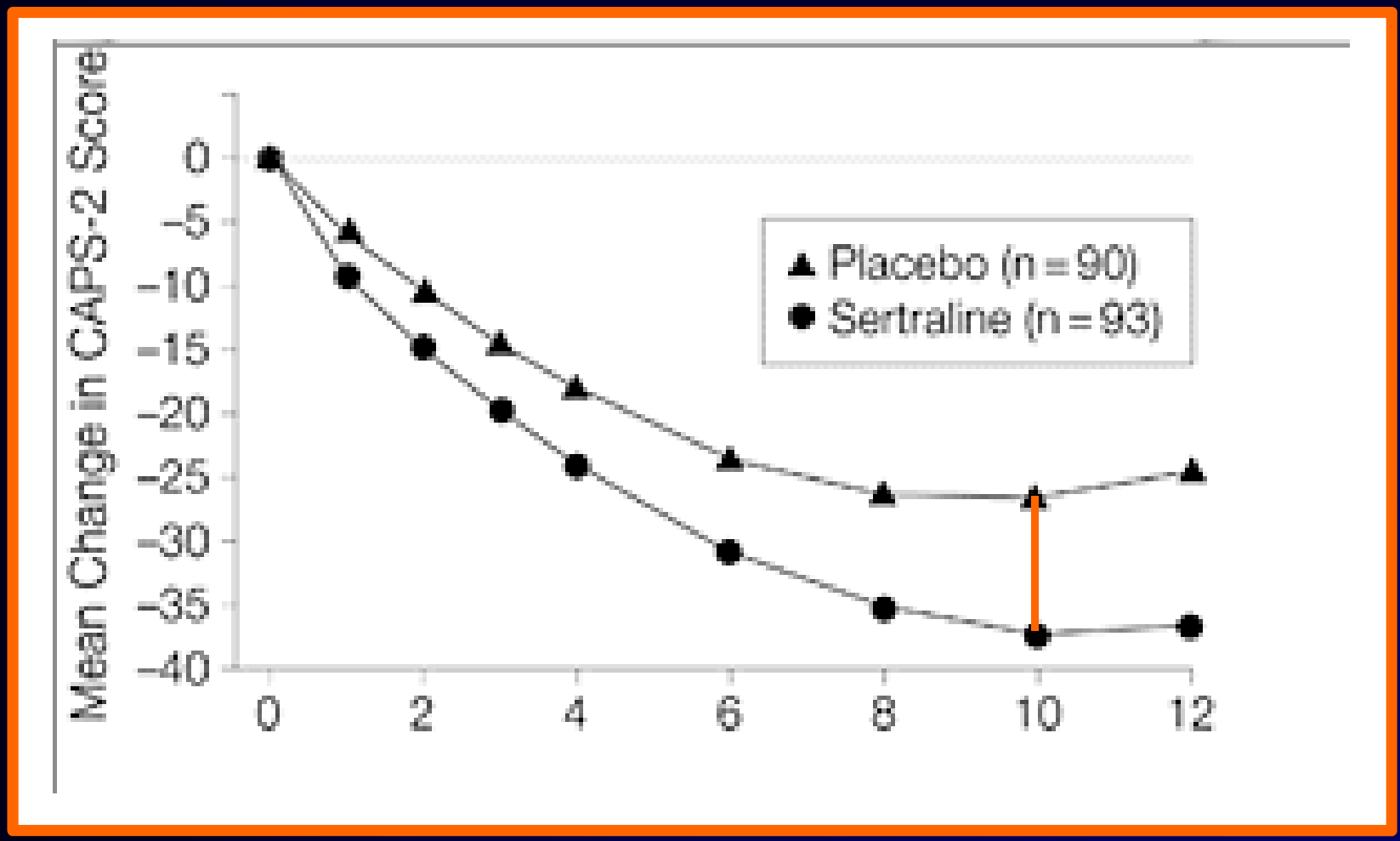
In a double-bli
ficacy of imipram
with that of plac
traumatic stress d
duced PTSD sym
(Am J Psychiat

he extent of trauma
o assess PTSD symp-
nd the Raskin scale
Event Scale includes
ssess intrusion and
le scores above 3 in-
ure. Subjects were
nt, Covi, and Raskin

Findings

- IMI and MAOI both effective (MAOI>IMI)
- Intrusion (hyper-arousal and reexperiencing) better than avoidance (avoidance, numbing)
- Depression did not improve much

Sertraline efficacy emerges slowly
K. Brady et al. *JAMA* 2000;283



FDA-Approved SSRI's: Sertraline and Paroxetine

- Better for some symptoms?
  - Sertraline: avoidance/numbing≥ hyperarousal > reexperiencing? (Brady JAMA 2000; Davidson Arch Gen Psychiatry 2001)
- Profile of best response:
  - Positive studies: 10% - 20% bigger reduction from baseline than placebo
  - single trauma, acute, female, no substance abuse
- Veterans: A negative sertraline study (Friedman J Clin Psychiatry 2007)

Do SSRI's Compromise Resilience?

Shalev et al. Arch Gen Psychiatry 2012

12-week study follow-up

PLA: Placebo

SSRI: S-citalopram 10 mg

WL: Wait list control

CBT: Cog.-Behav Therapy

PE: Progressive Exprosure

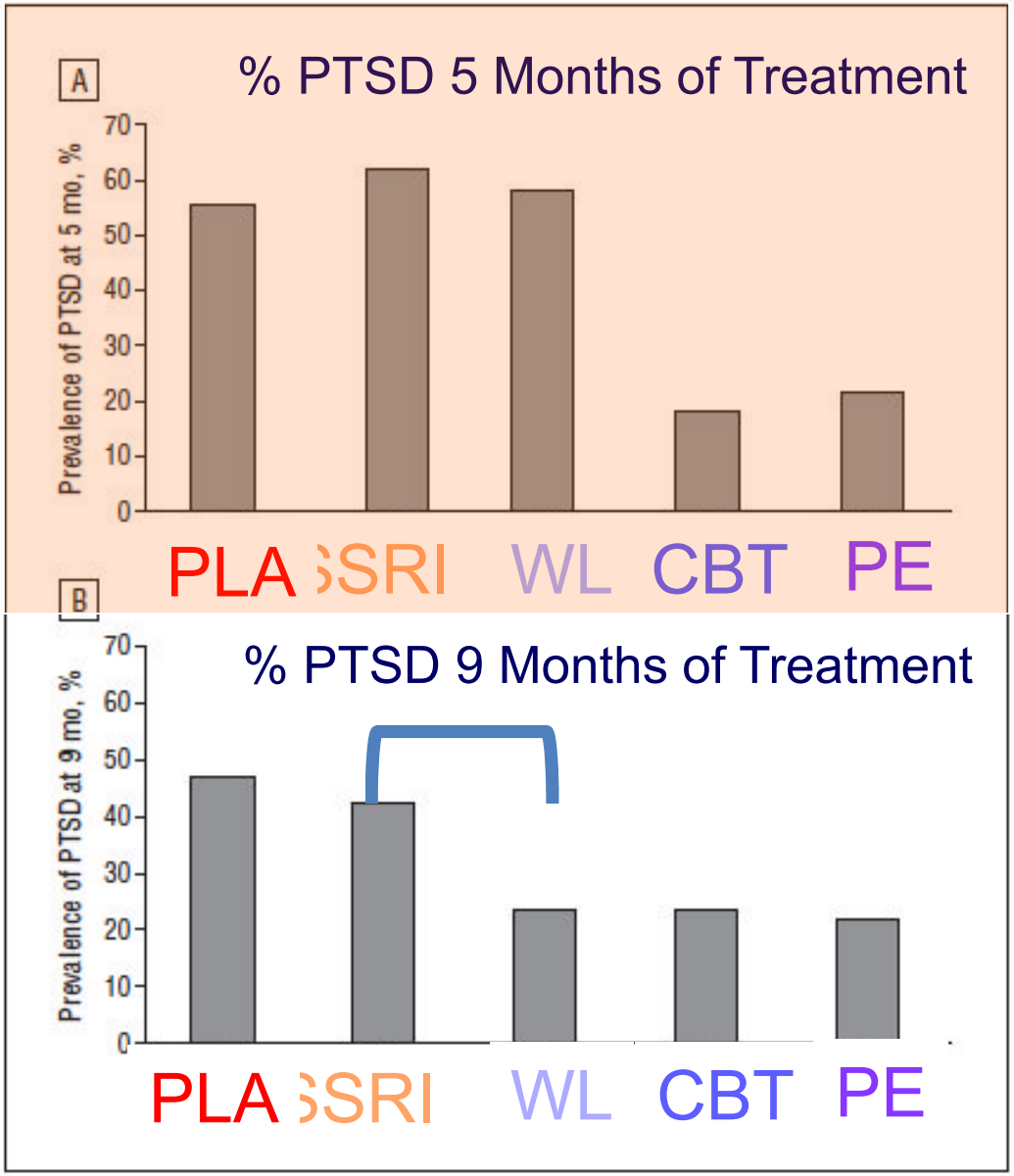
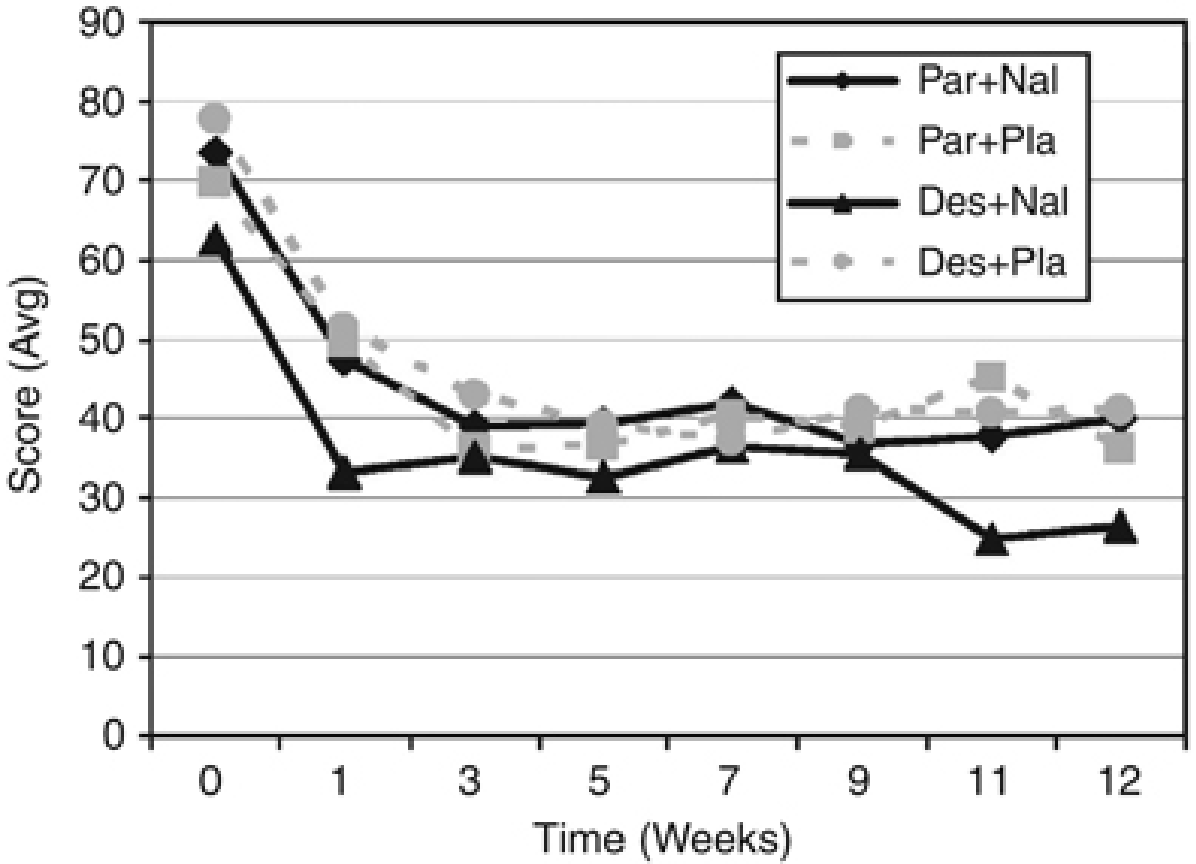


Figure 2. Prevalence of posttraumatic stress disorder (PTSD) at 5 and 9 months, by study group. CT indicates cognitive therapy; PE, prolonged exposure; SSRI, selective serotonin reuptake inhibitor; WL, waiting list (participants received delayed PE).

Norepinephrine Reuptake Inhibition:

Desipramine (DMI) = Paroxetine (± Naltrexone)

Petrakis et al. Neuropsychopharm 2011



Par = Paroxetine; Nal = Naltrexone; Pla = Placebo; Des = Desipramine

Slight advantage for SRI + NRI?
Davidson et al J Clin Psychopharm 2006

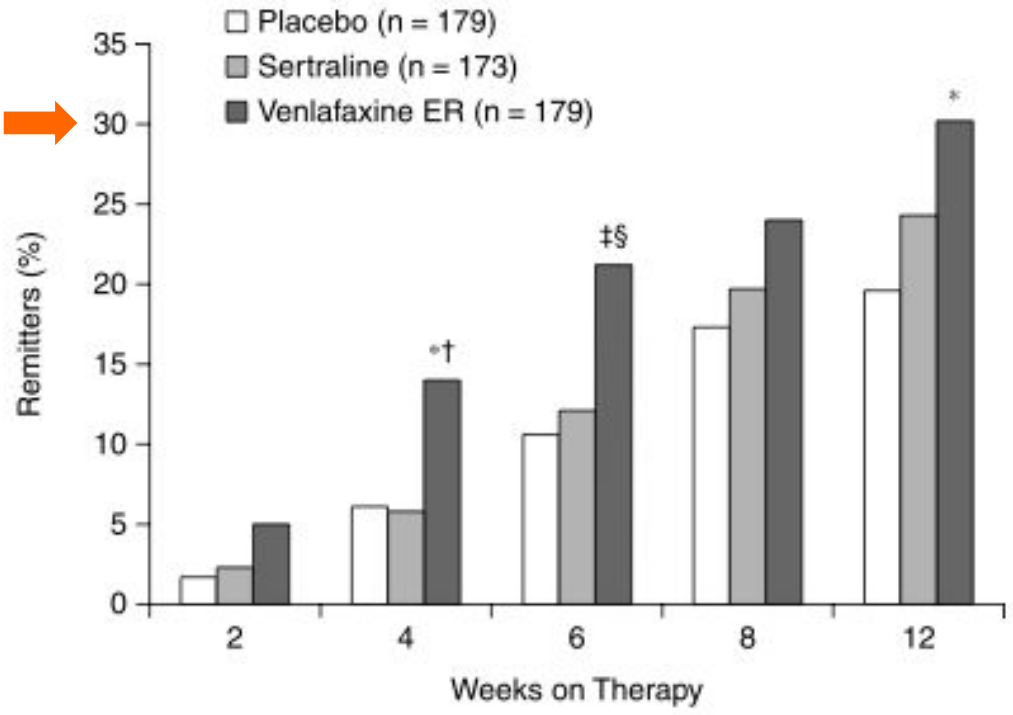


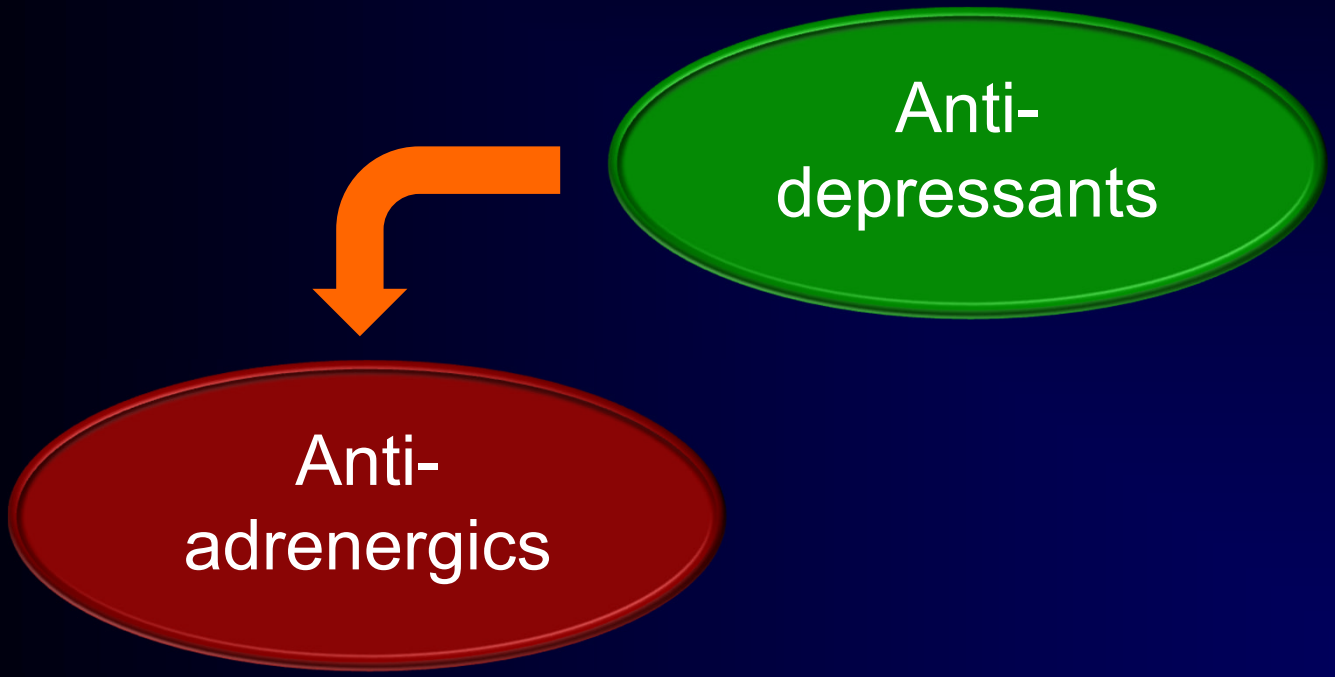
FIGURE 2. *P* value for the treatment differences are based on the Pearson χ^2 test. Remission = CAPS-SX_{17} total score $\leq$ 20. **P*<0.05 venlafaxine ER vs placebo; †*P*<0.01 venlafaxine vs. sertraline; ‡*P*<0.001 venlafaxine ER vs. placebo; §*P*<0.05 venlafaxine ER vs. sertraline.

- Venlafaxine ER
- 12-week
- Flexible dose
- 538 randomized
- 350 completers
- Vs PLA: 10%
- Vs SSRI: 5%

Antidepressant summary

- All helpful (TCA, MAOI, SRI, NRI, SNRI)
- Slow onset of efficacy (~10 wks)
- SSRI's better for "negative" (avoidance numbing) than "positive" (hyperarousal, reexperiencing)?
- Tolerability an issue: slow, flexible titrations
- In chronic populations, low remission rates

The pharmacotherapy of PTSD



Noradrenergic hyperactivity: Pathological Alarm

W.B. Cannon

- NE: FIGHT or FLIGHT
- Dysregulation: NE hyperactivity at rest
- Learning: Reminders activate NE systems

Kosten et al. J Nerv Ment Dis 1987; Yehuda et al. Biol Psychiatry 1988; Sher et al. Eur Neuropsychopharm 2005;

Yohimbine-Induced Flashback: Combat Veteran with PTSD

Patient:	(Appears agitated)
Dr. Krystal:	What's happening?
Patient:	The helicopter is going down!
	I saw the flash of light and the smoke trail! It's crashing! I can hear it! I can smell smoke!

Reduced Norepinephrine Uptake May Increase Synaptic NE in PTSD

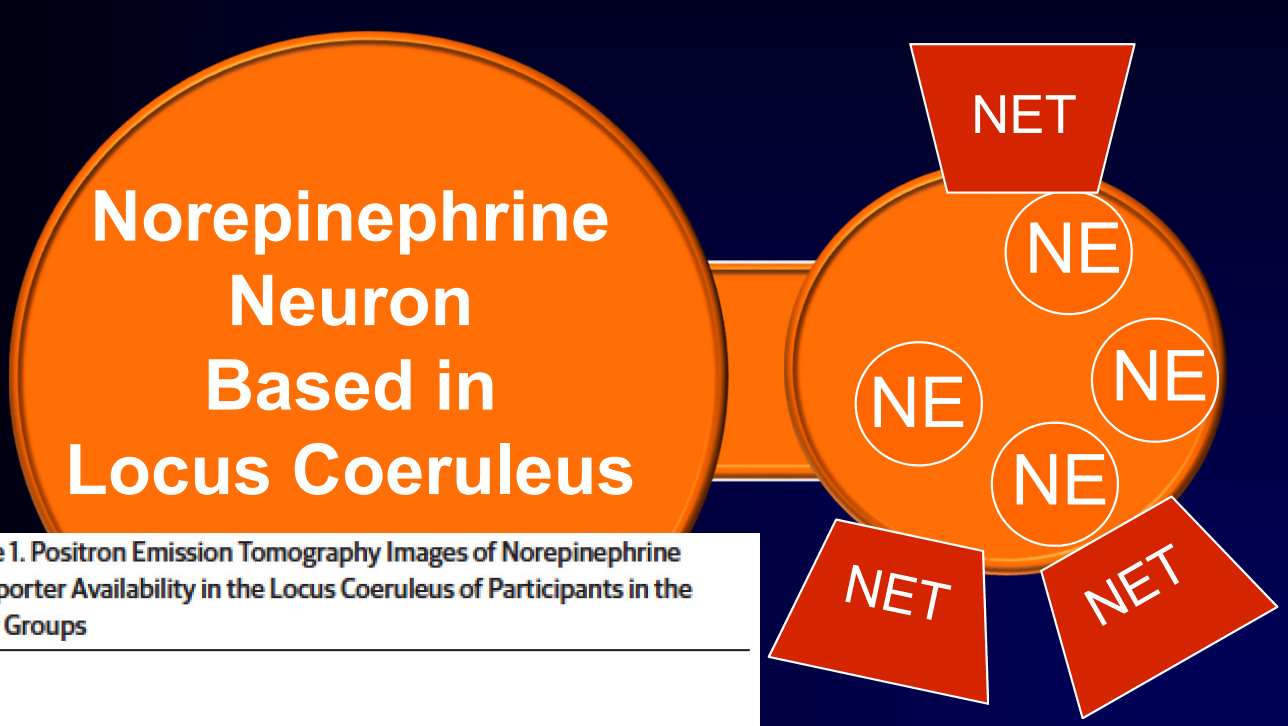
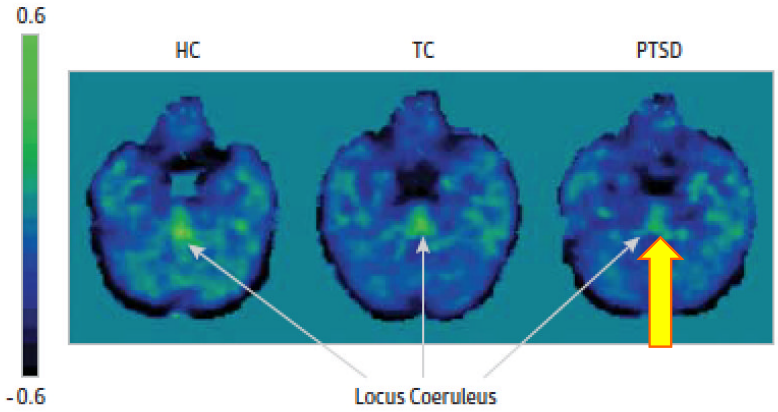


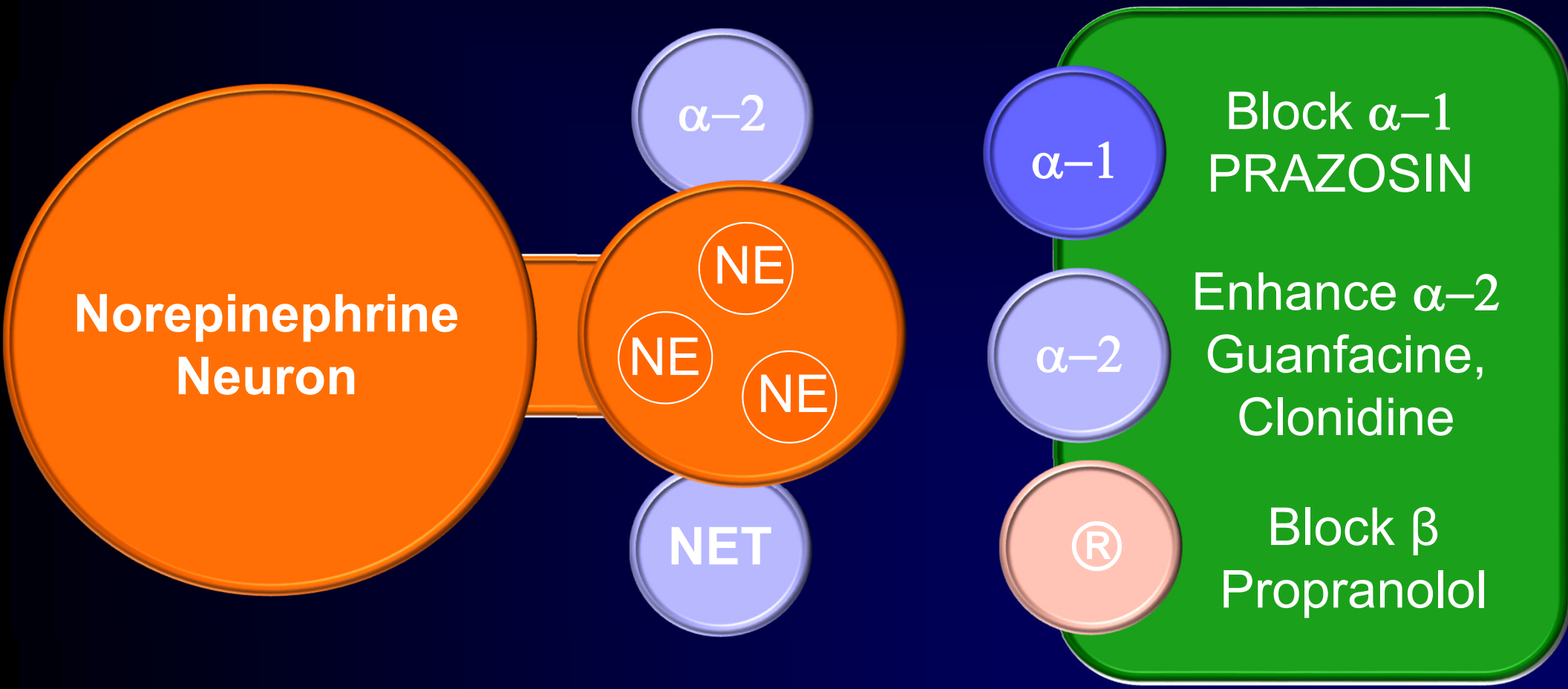
Figure 1. Positron Emission Tomography Images of Norepinephrine Transporter Availability in the Locus Coeruleus of Participants in the Study Groups



NET: Norepinephrine Transporter

Pietrzak RH, et al. JAMA Psychiatry 2013

Decrease NE Tone



Krystal et al. Behav Ther 1989; Taylor et al. Biol Psych 2008

Prazosin

- Reduced nightmares, awakenings
- 1 mg at bedtime: "first dose effect"
- Increase by 1 mg every 3-7 days
- Usual dose: 3-4, Usual max dose: 6-10
- Side effects: hypotension, tachycardia

Raskind et al. AJP 2003; Taylor et al. Biol Psychiatry 2006; Taylor et al. Biol Psychiatry 2008

Clonidine-Guanfacine

- Clonidine: α2 + imidazoline agonist
  - 0.05 mg gradually increasing to 0.1-0.2 t.i.d.
  - Sleep, nightmare, hyperarousal
  - Adjunctive to antidepressants
  - Side effects: sedation, hypotension
- Guanfacine: more selective α2
  - Inconsistent efficacy across studies

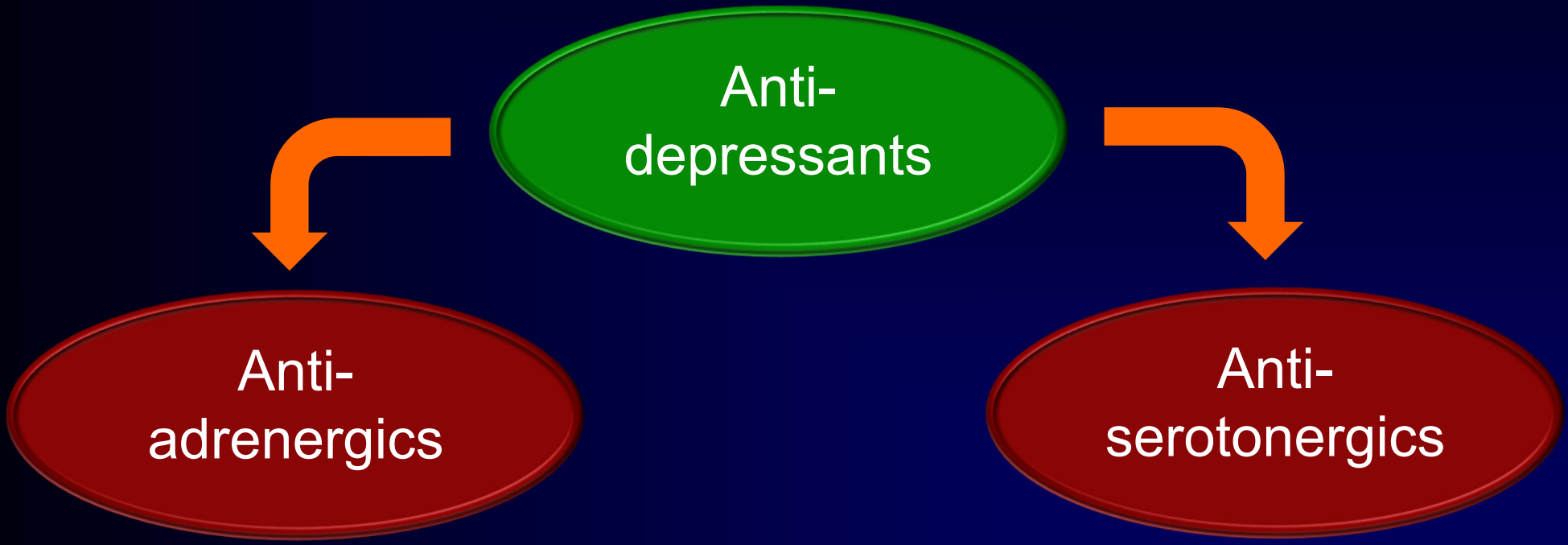
Kolb APA Press 1983, Kinzie & Leung JNMD 1989, Davis et al. Psychopharm Bull 2008

β-Blockers

- Limited direct efficacy
- Interference with fear consolidation in animal models
- Prophylactic efficacy not holding up
- Reactivation of memories "reconsolidates" fear…role for β-blockers?

Kolb APA Press 1983, van der Kolk Hosp Comm Psychiatry 1983, Pitman et al. Biol Psychiatry 2002, Stein et al. J Traum Stress 2007, Schwabe et al. Biol Psychiatry 2011;

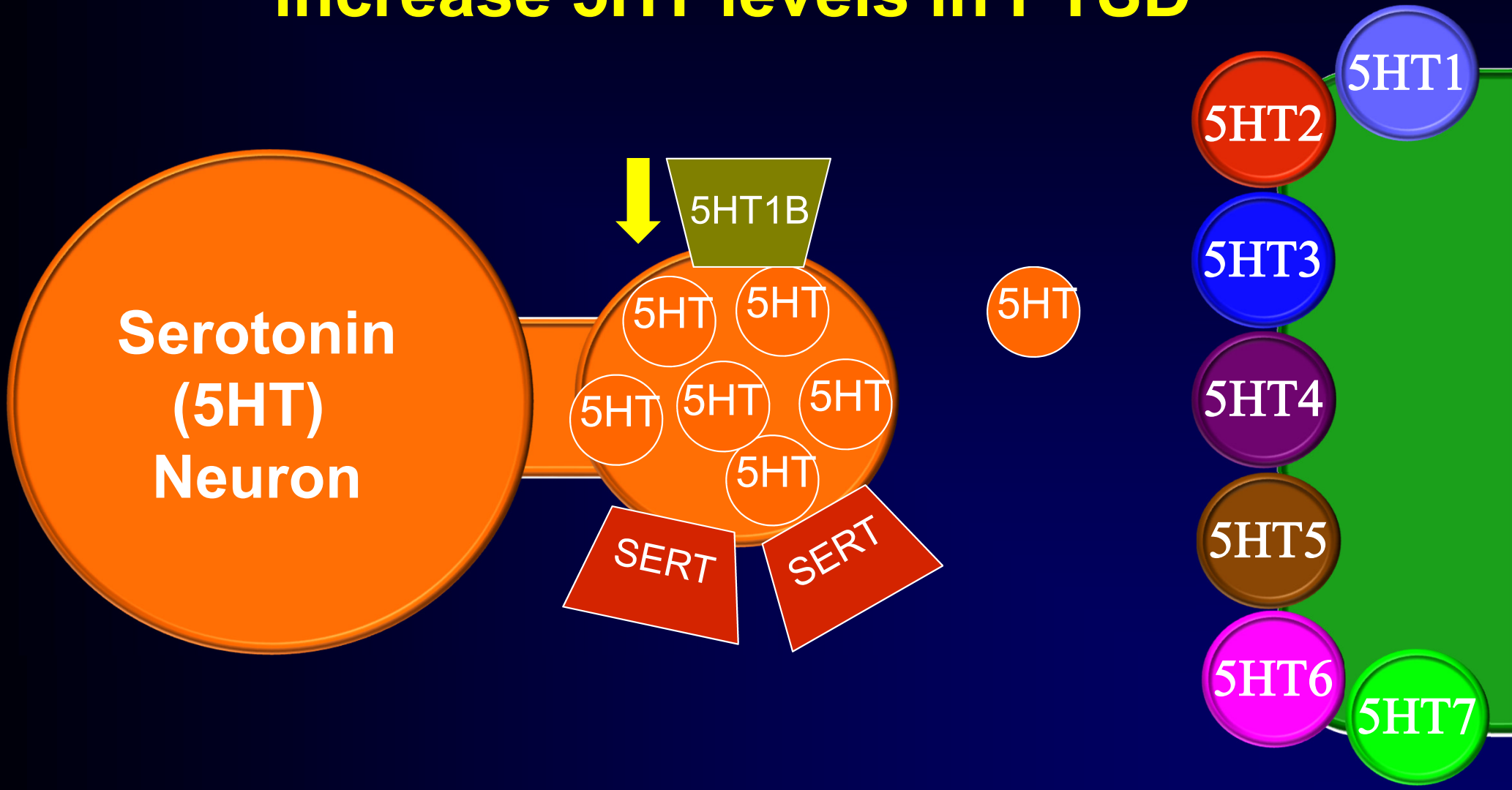
The pharmacotherapy of PTSD



5HT Activation in PTSD?

- Stimulation of 5HT receptors with mCPP worsens symptoms (Southwick et al. AJP 1996)
- Reduced 5HTT and 5HT1B receptors may increase 5HT release (Neumeister Biol Psych 2011; Murrough et al. AGP 2011; Pietrzak et al. Mol Psych 2013)

Reduced serotonin (5HT) uptake (SERT) and feedback inhibition (5HT1B) may increase 5HT levels in PTSD

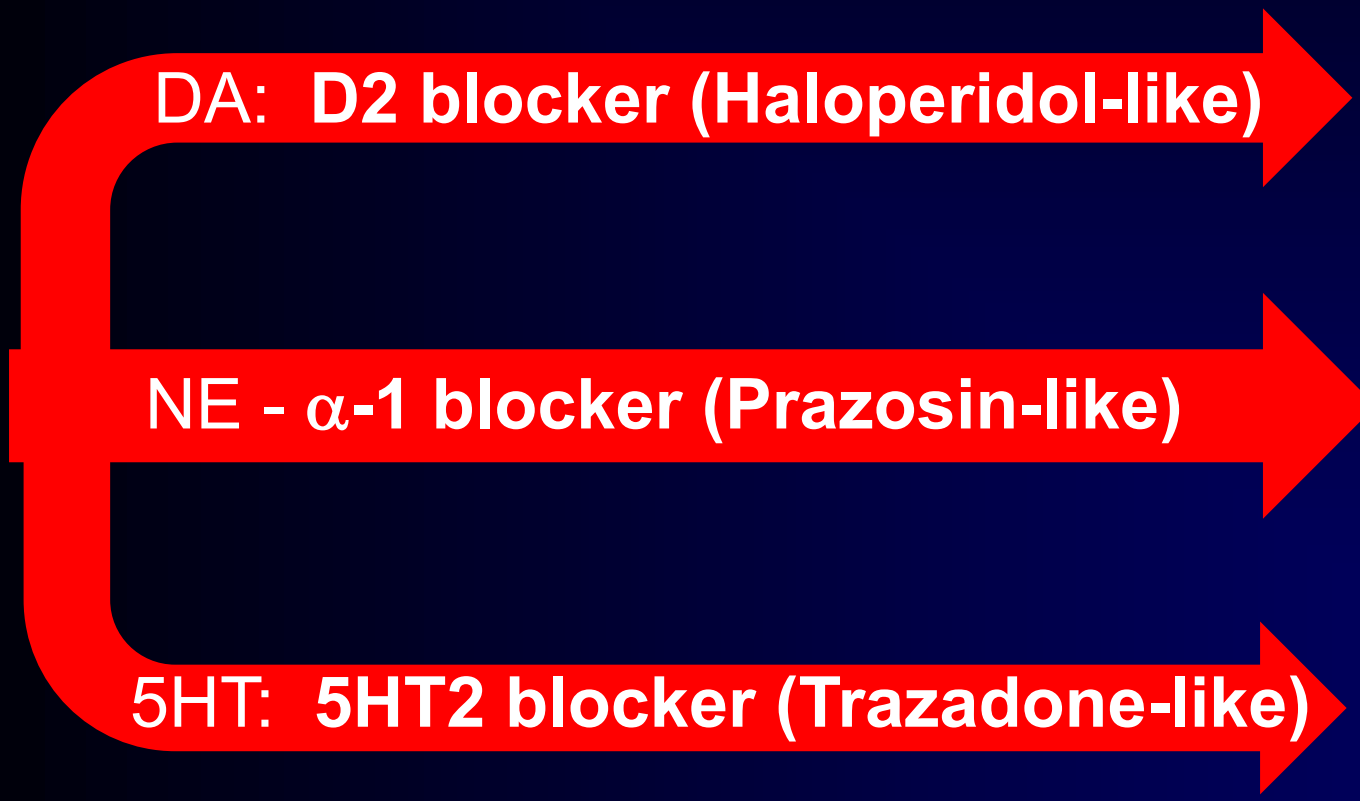


Trazodone and Nefazodone

- 5HT2-R antagonist (NEF also SRI)
- Trazodone
  - most commonly prescribed medication for PTSD in VA in 2010
  - No placebo-controlled trials
  - 25-50 mg commonly increased to up to 200 mg for sleep
  - Concerns include daytime sedation, headache, priapism
- Nefazodone start at 100 mg qhs increase to 200-300 mg BID; pilot studies positive

Neylan et al. J Clin Psychiatry 2003; Davis et al. J Clin Psychopharm 2004; McRae et al. Depression Anxiety 2004; Hertzberg et al. J Clin Psychopharm 1996

Second Generation Antipsychotics



Risperidone

Olanzepine

Quetiapine

Ziprasidone

Clozapine

Aripiprazole

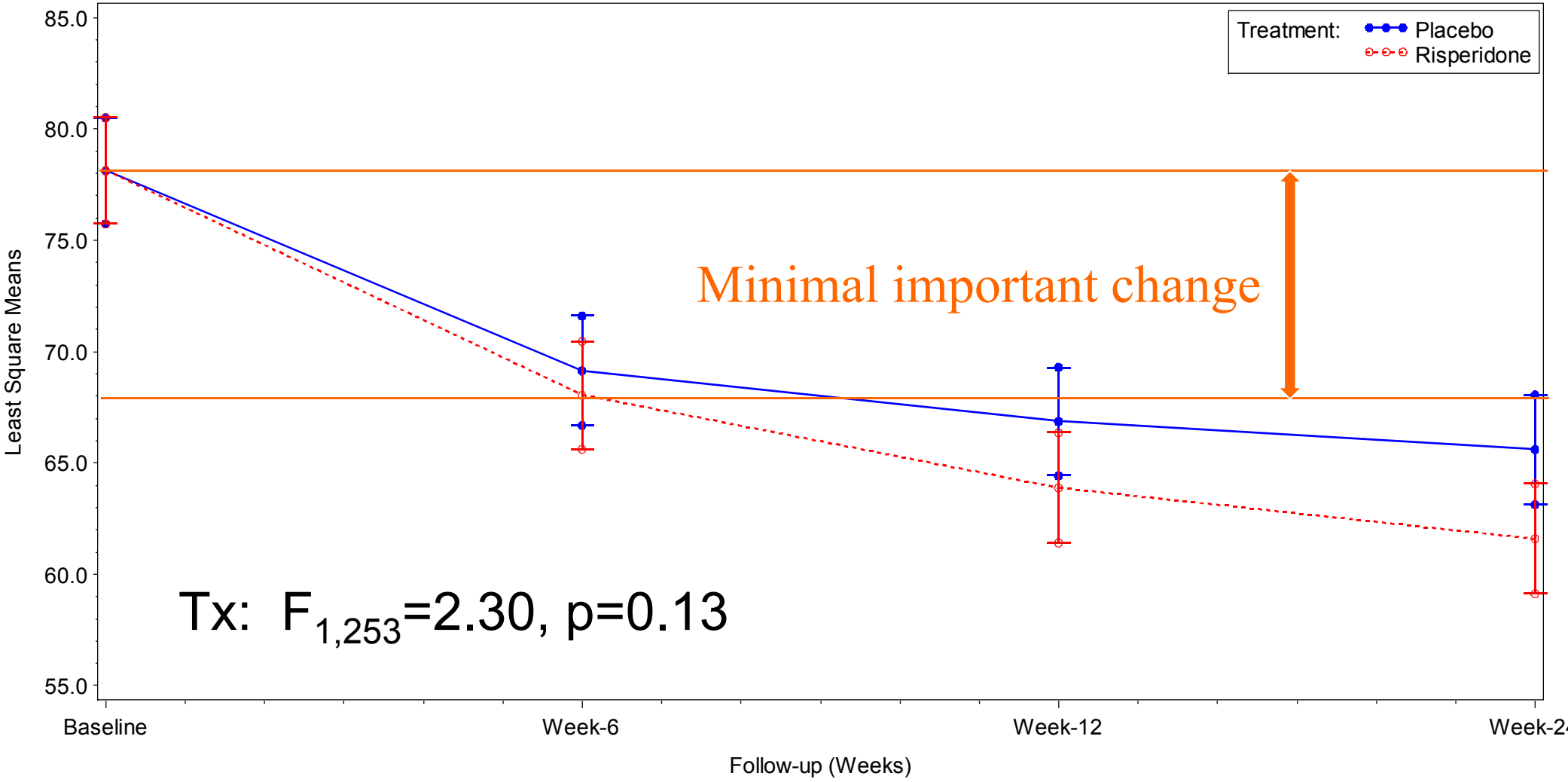
Adjunctive Risperidone for SRI resistant PTSD symptoms: VA Cooperative Study 504

- SRI-resistant chronic military-related PTSD
- 6-month trial
- 247 patients in the ITT

Krystal et al. JAMA 2011;306(5):493-502.

No significant effect of risperidone on CAPS total score

Study#504: Risperidone Treatment for Military Service Related
Chronic Post-Traumatic Stress Disorder
Figure-1: LSmeans of CAPS Scores



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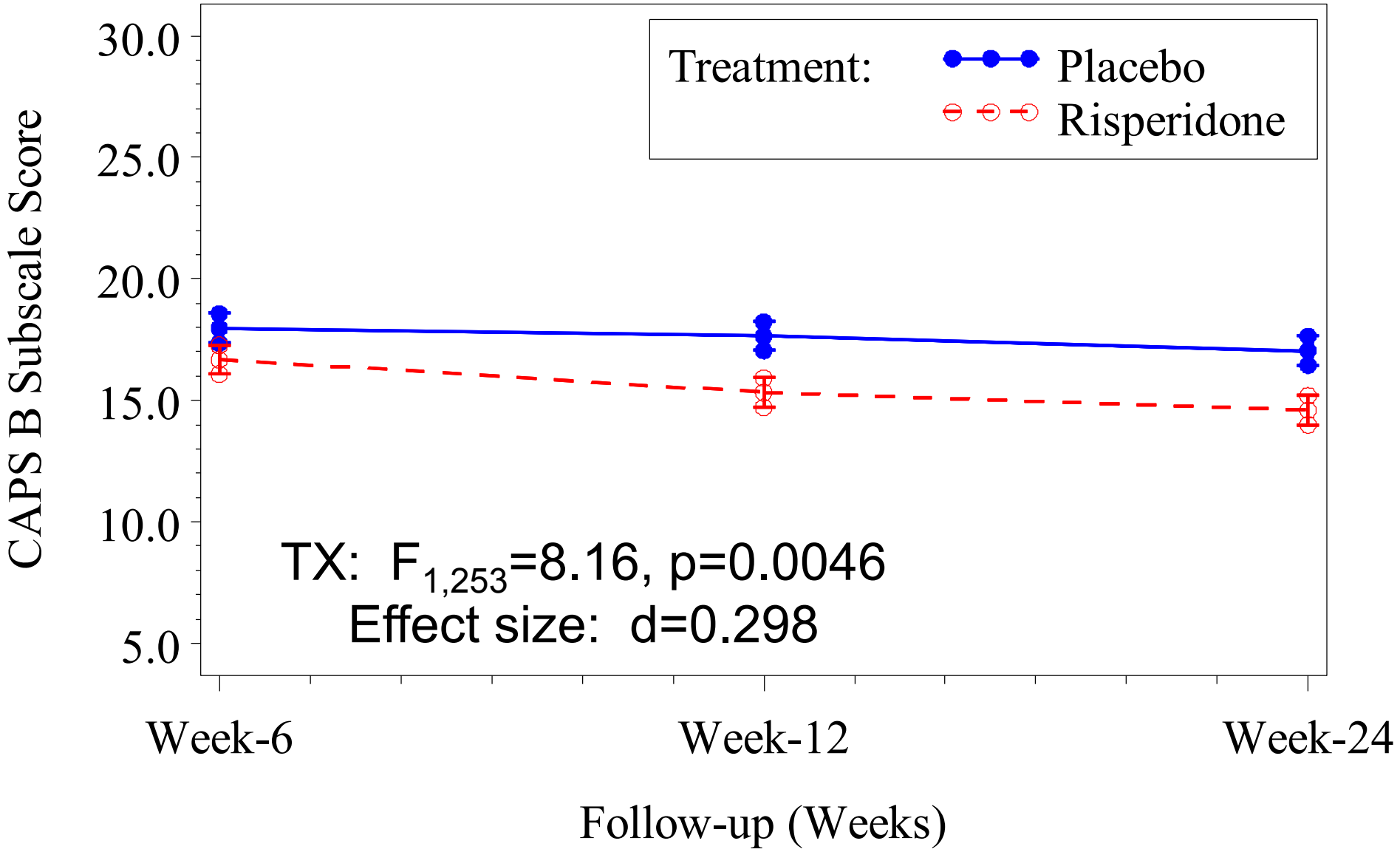
Significant but small effect on Reexperiencing Symptoms



Least Square Means for CAPS Reexperiencing Symptoms

Side effects associated with risperidone

- Adverse events:
  - Somnolence: 9.9% vs. 1.5% (p=.001)
  - Hypersalivation: 9.9% vs. 0.8% (p=.001)
  - Weight gain: 15.3% vs. 2.3% (p=.001)
  - Decreased libido: 6.1% vs. 0.0% (p=.001)
  - Dyspnea: 6.1% vs. 0.0% (p=.001)
- Measured side effects not significant
  - EPS, akathisia, weight gain
- No difference in “added” medications during trial

POLITICS
Obama Falls to New Lows in End-of-Summer Polling

CAMPAIGN 2012
Huntsman Slams Palin's Tax Proposal

CONGRESS
PICTURES: The Odd Jobs of Members of Congress

9/11 ANNIVERSARY
Share Your Memories and Photos of 9/11

NATIONAL SECURITY

VA Spent $717 Million on a Drug Deemed as Effective as a Placebo

By **Bob Brewin, Nextgov.com**

Updated: August 23, 2011 | 12:24 p.m.
August 23, 2011 | 12:25 p.m.

EDITOR'S NOTE: This is the 13th story in an ongoing Nextgov series that examines the invisible wounds of war.

Over the past decade, the Veterans Affairs Department spent $717 million for an antipsychotic drug to treat post-traumatic stress disorder that a recent study shows is no more effective than a placebo.

Data provided by the department in response to a *Nextgov* query showed that VA doctors wrote more than 5 million prescriptions for risperidone from October 2000, the beginning of fiscal year 2001, through June 2010. Risperidone is the generic name for Risperdal, a second-generation antipsychotic drug originally developed by the Janssen Pharmaceuticals division of Johnson & Johnson to treat severe mental conditions such as schizophrenia and bipolar disorder.

But a paper by VA researchers published on August 2 in the *Journal of the American Medical Association* concluded, "Treatment with risperidone compared with placebo did not reduce PTSD symptoms."

Nextgov.com is part of the National Journal Group Inc. and the Atlantic Media Company. It is a spin off of GovernmentExecutive.com and provides coverage and commentary on the management of information technology in the federal government. From time to time, Nextgov and GovernmentExecutive.com will share content and collaborate on features and events.

Caveats

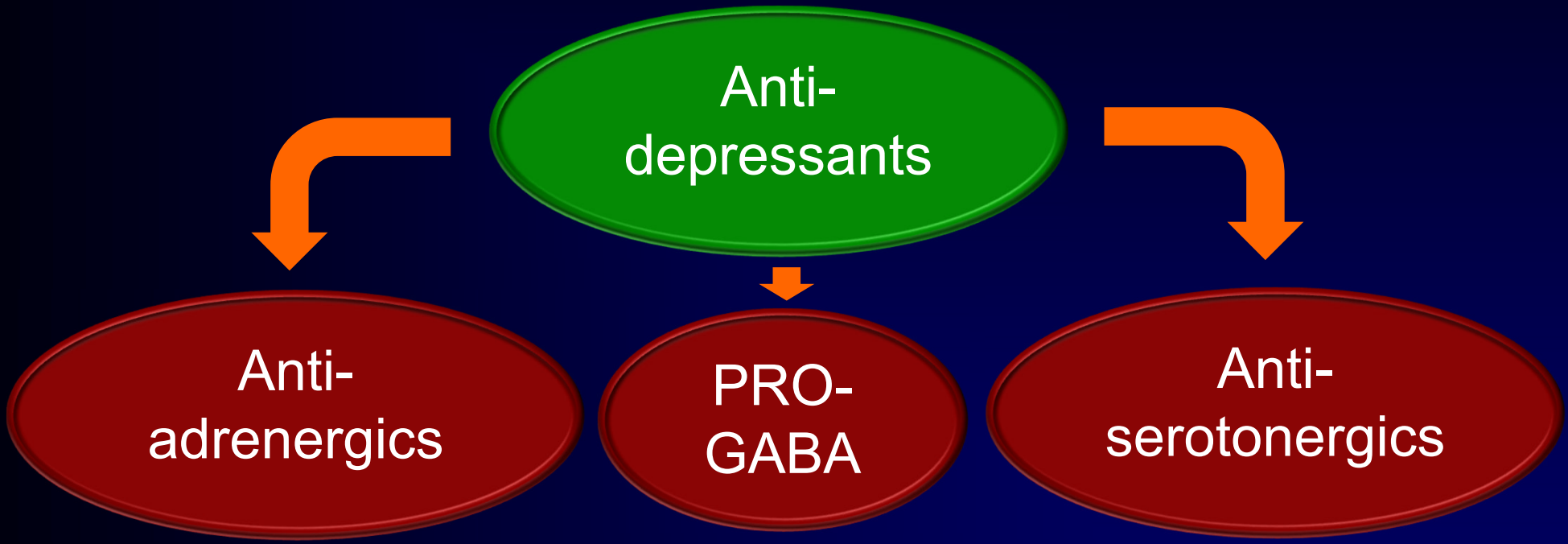
- Beneficial for paranoia/psychosis
- Might have greater effects in less severe population on fewer other medications

Other SGA's

- Quetiapine (Seroquel)
  - Most commonly prescribed SGA
  - Start: 25 mg, commonly increased to 100-200 mg
  - Encouraging preliminary data
  - Concerns: Daytime Sedation, Weight gain
- Others: Olanzapine, Aripiprazole

Ahearn E Int Clin Psychopharm 2006; Robert J Clin Psychopharm 2005; Stein M et al. AJP 2002

The pharmacotherapy of PTSD

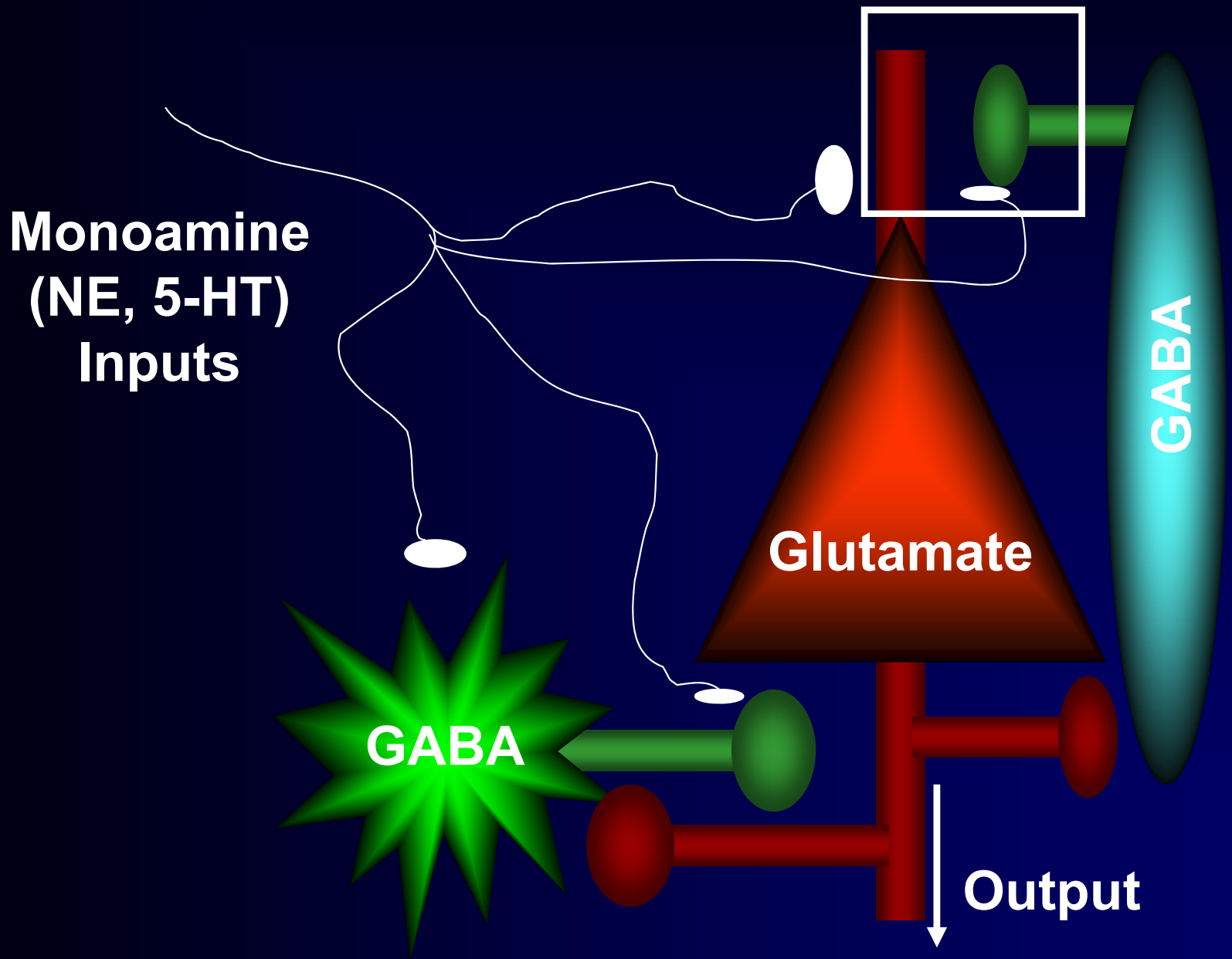


BZD: Wide but Declining Prescription

- From 1999 to 2009: 36.7% to 30.6%
- Chief concerns:
  - Abuse liability (esp. with substance use history)
  - Limited evidence of efficacy in pilot study

Lund et al. J Clin Psychiatry 2011; Hermos et al. J Traum Stress 2007; Gilpen et al. J Clin Psychiatry 1996

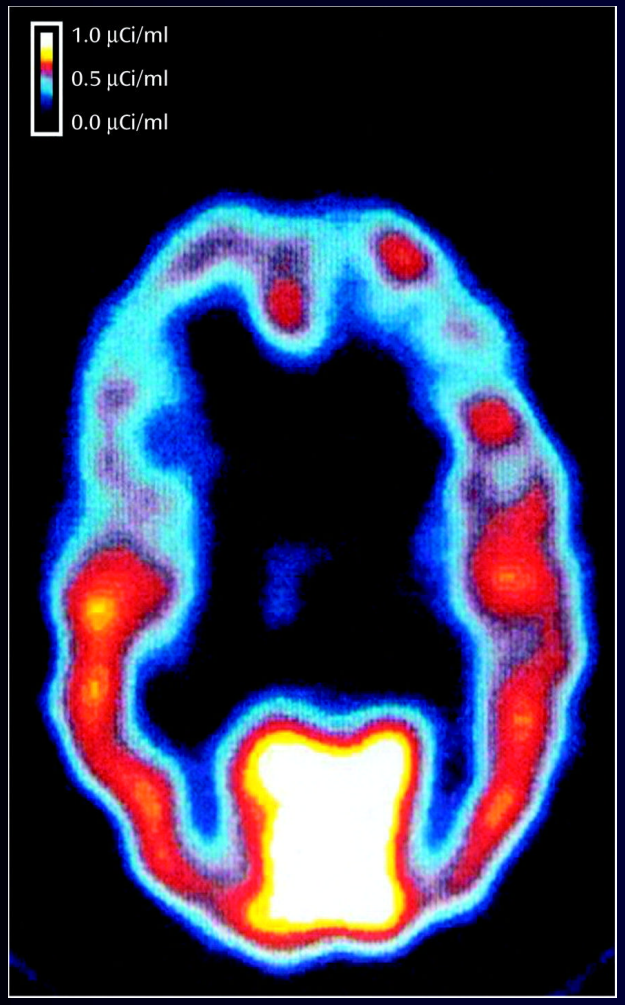
GABA: Another Layer of Stress-Dampening Deficit in PTSD?

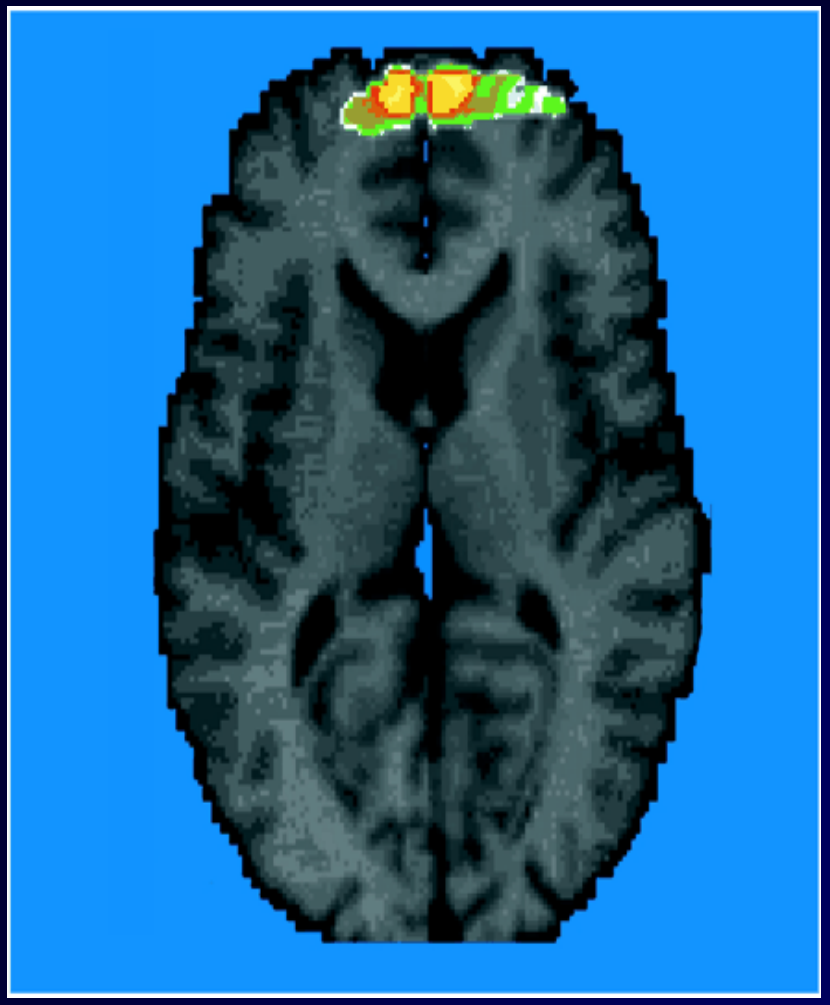


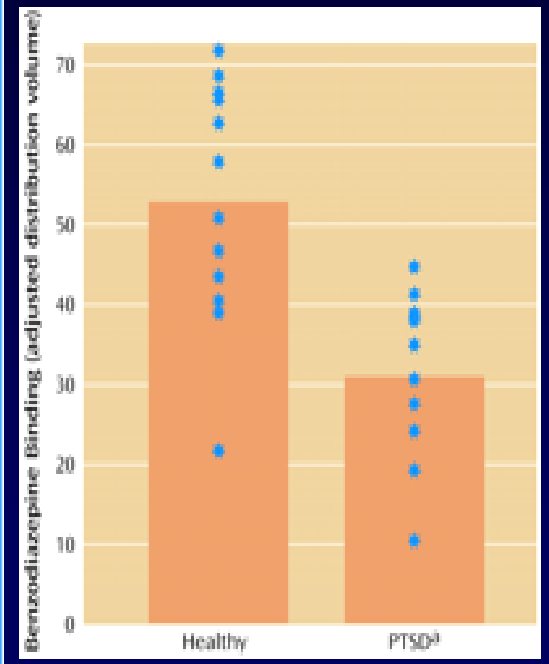
Reduced Orbital Frontal Cortex [123]Iomazenil Binding in PTSD

(Bremner et al. American Journal of Psychiatry 2000)

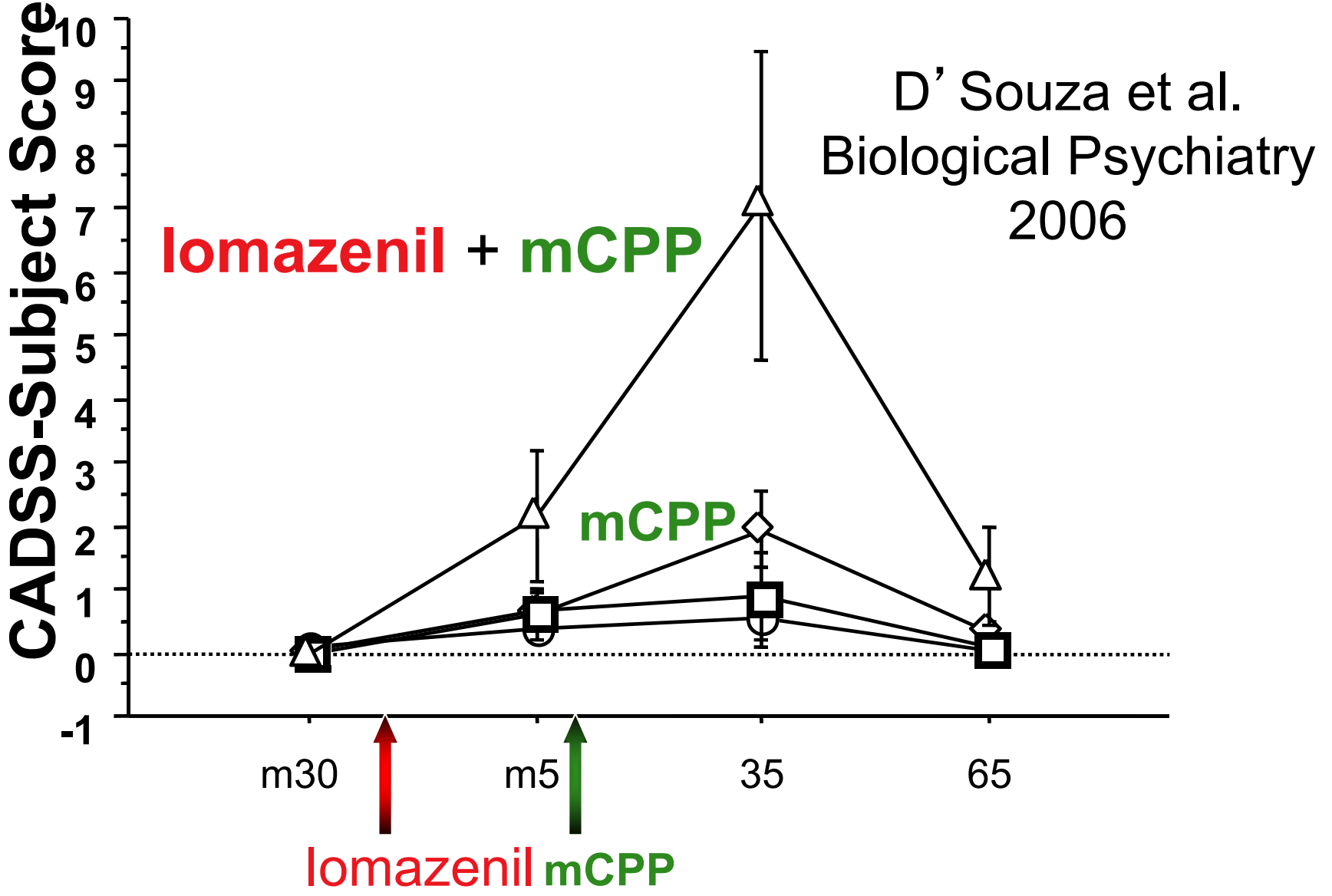
SPECT Image **Group Difference** **Data**







GABA deficits increase risk for dissociation with 5HT activation (mCPP)



Eszopiclone for the Treatment of Posttraumatic Stress Disorder and Associated Insomnia: A Randomized, Double-Blind, Placebo-Controlled Trial

Mark H. Pollack, MD; Elizabeth A. Hoge, MD; John J. Worthington, MD; Samantha J. Moshier, BA; Rachel S. Wechsler, BA; Mina Brandes, MD; and Naomi M. Simon, MD

- S-Zopiclone (Lunesta): relatively high affinity for α2/3 GABA-A receptors
- Improved sleep and reduced PTSD symptoms
- Starting dose: 2-3 mg; Max: 4 mg

J Clin Psychiatry 2011

Other GABA modulators?

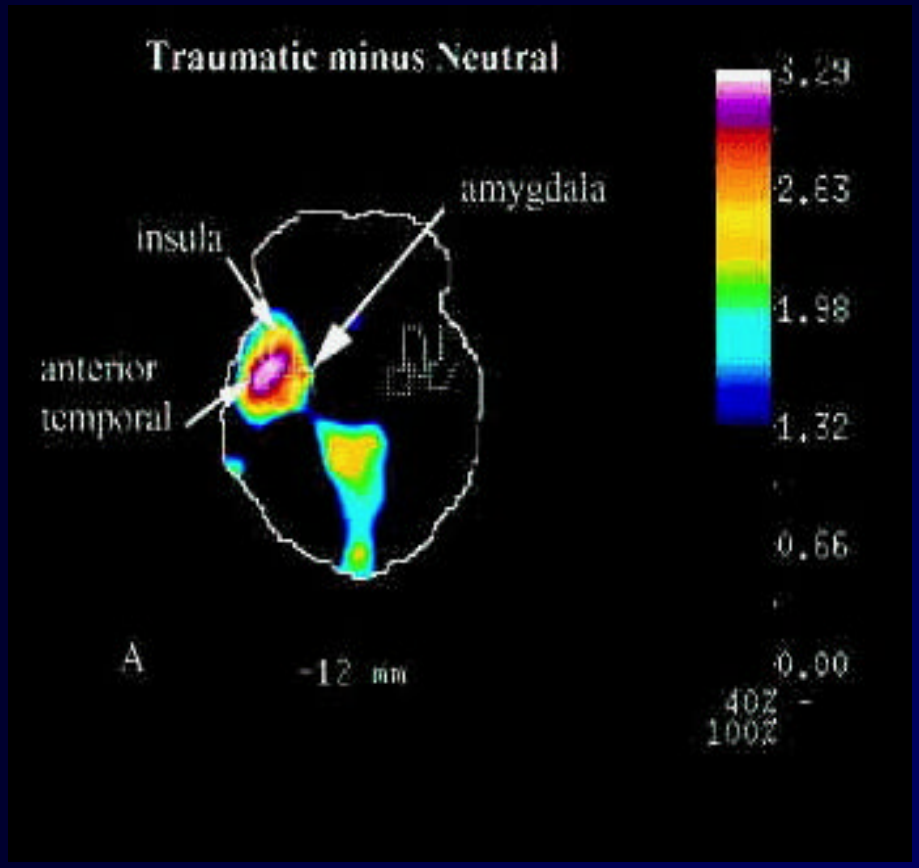
- Anticonvulsant medications
  - TIAGABINE: Large negative trial (Davidson et al. J Clin Psychopharm 2007)
  - VALPROATE: Small negative trial (Hamner et al. Ann Clin Psychiatry 2009)
  - TOPIRAMATE: Small (12-14/group in completer analysis) encouraging study (Yeh et al. CNS Neurosci Ther 2010)

Toward the future!

- Promoting neuroplasticity (extinction)
- Rapid-acting antidepressants
- Anti-inflammatory agents
- Promoting resilience

Traumatic Memories Activate Amygdala

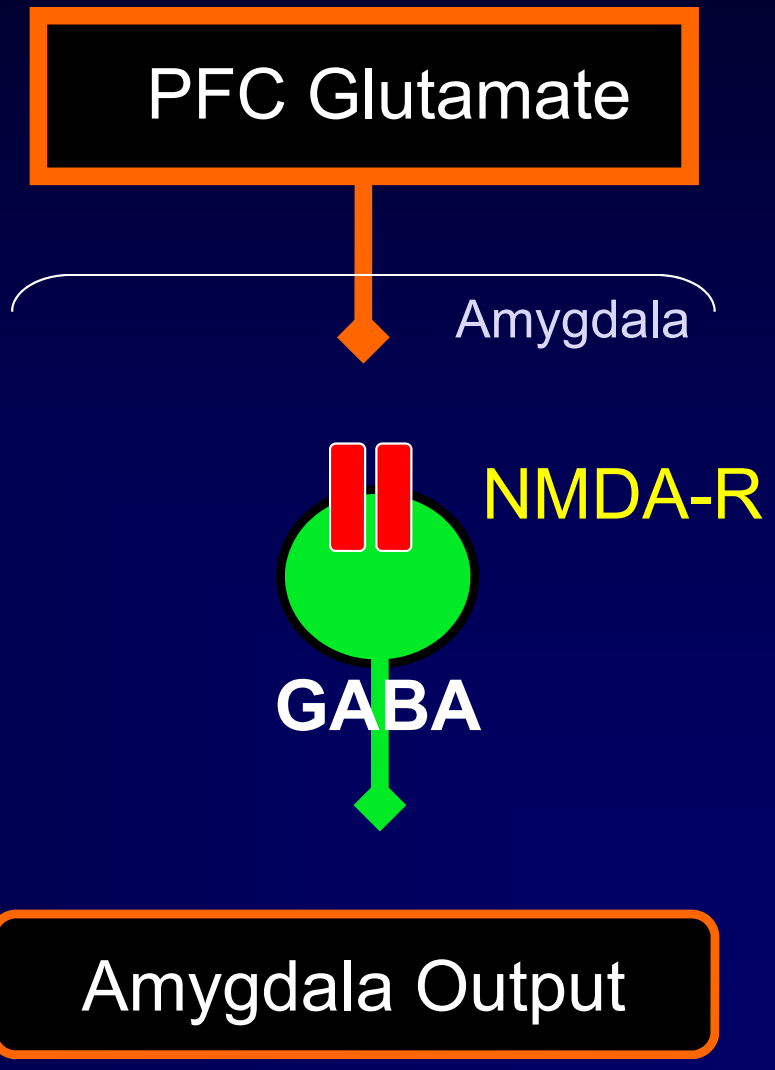
(Rausch et al. Arch Gen Psychiatry 1996)



Regions Activating During Trauma Scripts: [15O] PET

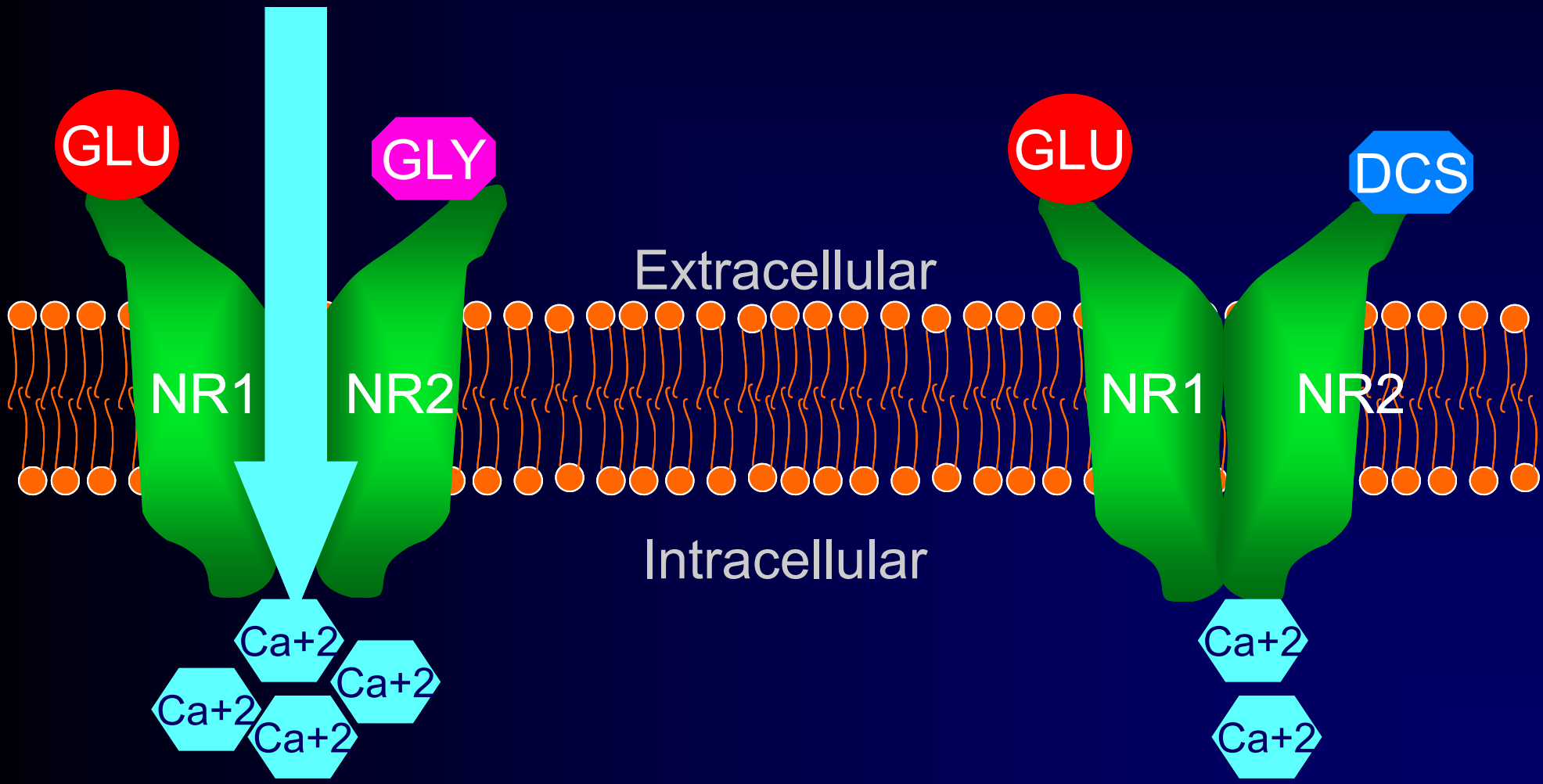
Fear Extinction is dependent upon NMDA receptors

- Extinction might reduce amygdala output
  - LTP of GABA neuron that inhibits amygdala output



After M. Davis

D-cycloserine (DCS) facilitates NMDA-R function with half of the efficacy of glycine



DCS Findings

- Helpful for other anxiety disorders (phobia)
- PTSD studies: modest benefit or even worsening

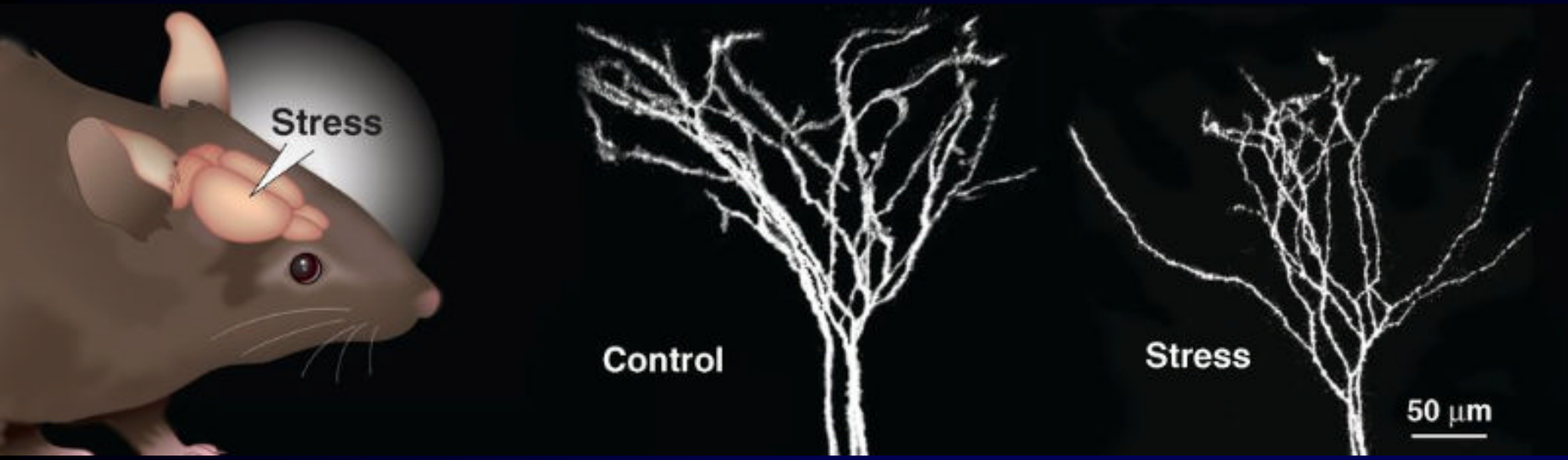
Ressler et al. Arch GenPsychiatry 2006; Norberg et al. Biol Psychiatry 2008; Litz et al. J Psychiatry Res 2012; de Kleine et al. Biol Psychiatry 2012

Toward the future!

- Promoting neuroplasticity (extinction)
- Rapid-acting antidepressants

Loss of spines

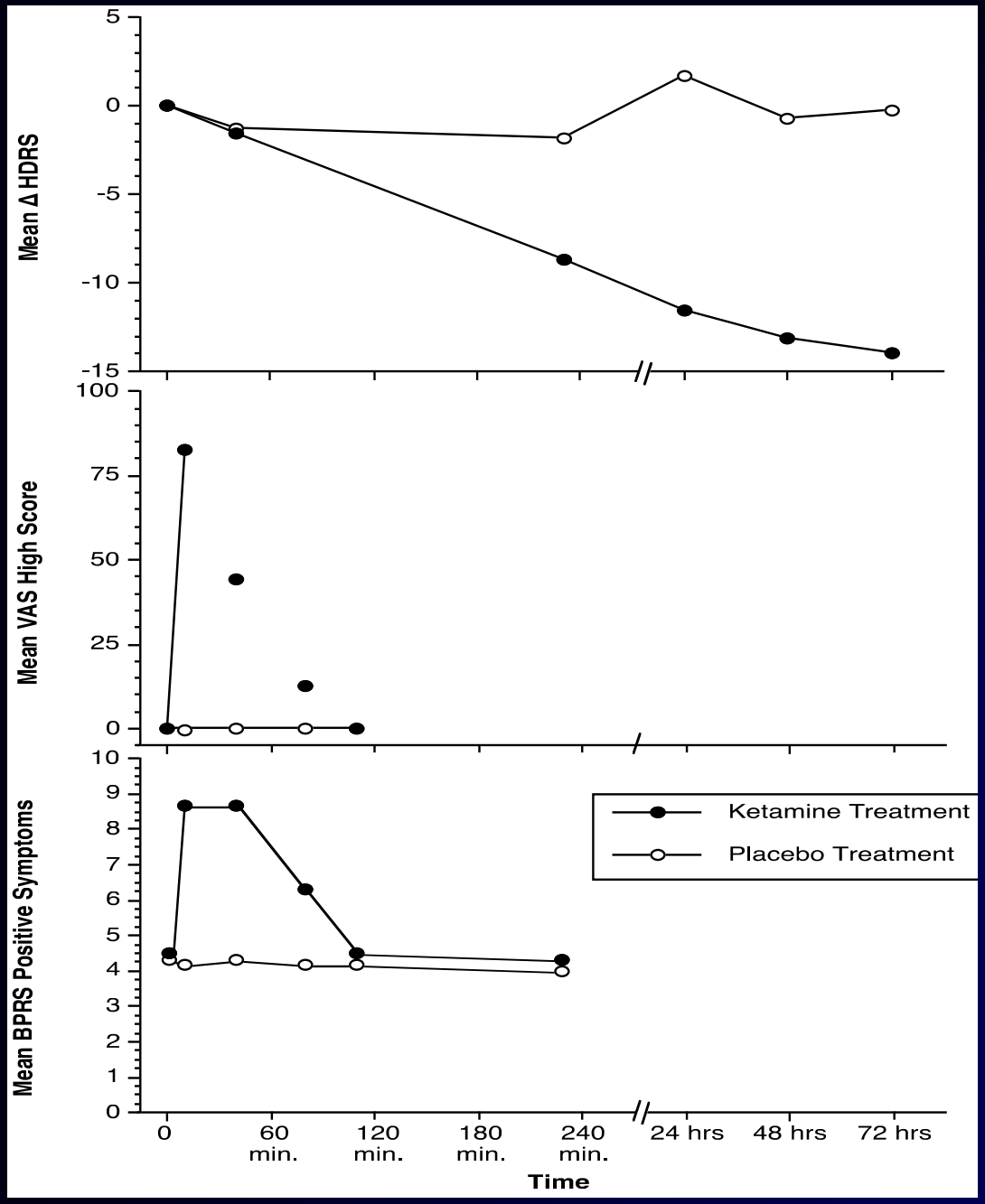
Stress reduces dendritic spines and causes dendrite atrophy



Contribute to reduced structural and functional connectivity in PTSD?

Duman and Aghajanian Science 2012

Antidepressant Actions of Ketamine

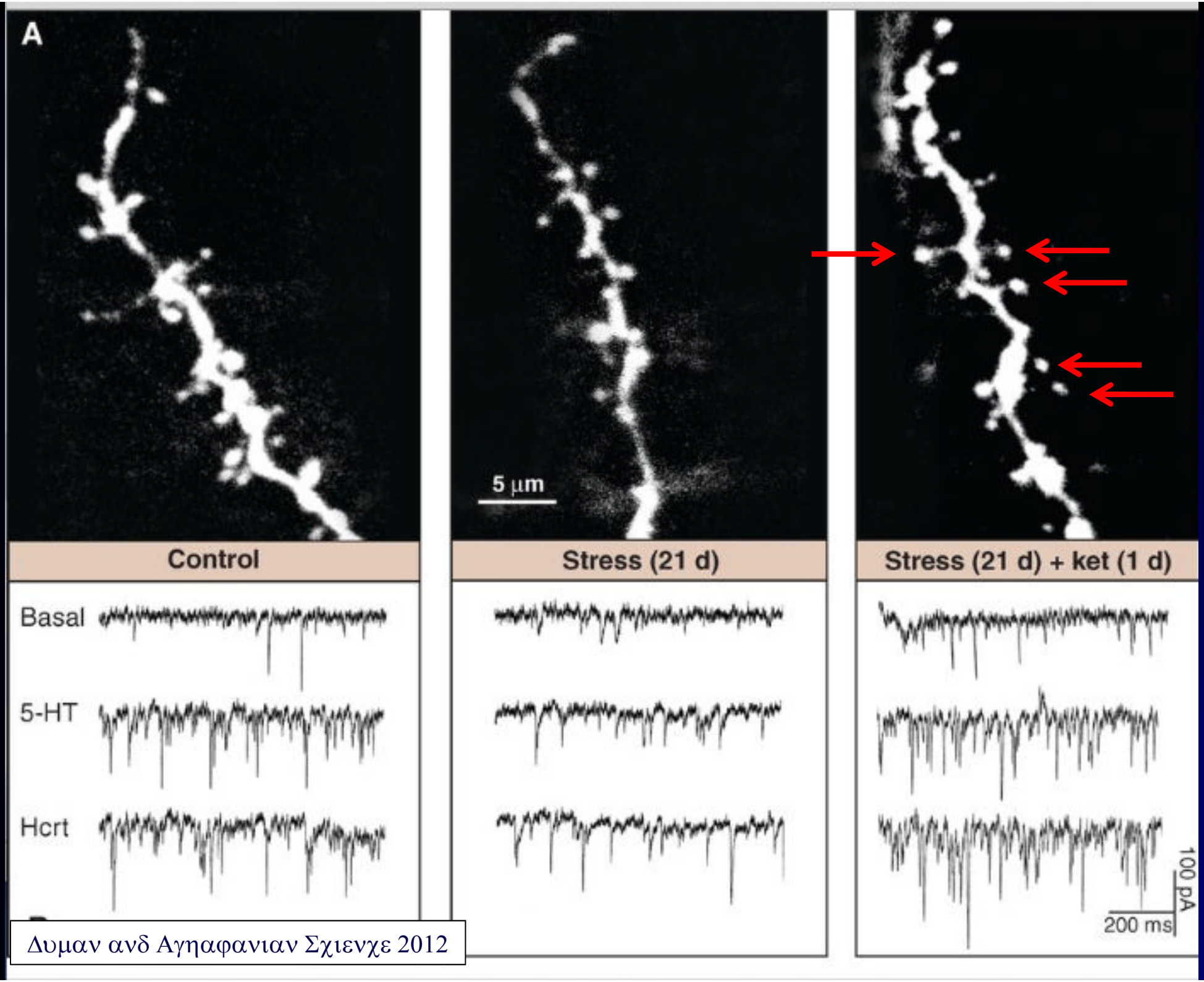


Hamilton Depression Scale: p=.0001

VAS, "High" P=.0001

BPRS, Positive Symptoms of Schizophrenia P=.007

R. Berman Biol Psychiatry 2000



Δυμαν ανδ Αγηαφανιαν Σχιενχε 2012

Toward the future!

- Promoting neuroplasticity (extinction)
- Rapid-acting antidepressants
- Anti-inflammatory agents

Anti-inflammatory Agents

- Stress and TBI promotes neuro-inflammation
- Anti-inflammatory strategies:
  - Cytokine receptor antagonists (TNFα; infliximab)
  - Drugs that promote glutamate uptake (minocycline, riluzole)
  - Raise glutathione levels (N-acetyl-cysteine)

Toward the future!

- Promoting neuroplasticity (extinction)
- Rapid-acting antidepressants
- Anti-inflammatory agents
- Promoting resilience

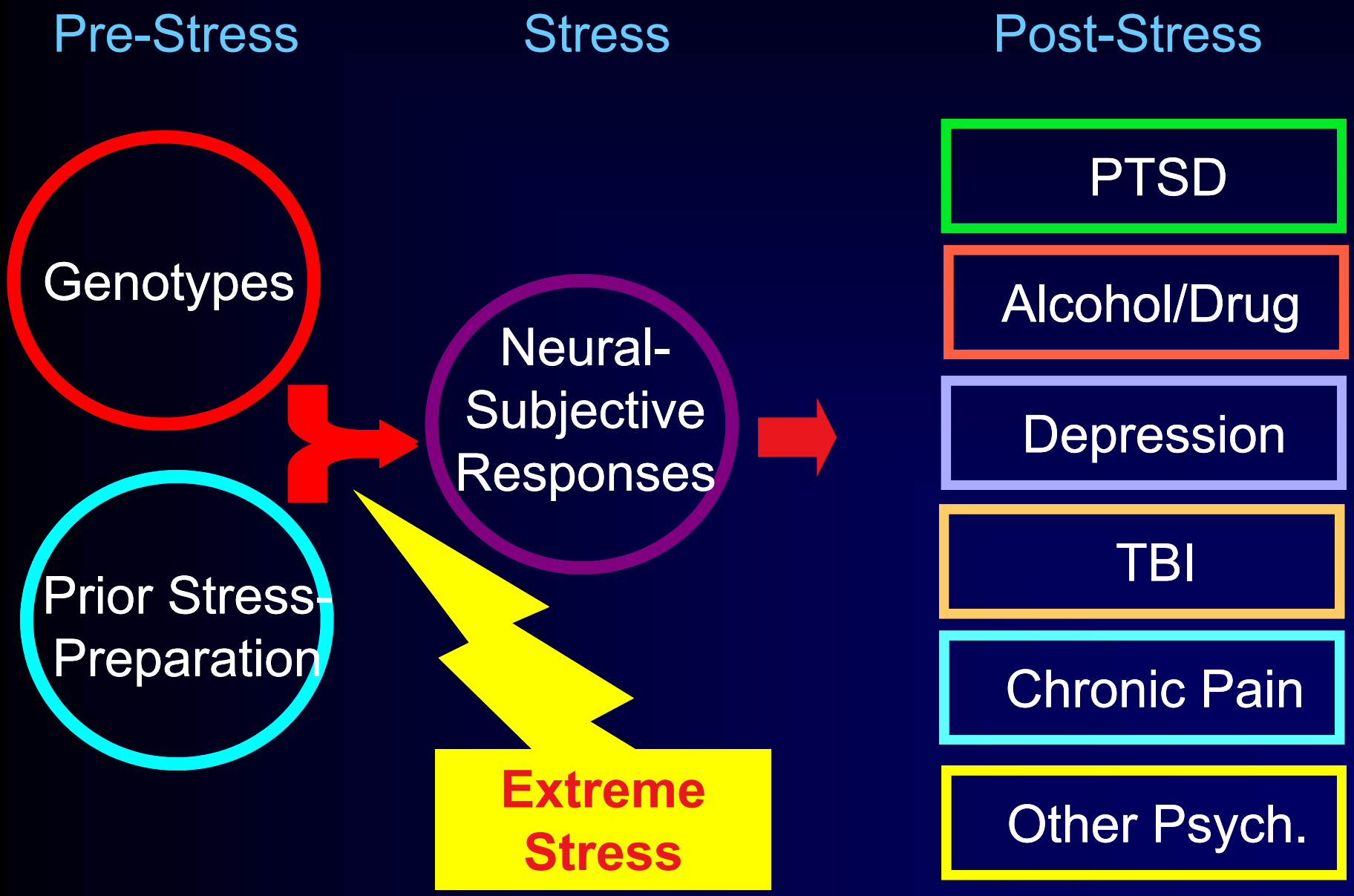
Promoting resilience?

- Glucocorticoids
- Opiate receptor agonist/partial agonist
  - Experience with burn patients
- Neuropeptide Y

Summary

- SRI's: validated, but limited, efficacy
- Other medications: only preliminary support
- Open questions: Relative efficacy, adjunctive treatment, personalized treatment?
- Exciting possibilities for the future

Its More than PTSD



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