

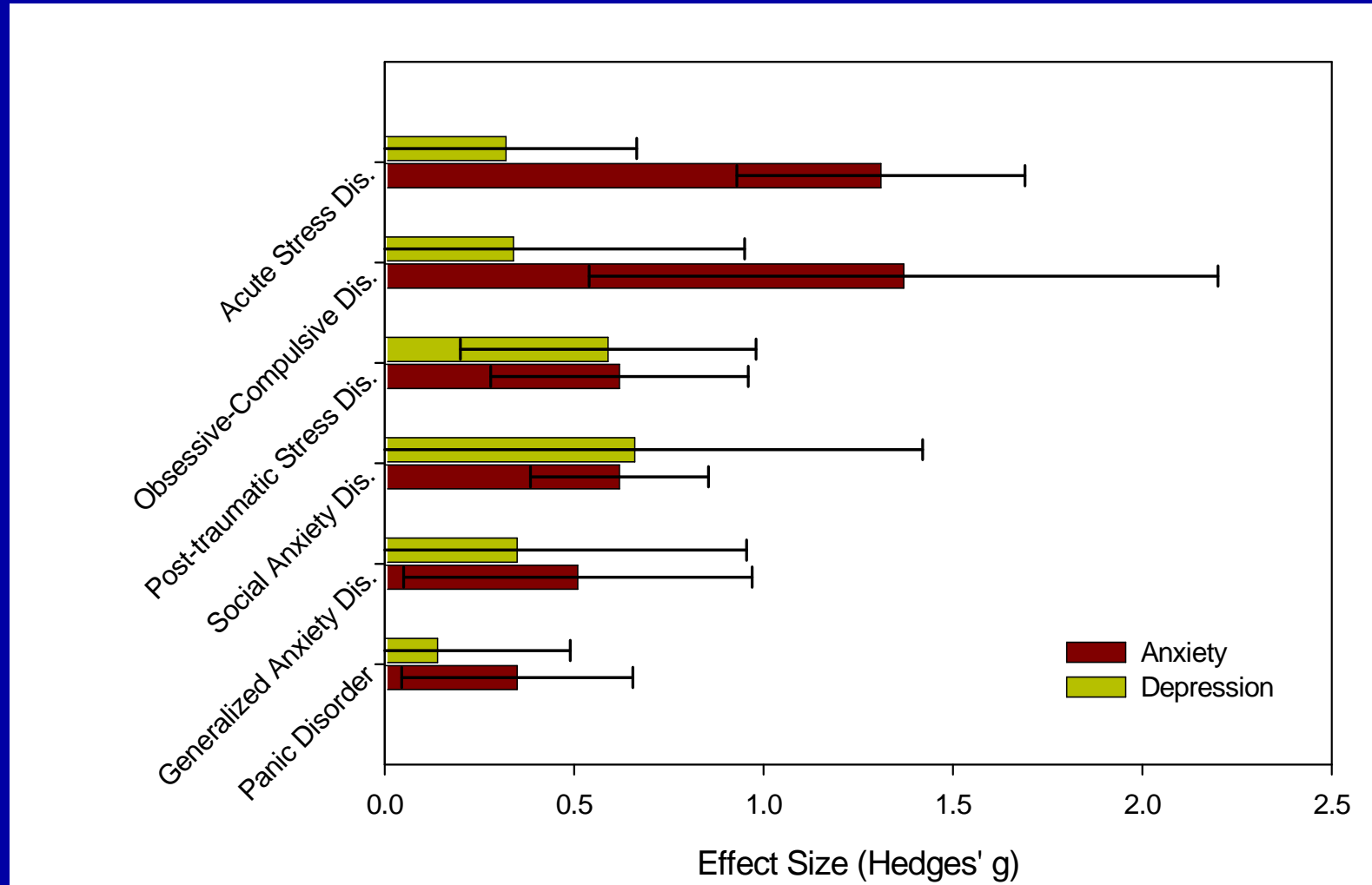
# Treatment of Complex Anxiety Disorder: State of the Art and New Developments

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# Financial Disclosure

- Paid consultant by Merck/Organon/Schering Plough
- Supported by NIMH grants R01MH078308 (PI: Hofmann) and R01MH093328 (PI: Otto).

Average effect size estimates (Hedges' g) and corresponding 95% confidence intervals of the acute treatment efficacy of CBT as compared to placebo on the various anxiety disorders for the primary continuous anxiety measures (red bars) and depression measures (green bars).



Hofmann & Smits (2008). *Journal of Clinical Psychiatry*

# How Good are Combination Treatments for Anxiety Disorders?

Meta-analysis of RCTs comparing CBT plus Med vs. CBT plus PLA

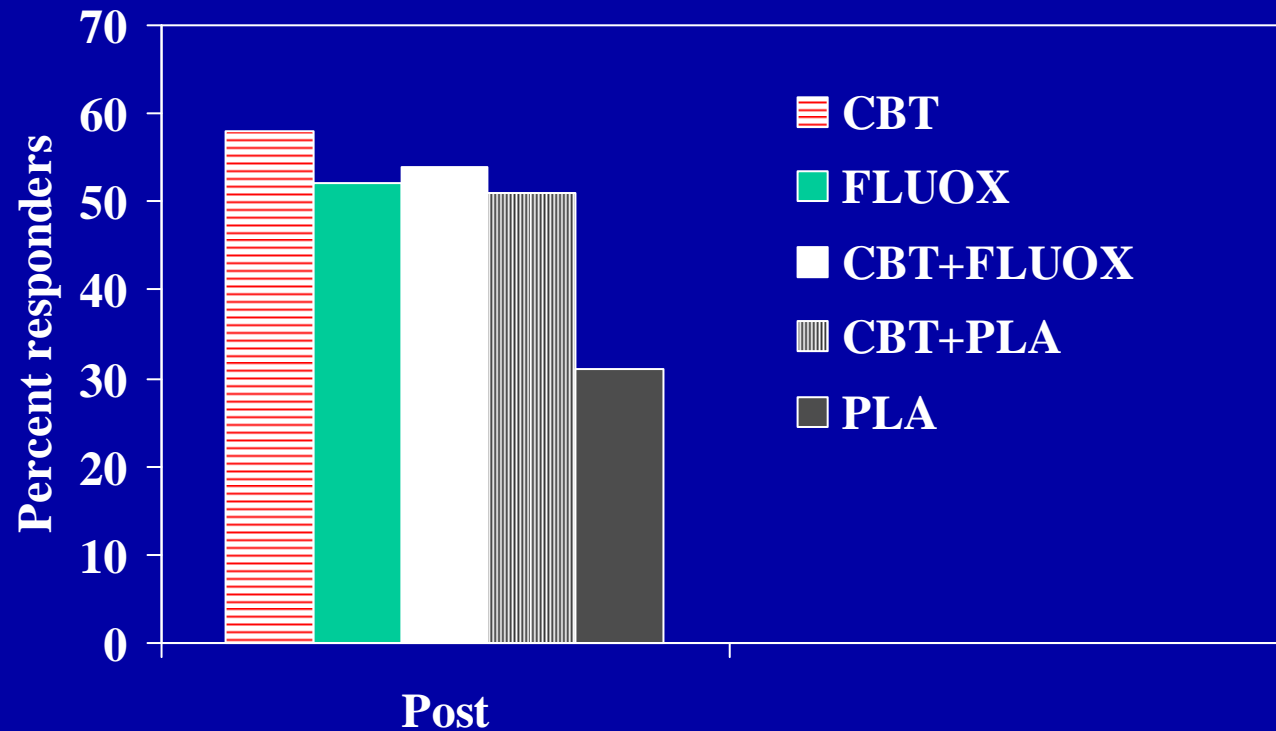
Effect sizes at post-treatment:

PD and GAD: moderate

OCD and SAD: small and not significant.

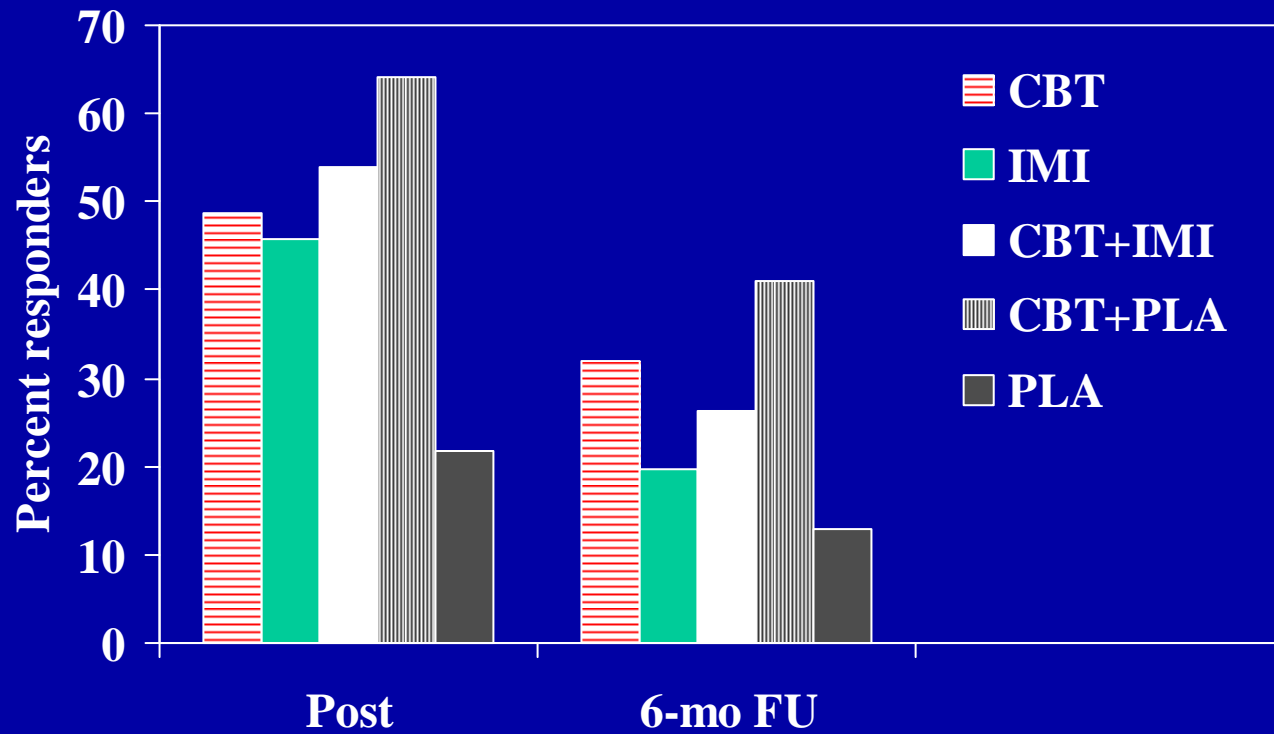
Hofmann et al. (2008). *Int J Cogn Therapy*

# Treatment of Social Anxiety Disorder



Davidson et al. (2004), *Archives of General Psychiatry*

# Panic Disorder



Barlow et al. (2000), *JAMA*

# Why is Combination Therapy Not Doing Better?

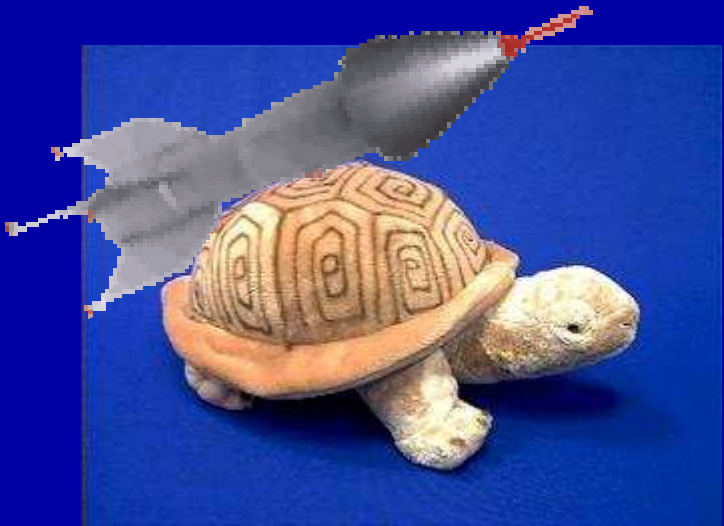
- State-dependent learning?
- Attribution?
- Turtle race?

# Why is Combination Therapy Not Doing Better?

- State-dependent learning?
- Attribution?
- Turtle race?

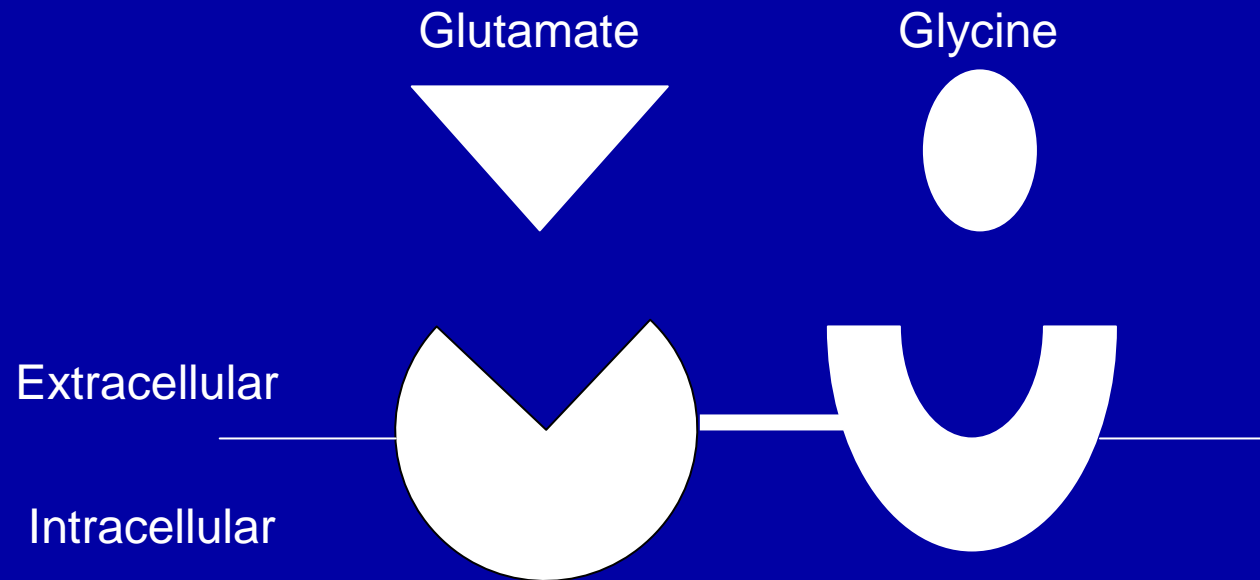


GOAL

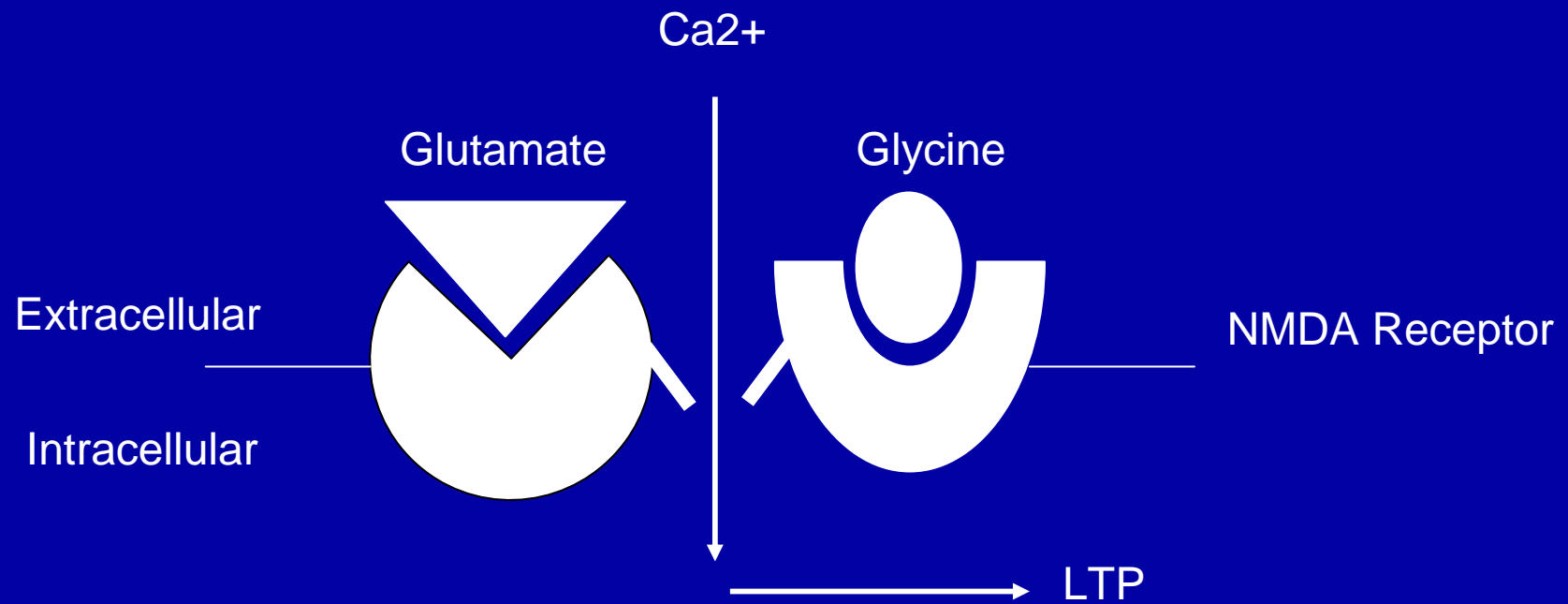


GOAL

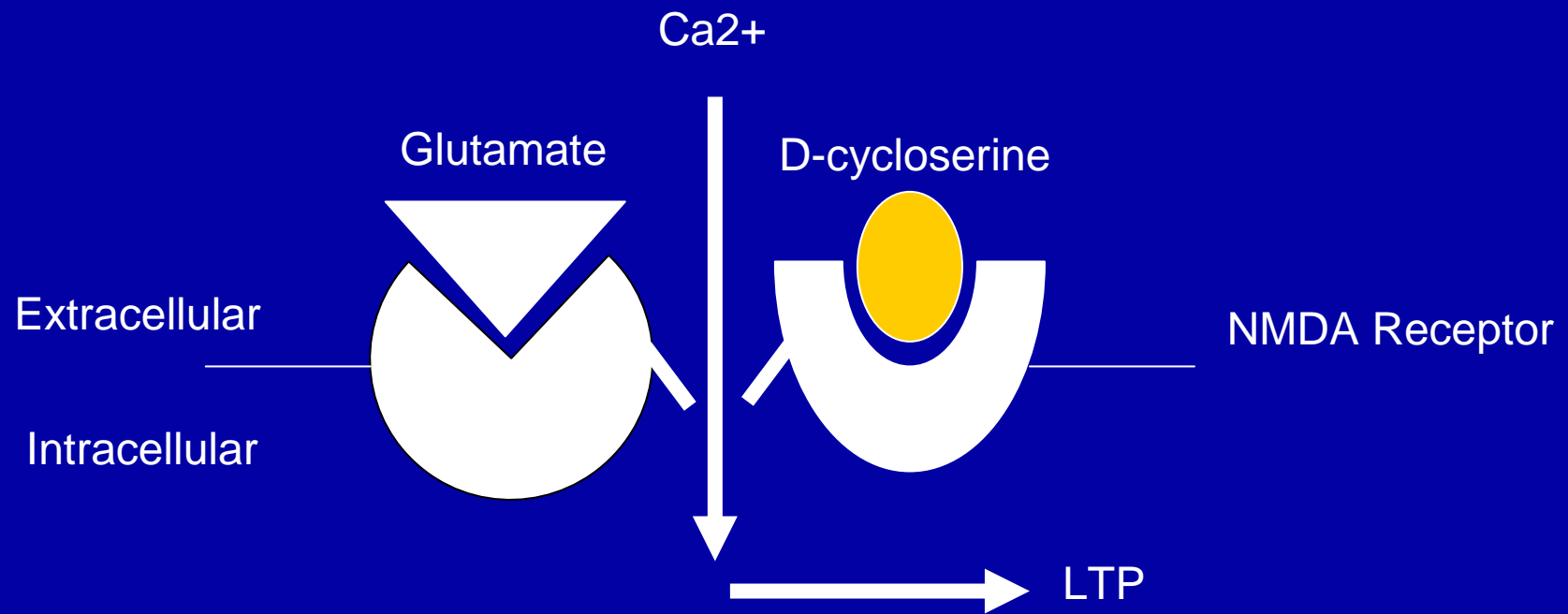
# NMDA Receptor

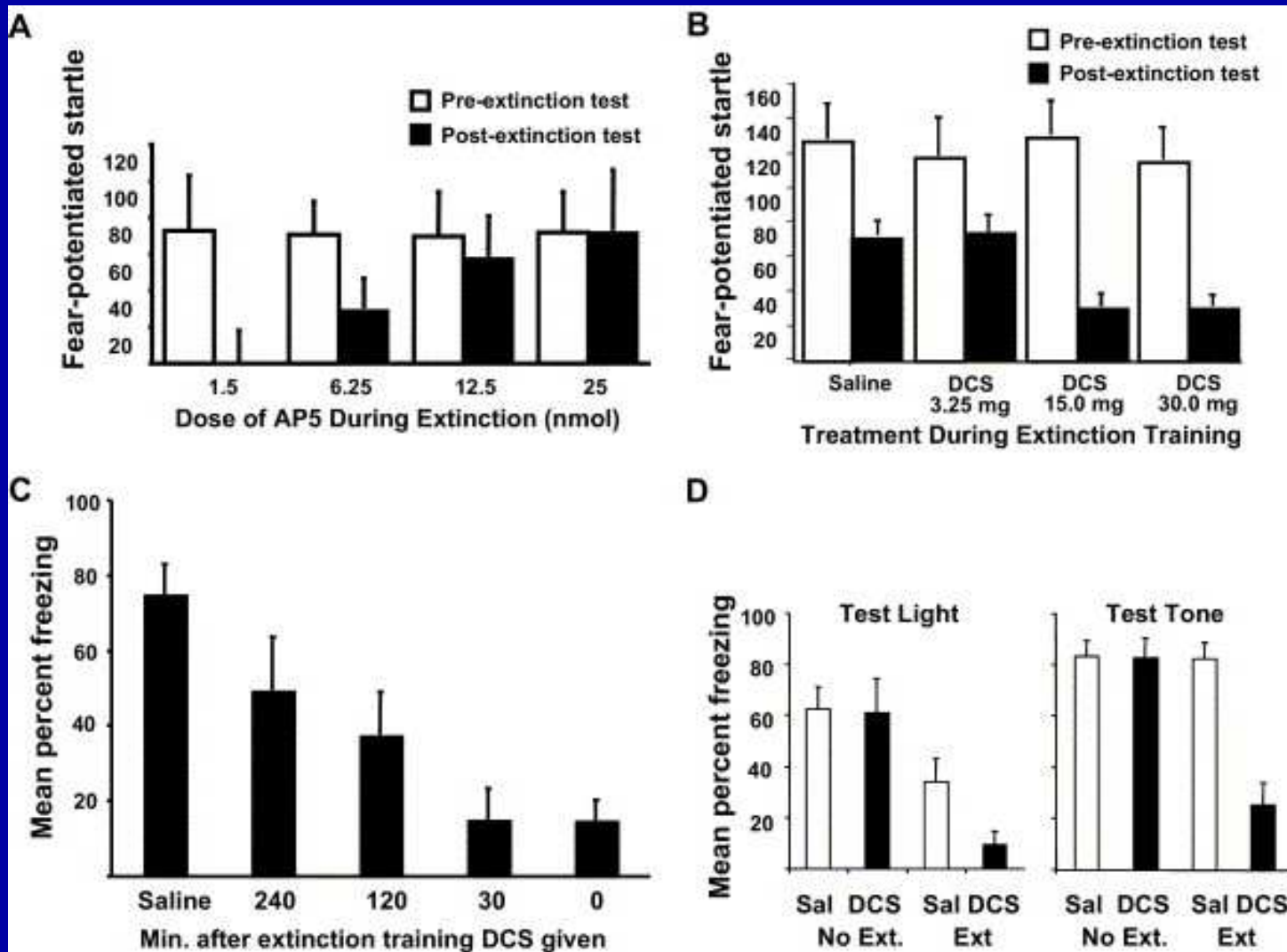


# NMDA Receptor



# NMDA Receptor



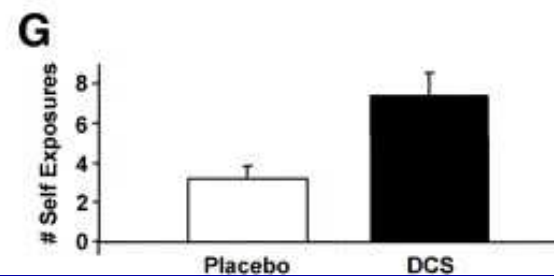
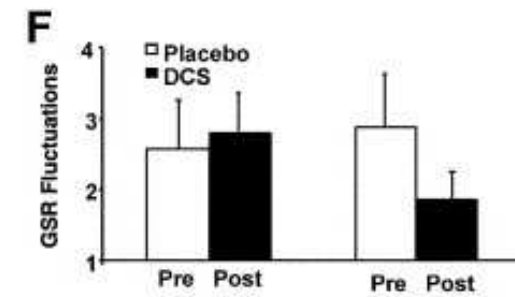
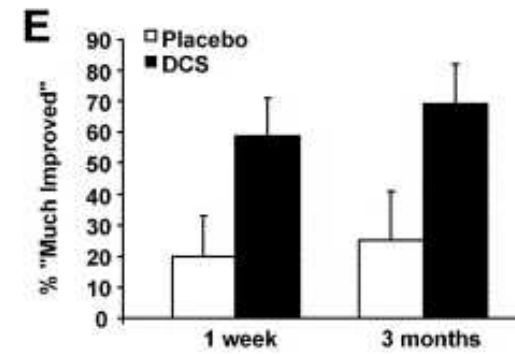
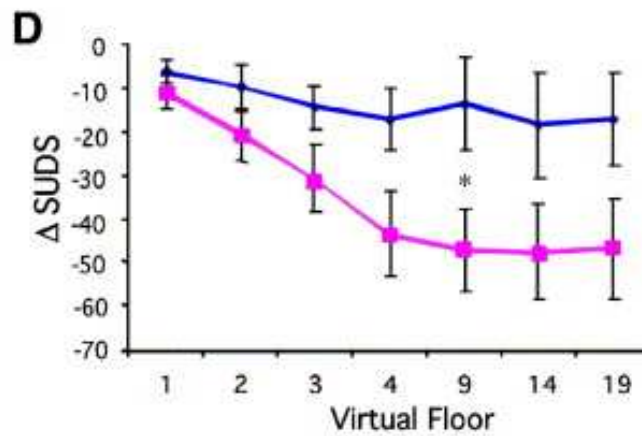
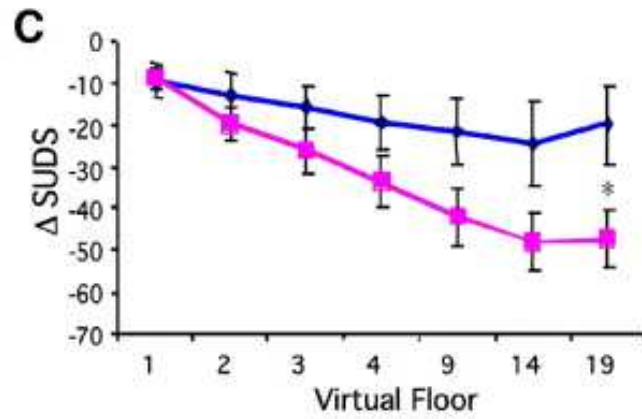
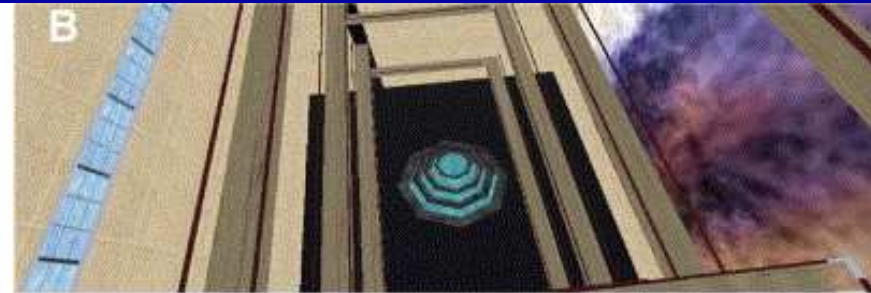
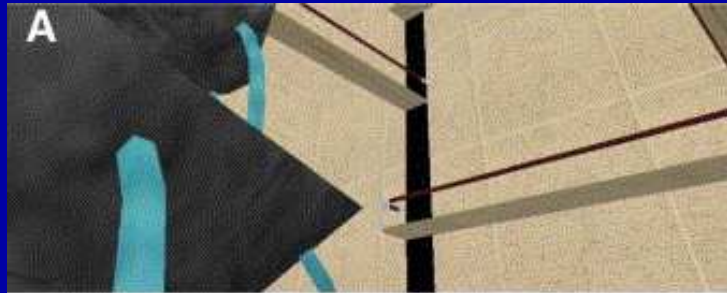


Falls et al., 1992; Walker et al., 2002; Ledgerwood et al., 2003, 2005.

# Specific Phobia

- N = 28 Patients with Acrophobia
- Assessments: Pre, post, 3-mo. FU
- Groups:
  - 2 VR-EXP sessions plus 50 or 250 mg DCS
  - 2 VR-EXP sessions plus Placebo

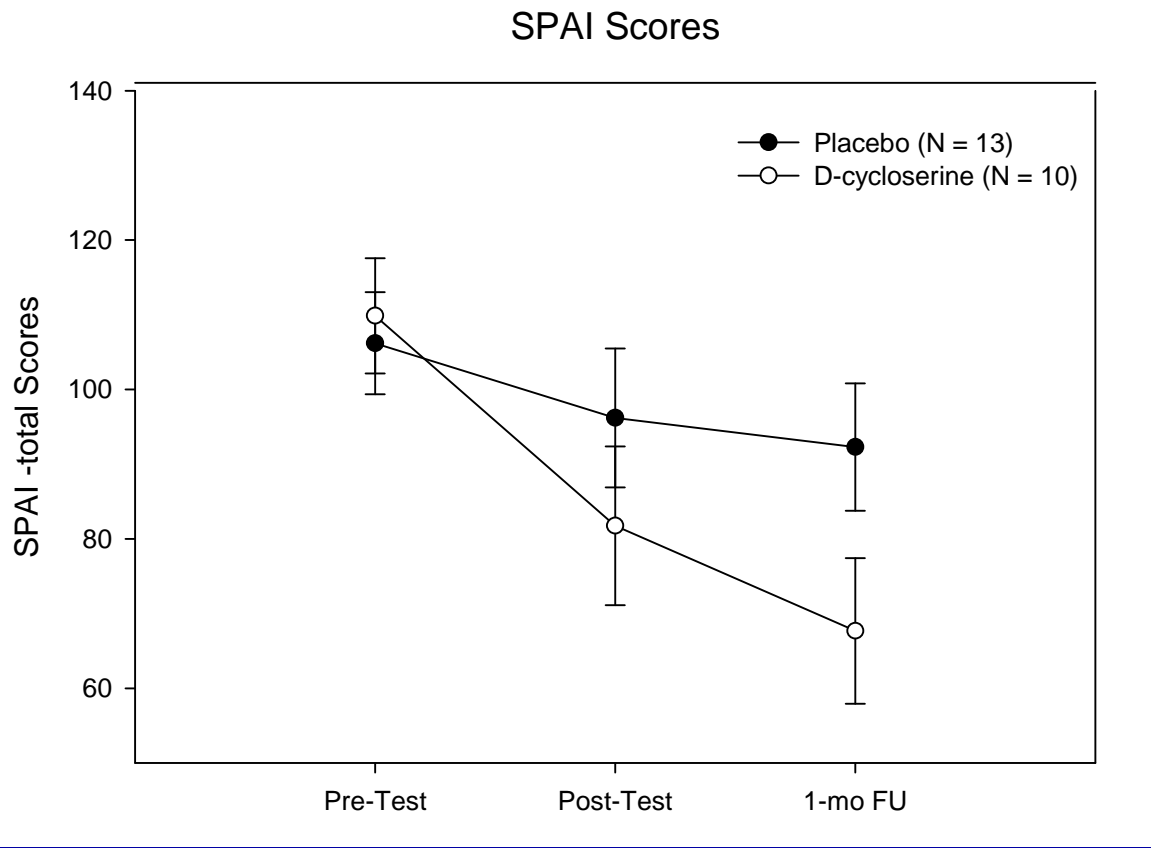
Ressler et al. (2004), *Archives of General Psychiatry*



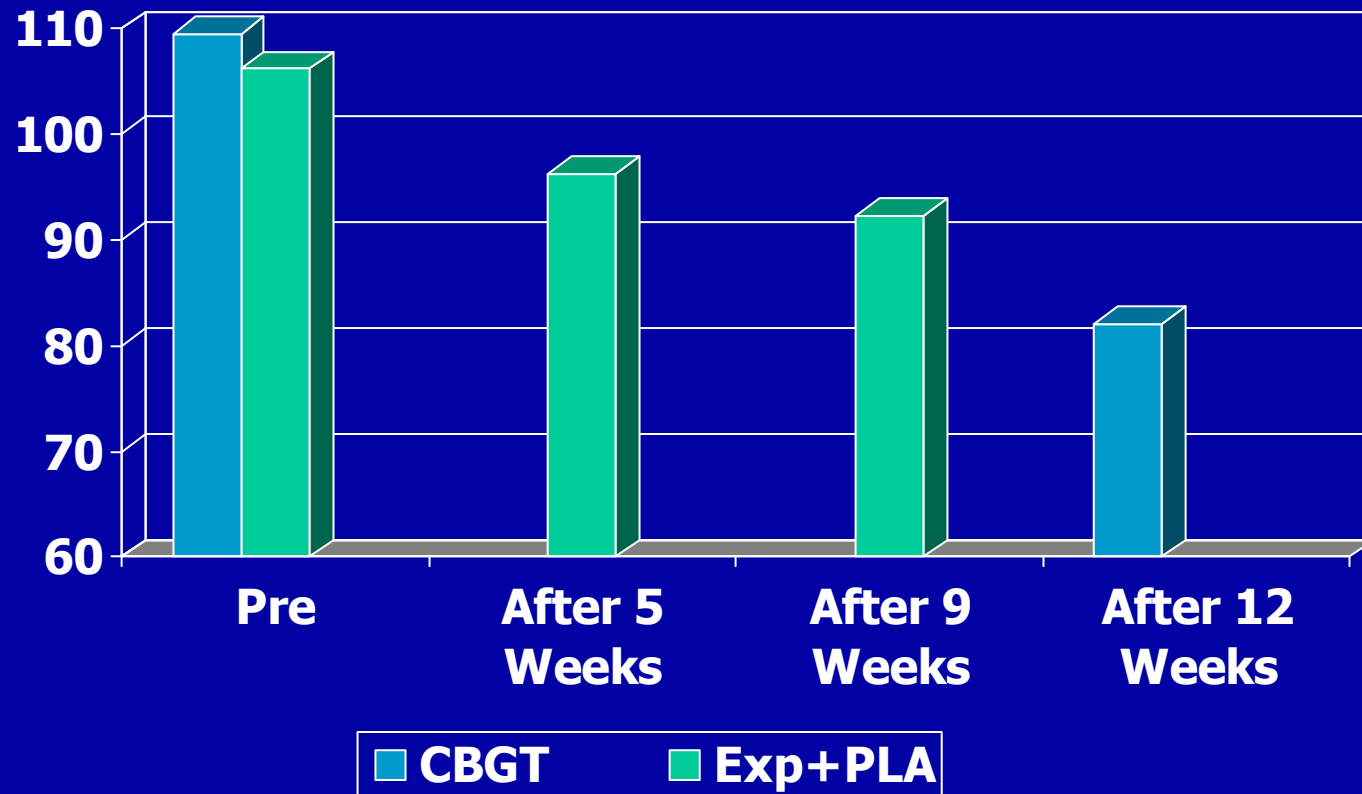
# Social Anxiety Disorder

- N = 27 Patients with SAD
- Assessments: Pre, post, 1-mo. FU
- Groups:
  - 5 EXP sessions plus 50 mg DCS
  - 5 EXP sessions plus Placebo

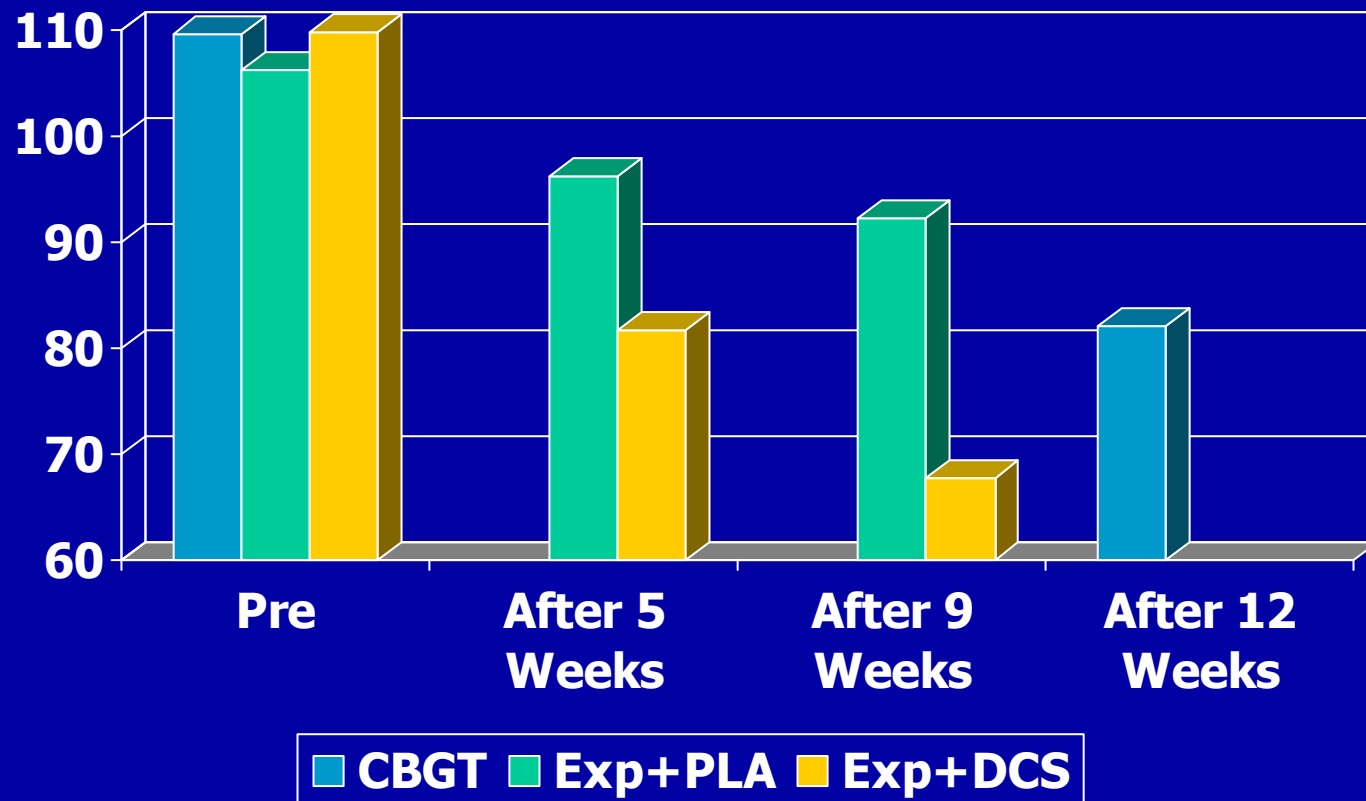
Hofmann et al. (2006), *Archives of General Psychiatry*



# Changes in SPAI



# Changes in SPAI



# Study Conclusion

Only three administrations of a small dose of DCS 1 hour before a brief exposure session (exposure to public speaking situations) leads to better outcome than 12 weekly sessions of comprehensive CBT with 2.5 hours per session.

# Independent Replication

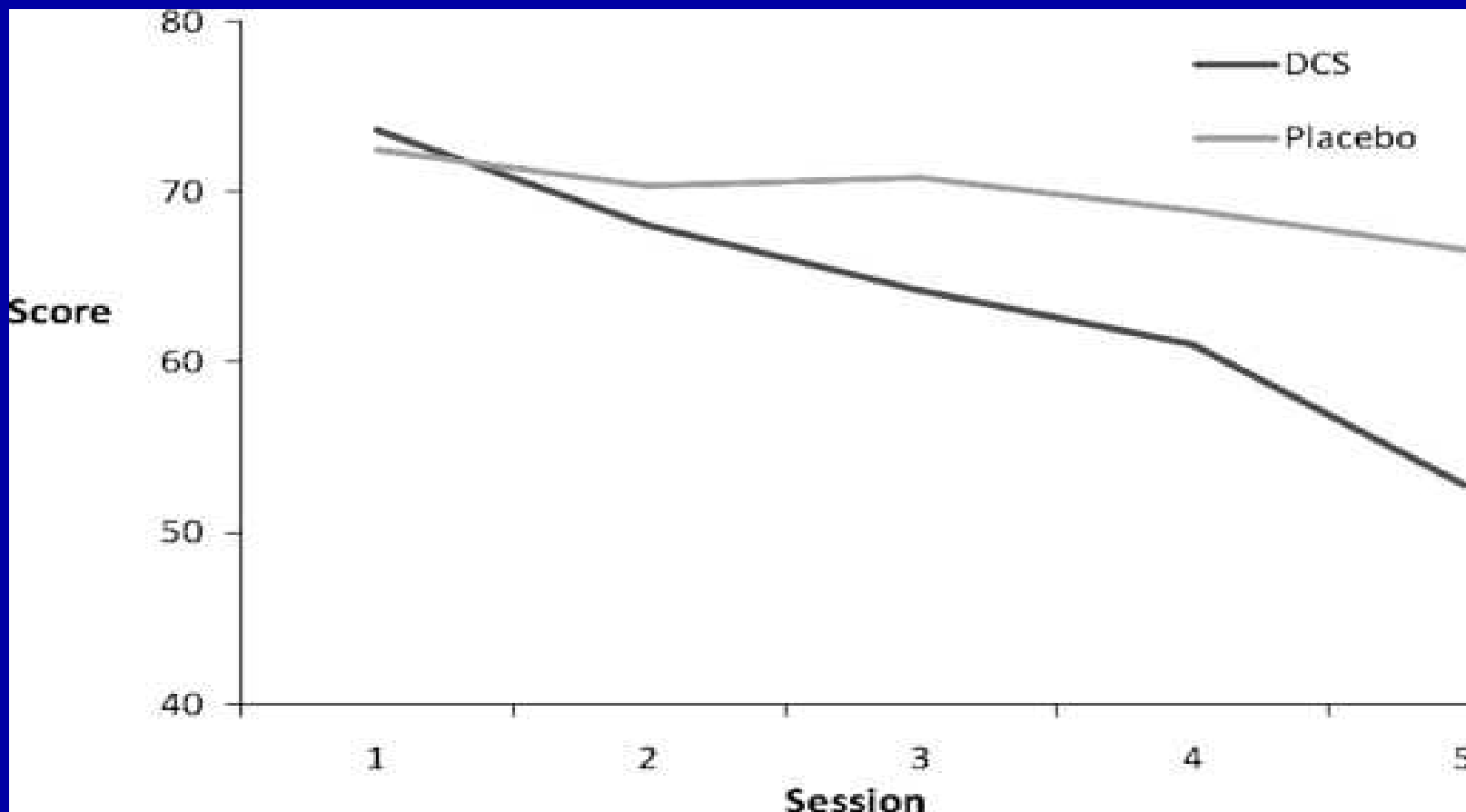
- By skeptical investigators
- At a different location (Australia)
- Using a larger sample

Guastella (2008). *Biological Psychiatry*.

# Method (Guastella et al.)

- N = 56 Patients with SAD
- Assessments: Pre, post, 1-mo. FU
- Groups:
  - 5 EXP sessions plus 50 mg DCS
  - 5 EXP sessions plus Placebo

# Total scores on the Liebowitz Social Anxiety Scale for each drug group before each treatment session

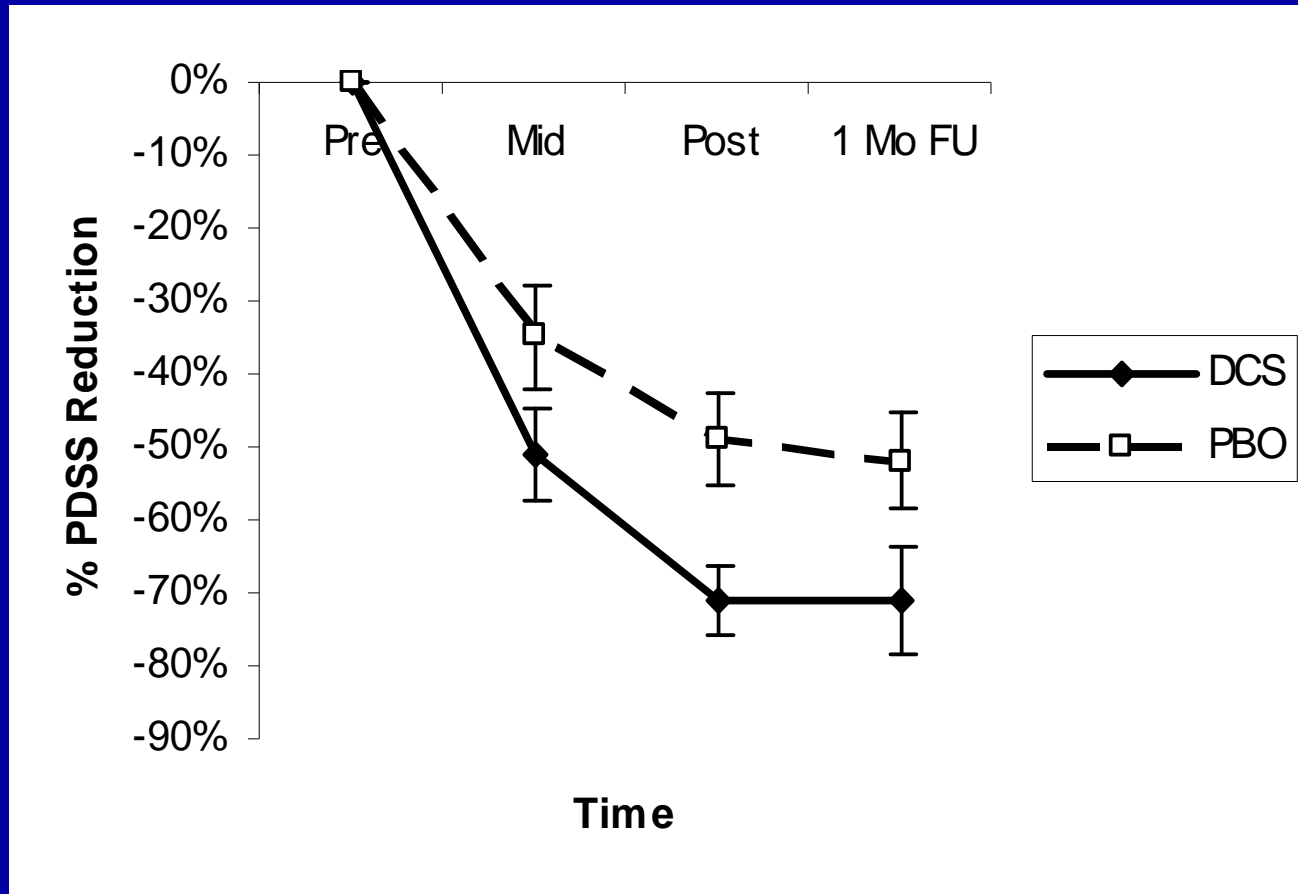


# Panic Disorder

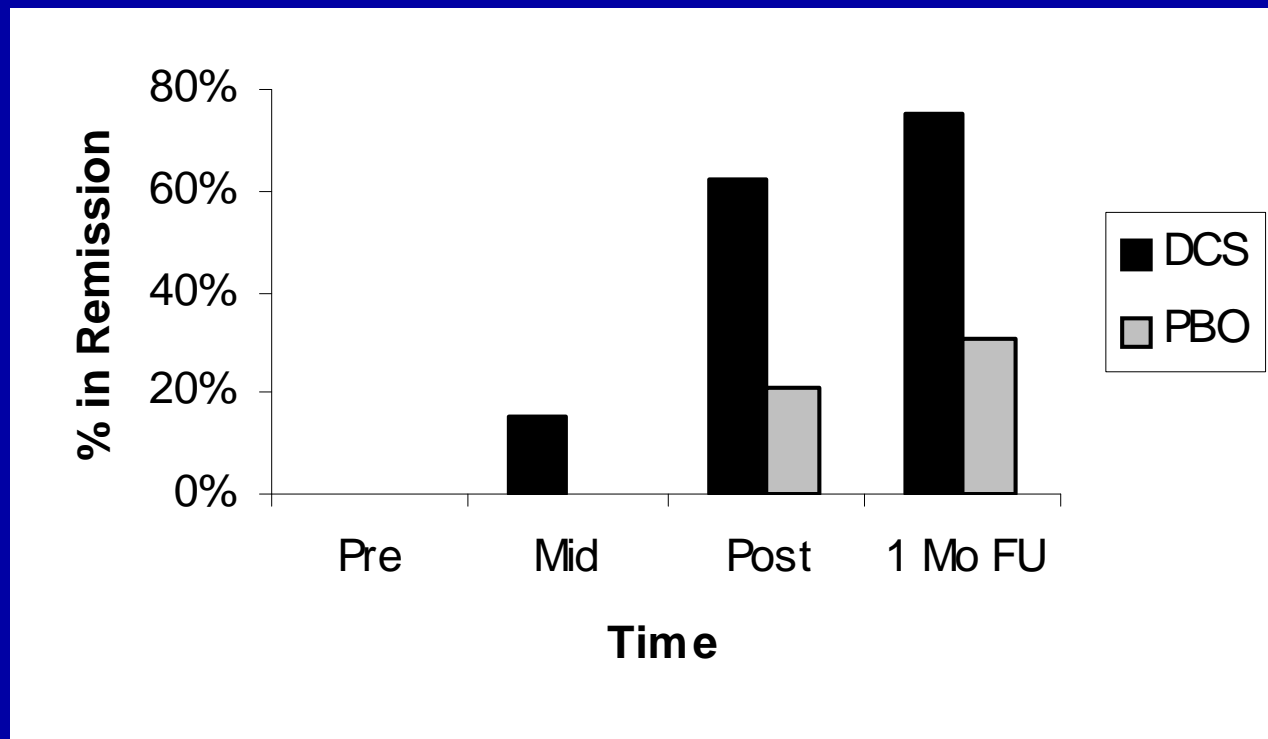
- N = 25 Patients with panic disorder (no or mild agoraphobia)
- Assessments: Pre, mid, post, 1-mo. FU
- Groups:
  - 5 EXP plus 50 mg DCS
  - 5 EXP plus Placebo

Otto et al. (2010). *Biological Psychiatry*.

# PDSS Scores



# Remission

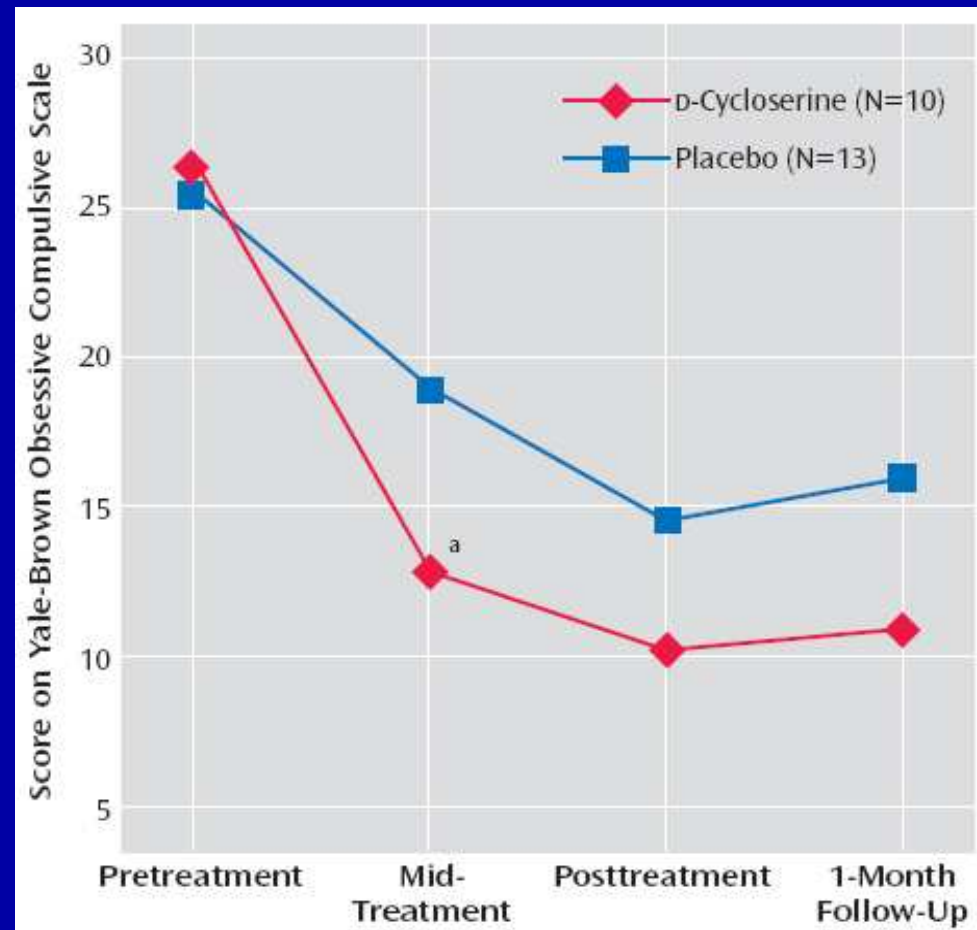


# Obsessive-Compulsive Disorder

- N = 17 Patients with OCD
- Assessments: Pre, mid, post, 1-mo. FU
- Groups:
  - 10 ERP sessions plus 100 mg DCS
  - 10 ERP sessions plus Placebo

Wilhelm et al. (2007). *American Journal of Psychiatry*

# Percent Reduction on Y-BOCS



<sup>a</sup>  $p = .009$

$d = 1.17$   $d = .63$   $d = .66$

# Human Clinical Studies

Study name	Dose	Dose Timing	Measure	# Sessions
<i>Specific Phobia</i>				
Ressler et al. (2004)	50 vs. 500	-3 hrs	SUDS	2
<i>Social Phobia</i>				
Guastella et al. (2008)	50	-1 hr	LSAS	4
Hofmann et al. (2006)	50	-1 hr	SIAS	4
<i>Panic Disorder</i>				
Tolin et al. (2007)	50	-1 hr	PDSS	3
<i>Obsessive-Compulsive Disorder</i>				
Kushner et al. (2007)	125	-2 hrs	SUDS	5
Storch et al. (2007)	250	-4 hrs	Y-BOCS	12
Wilhelm et al. (2008)	100	-1 hr	Y-BOCS	5

Norberg et al. (2008). *Biological Psychiatry*

# Conclusion

- CBT is effective, but there is still room for improvement.
- Combining CBT with traditional anxiolytic pharmacotherapy is not a lot more effective than monotherapy
- Augmenting CBT with a partial NMDA agonist (d-cycloserine) dramatically facilitates the learning processes during CBT

# Open Questions

Procedural issues:

- What is the optimal dosage of DCS?
- Are other NMDA agonists more effective?
- What is the optimal dosage of EXP?
- How does DCS interact with traditional pharmacotherapy?

# Open Questions

## Theoretical Issues:

- Are the effects of DCS limited to EXP/extinction learning (i.e., does it also work for acquisition learning)?
- Are the effects of DCS disorder specific (i.e., does it only work for extinction learning in anxiety disorders or does it also work for cue exposure for treating addiction)?
- Are there other cognitive enhancers (oxytocin, vasopressin, yohimbine, cortisol), what is their mechanisms (AMPA receptor?), and can they further enhance the DCS effect?
- Are there any DCS treatment predictors (neuromarkers)?