Biofluid Biomarkers in BPSD

Elaine R. Peskind, M.D.

Co-Director, VA Northwest Network
Mental Illness Research, Education, and Clinical Center, Seattle, WA

Friends of Alzheimer's Research Professor,
Department of Psychiatry and Behavioral Sciences
University of Washington School of Medicine

Classic AD CSF Biomarkers (Aβ, tau, p-tau) and BPSD

- Skogseth R et al. *Dement Geriatr Cogn Disorder* 2008; 25:559-63.
  - » Apathy significantly correlated with CSF tau and p-tau
  - » No significant correlations between psychosis, agitation, or depression and CSF Aβ42, tau, or p-tau

Classic AD CSF Biomarkers (Aβ, tau, p-tau) and BPSD (cont.)

- Koppel J et al. *Am J Psychiatry* 2013;170:1212-13.
  - 60 ADNI AD participants with psychosis assessed by Neuropsychiatric Inventory Questionnaire had elevated CSF tau compared to 115 AD participants without psychosis over a 36 month period.
- Bloniecki V…Cummings J, Blennow K. Dement *Geriatr Cogn Disorder Extra* 2014; 4:335-43.
  - In 33 AD participants, CSF total tau and p-tau significantly correlated with Cohen-Mansfield Agitation Inventory total scores
  - This relationship was not observed in 62 non-AD dementia participants

Classic AD CSF Biomarkers (Aβ, tau, p-tau) and BPSD (cont.)

- Roe CM, Fagan AM, Grant EA, Holtzman DM, Morris JC. *Neurology* 2013; 81:2028-2031.
  - For CSF Aβ42, tau, p-tau181, tau/Aβ42, p-tau181/Aβ42, abnormal values all predict worsening in Neuropsychiatric Inventory and Geriatric Depression Scale
- Ingbar AP, Hassenstab J, Fagan AM, Benzinger T, Grant E, Holtzman DM, Morris JC, Roe CM. *J Alzheimer's Dis* 2016; 52:1055-64.
  - Cognitively normal older persons had LP and MRI and followed for 5 years.
  - Smaller brain volumes predicted worse outcomes on Neuropsychiatric Inventory and Geriatric Depression Scale in those with abnormal CSF AD biomarkers

Classic AD CSF Biomarkers (Aβ, tau, p-tau) and BPSD (cont.)

- Ramakers IHGB, …Trojanowski JQ, Blennow K. *Psychol Med* 2013; 43:911-920.
  - » Measured CSF Aβ42 and total tau and performed NPI in 268 MCI participants.
  - » Presence of anxiety, agitation, and irritability all associated with abnormal concentrations of Aβ42.
  - » Anxiety also was associated with abnormal total tau.

CSF Biomarkers of Neuroinflammation and BPSD in AD

- Holmgren S at al. *Brain Res Bull* 2014; 108:88-93.
  - » Measured CSF Interleukin (IL)-6, IL-10, TNFα, and cytokine receptor sIL-1RII
  - » Significant inverse correlations ($p \leq 0.01$) between IL-10 and both agitation and "nighttime behavior" (likely confounded with agitation)
  - » Significant inverse correlation between IL-6 and anxiety ($p=0.049$).

CSF “Classic” Monoamines and BPSD in AD

- Brane G. *Alz Dis Assoc Dis* 1989; 3:148-56.
  - » CSF norepinephrine metabolite MHPG was significantly increased in “late onset” (≥65 years of age, N=28) and positively correlated with “restlessness” (? agitation).
  - » CSF serotonin metabolite 5HIAA in “early onset” AD (N=13) did not differ from controls, but was positively correlated with “anxiety” and “fear panic.”
  - » CSF dopamine metabolite HVA in late onset AD was negatively correlated with “impaired wakefulness” and “inability to increase tempo” (? apathy).

The Brain Noradrenergic System

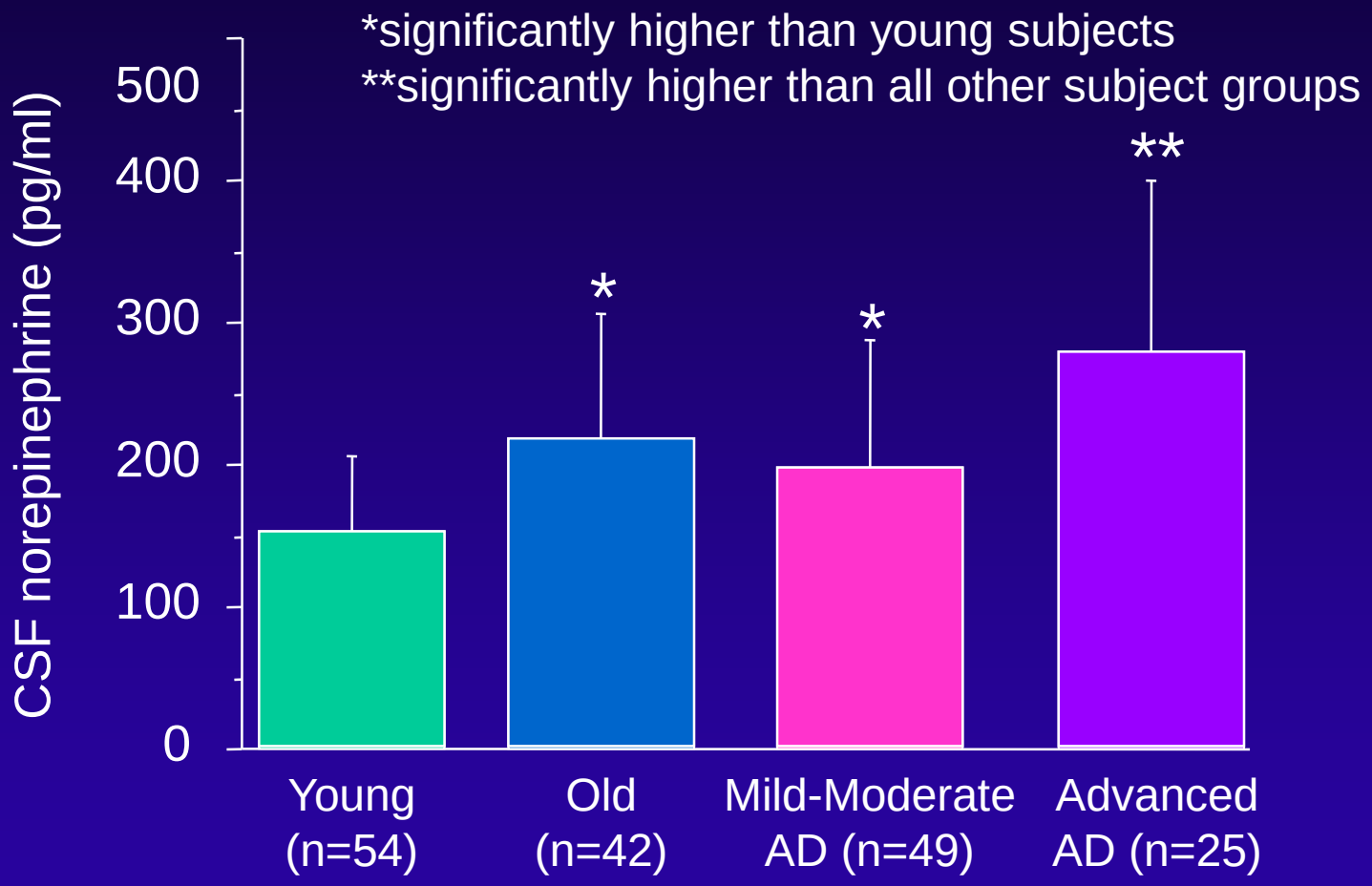
- The noradrenergic system is the brain “adrenaline” system for attention and arousal particularly to novel stimuli in environment.
- Excessive noradrenergic outflow and/or responsiveness produces anxiety and agitation.
- Does excessive noradrenergic activity contribute to agitation in AD?

Noradrenergic System Pathology in Alzheimer's Disease

- Despite loss of noradrenergic locus coeruleus neurons there is:
  - » increased cerebrospinal fluid (CSF) norepinephrine (NE) in AD[1]
  - » increased agitation response to NE in AD[2]

[1]Elrod et al., *Am J Psychiatry* 154:25-30, 1997.
[2]Peskind, et al., *Arch Gen Psychiatry, 1995*

CSF Norepinephrine: Effects of Aging and AD



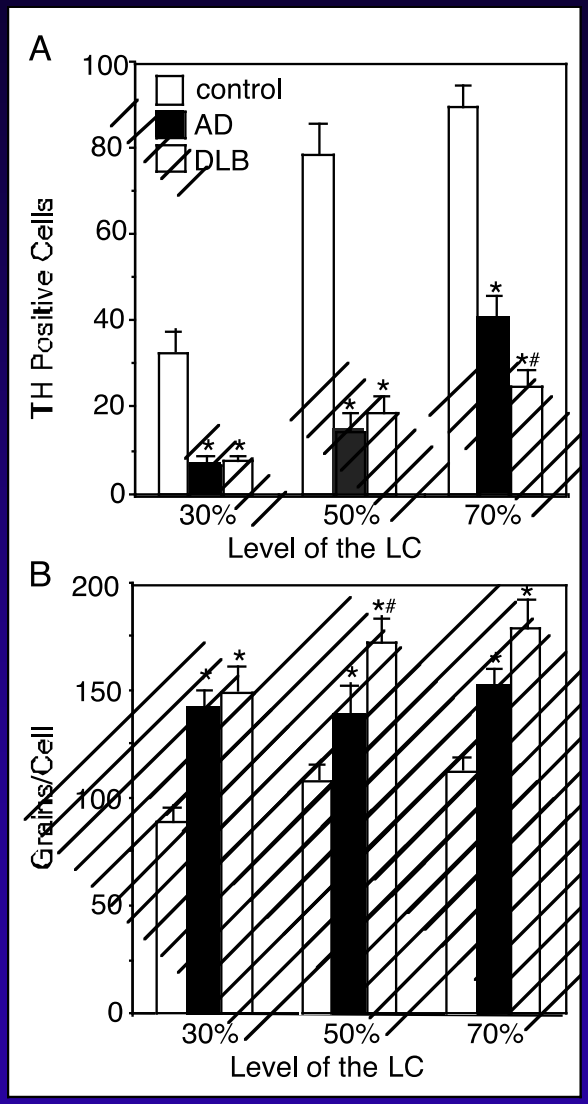
Elrod et al., *Am J Psychiatry* 154:25-30, 1997.

- In animal studies, partial denervation of the locus ceruleus causes compensatory upregulation of norepinephrine (NE) biosynthetic capacity in surviving locus ceruleus neurons.
- Does this phenomenon occur in AD?

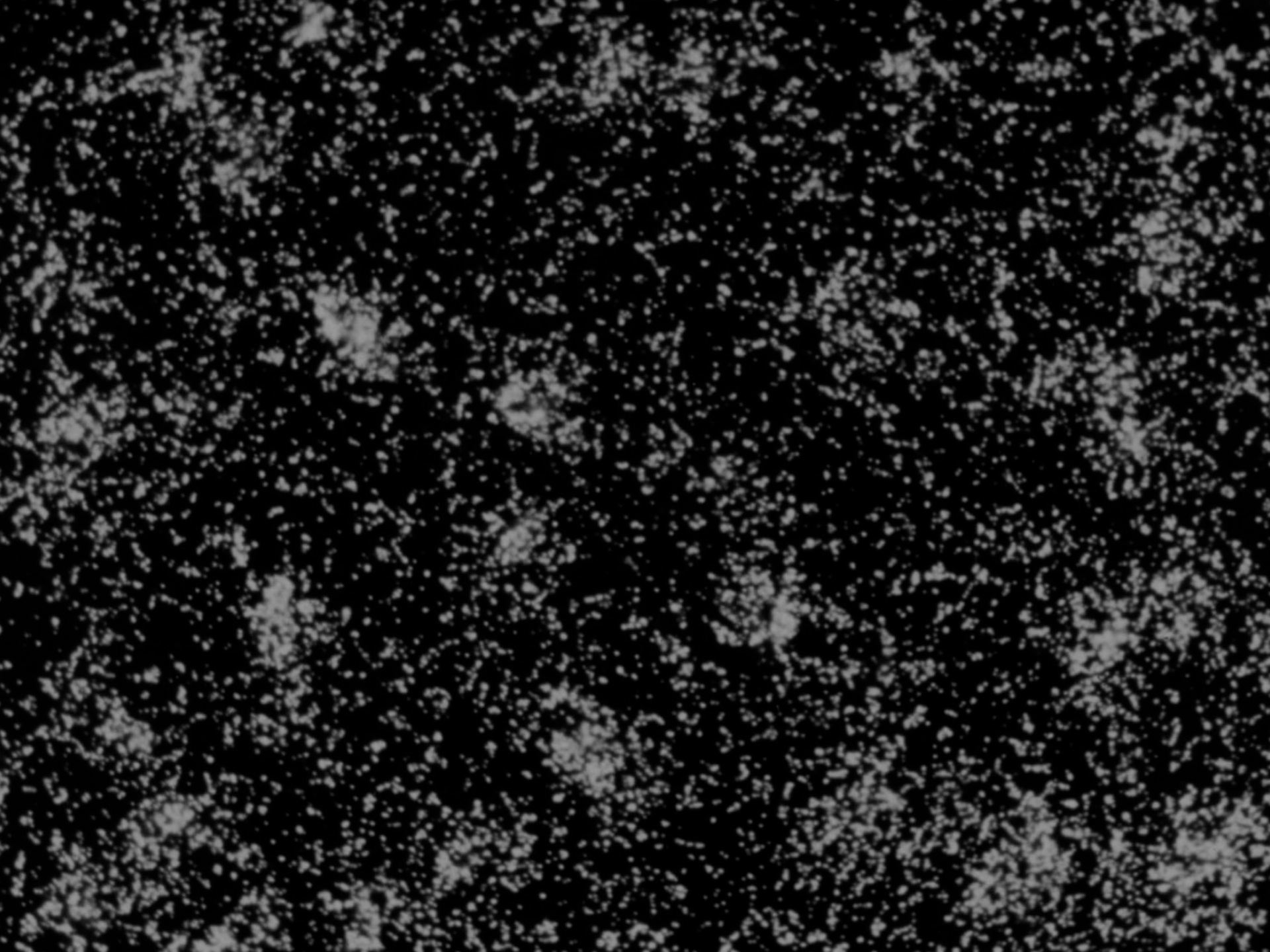
- Locus ceruleus NE biosynthetic capacity *antemortem* can be estimated by measuring tyrosine hydroxylase mRNA by *in situ* hybridization histochemistry in *postmortem* brain tissue.

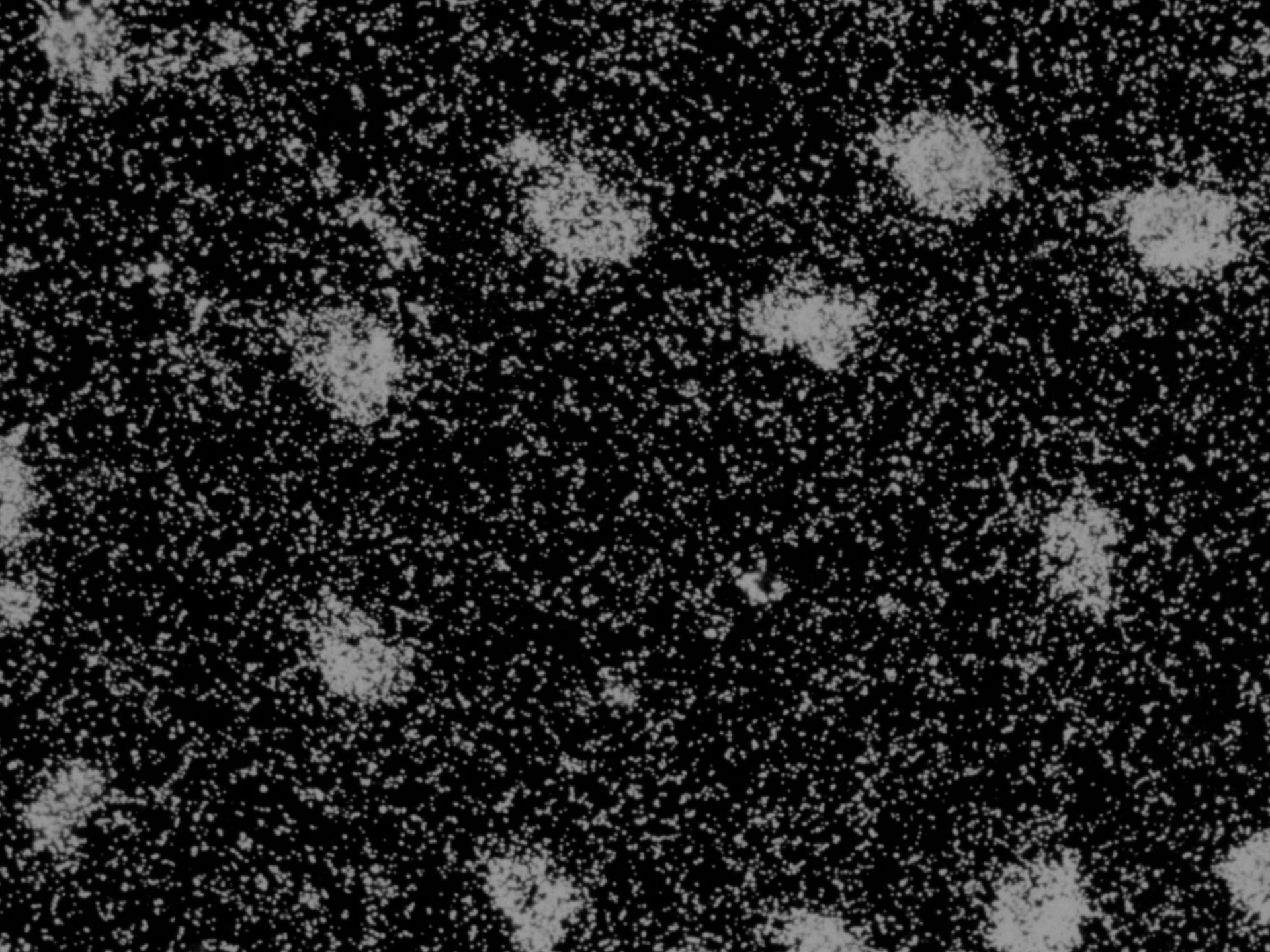
- We found increased TH mRNA per surviving LC neuron at all levels of LC in AD (N=15) and AD/LB (N=15) compared to nondemented older controls (N=17).

Szot P, et al., *J Neurosci* 26:467-478, 2006.



Szot P, et al., *J Neurosci* 26:467-478, 2006.





- In AD and AD/LB, surviving noradrenergic neurons are compensating by increasing the mRNA expression of the rate-limiting enzyme in the synthesis of NE at multiple levels of the LC.

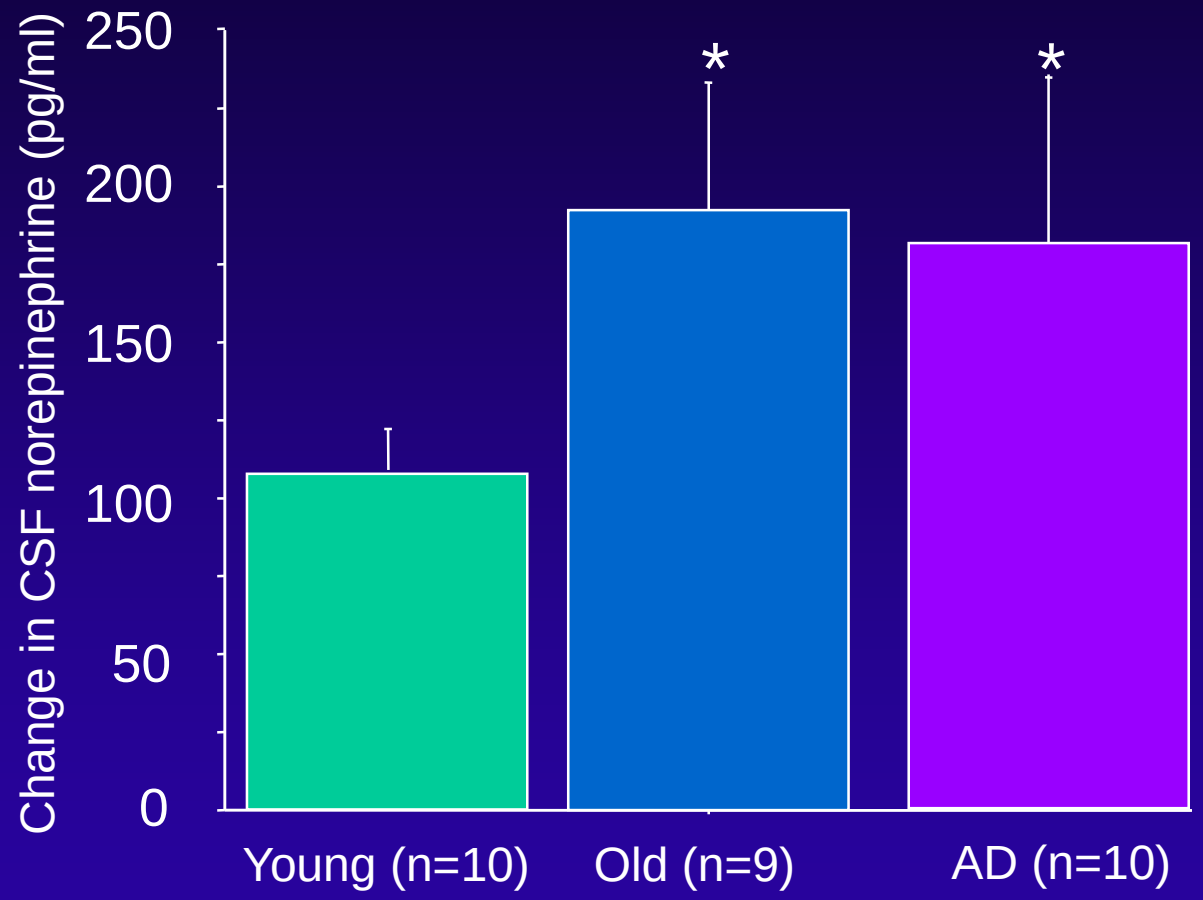
Szot P et al., *Neuroscience,* 2007.

We Stimulated Brain Noradrenergic System With the Drug Yohimbine

- We measured CSF NE responses to placebo or the alpha-2 adrenoreceptor antagonist yohimbine in 9 AD (MMSE = 14± 2), 10 normal older, and 17 normal young subjects.
- We measured behavioral responses using Brief Psychiatric Rating Scale (BPRS) items “Tension”, “Excitement”, “Anxiety”.

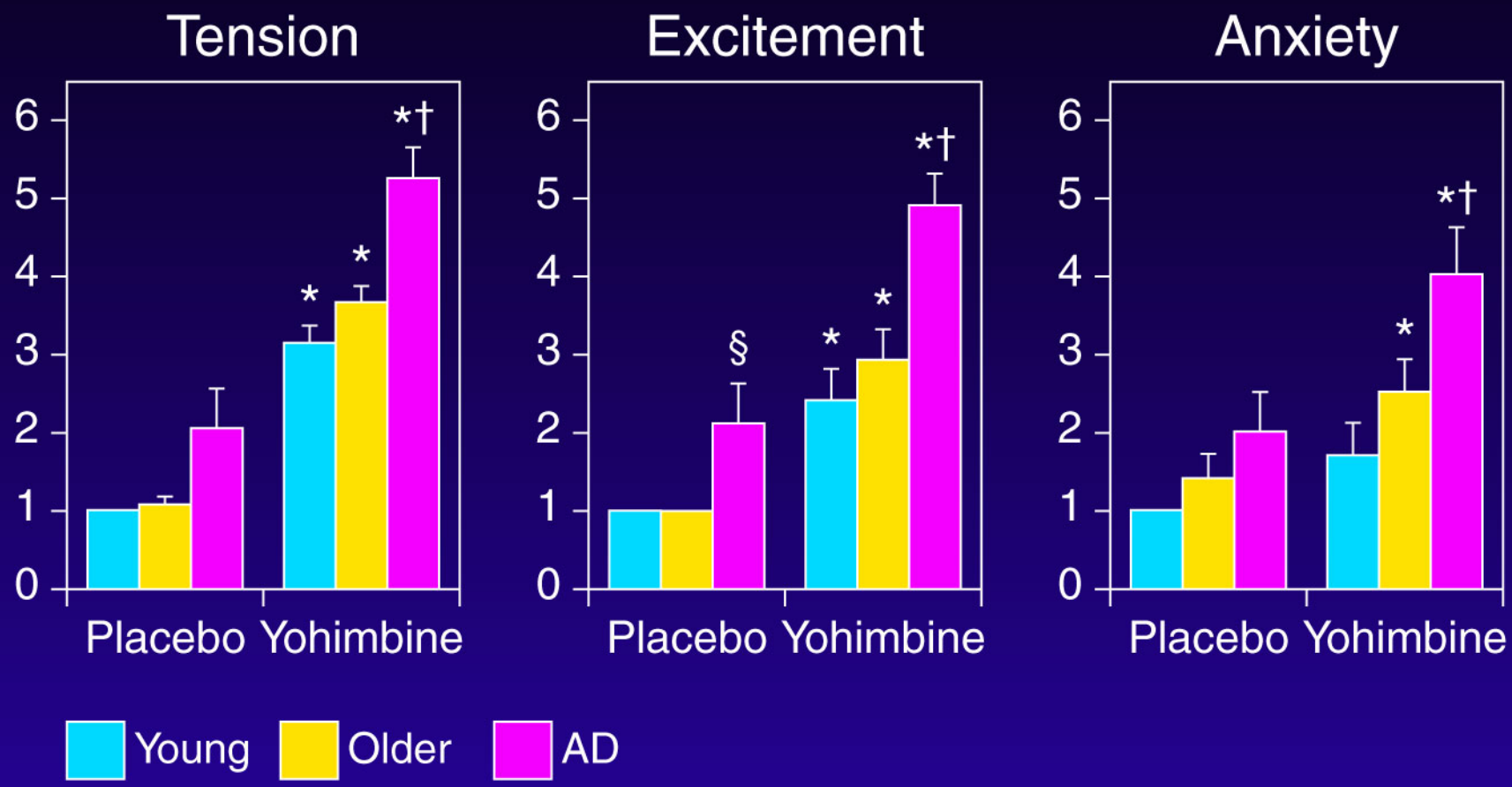
Peskind, et al., *Arch Gen Psychiatry* 52:774-782, 1995.

Change in CSF NE Concentrations Between Placebo and Yohimbine Conditions

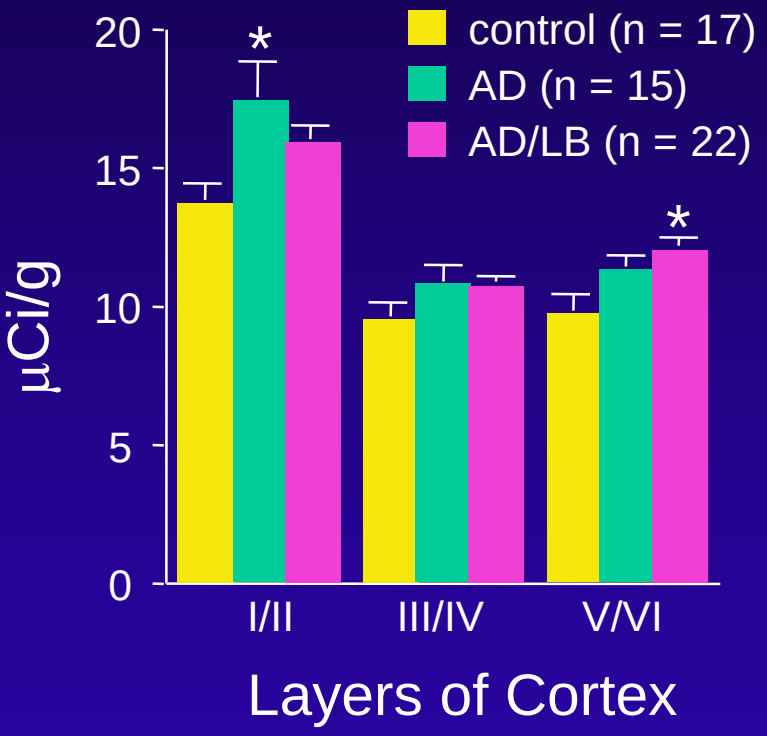


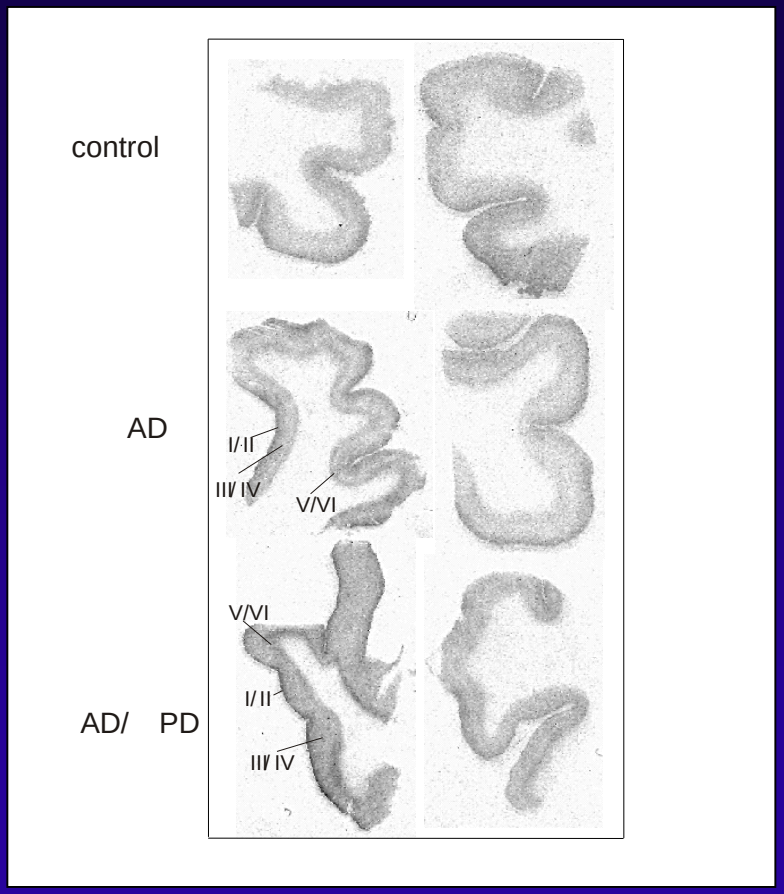
* significantly higher than young subjects

Effects of Yohimbine Administration on Tension, Excitement, and Anxiety Ratings



^{3}H Prazosin Binding - Prefrontal Cortex





Szot P, et al., *J Neurosci* 26:467-78, 2006.

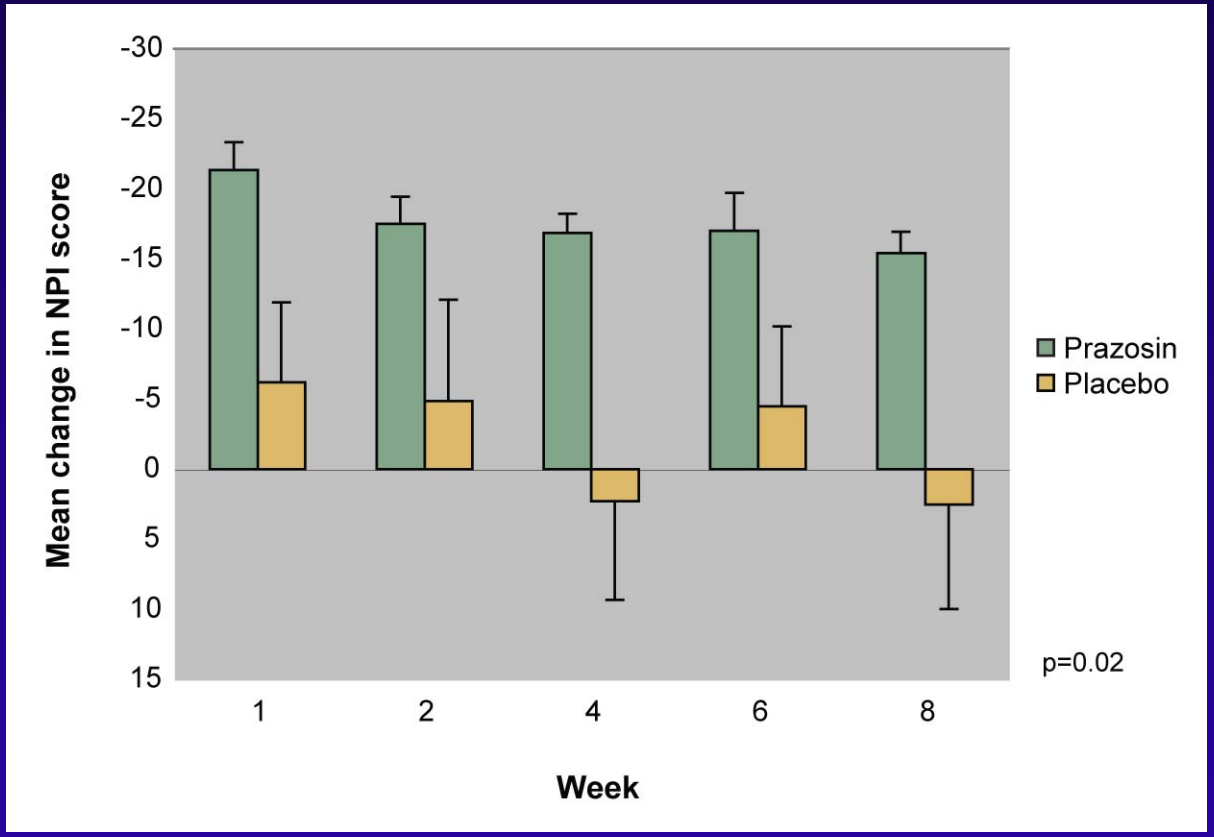
Postsynaptic Adrenergic Receptor Antagonism for Agitation in AD

- Enhanced agitation response to adrenergic stimulation in AD.
- Upregulation of the postsynaptic alpha-1 adrenoreceptor in AD.
- Would reducing brain responsiveness to NE by adrenergic receptor (AR) blockade reduce agitation in AD?
- Prazosin is alpha-1 AR antagonist that readily crosses the blood-brain barrier:

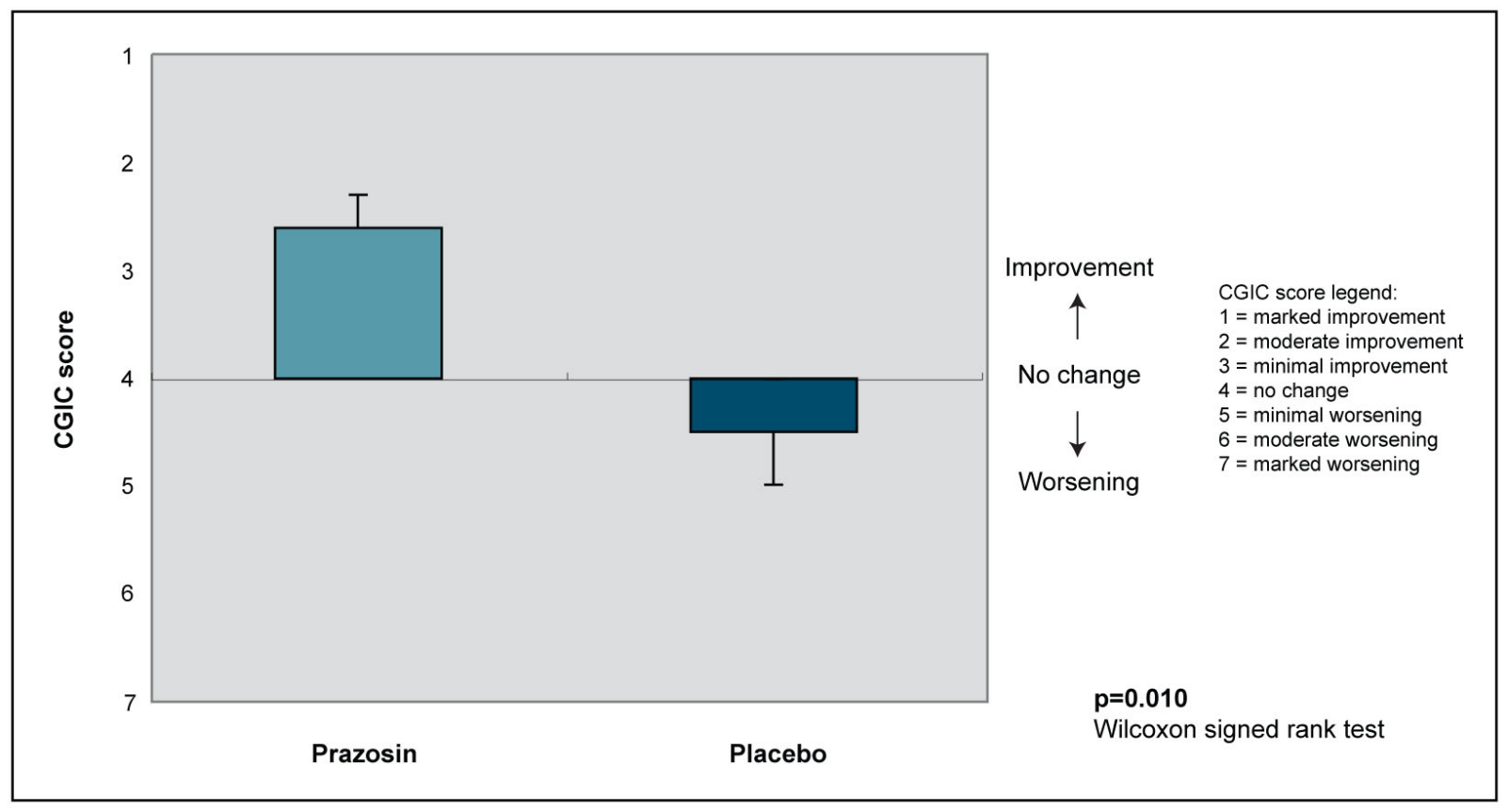
Placebo-Controlled Trial of Prazosin for Disruptive Agitation in Dementia

- Twenty-two mostly LTC residents (mean age 81 ± 11 years) with DSM-IV dementia (possible or probable AD) and frequent disruptive agitation.
- Randomized to prazosin (n=11) or placebo (n=11) for 8 weeks.
- Prazosin dose range 2-6 mg/day (mean dose 5.7 ± 0.9 mg/day).
- Primary outcome measures: NPI, BPRS CGIC.

Placebo-Controlled Trial of Prazosin for Disruptive Agitation in Dementia: NPI



Placebo-Controlled Trial of Prazosin for Disruptive Agitation in Dementia: CGIC



Adverse Events Were Similar for Prazosin and Placebo Groups

Number of Occurrences of Adverse Events

	Prazosin group	Placebo group	Both groups combined
Sedation	3	3	6
Confusion	2	4	5
Hypotension	2	1	3
Dizziness on Standing	1	0	1

Conclusions

- Prazosin may be effective for the treatment of disruptive agitation in AD.
- Prazosin is generally well-tolerated
  - » Non-sedating, no EPS; symptomatic hypotension rare.
- About to launch ADCS PEACE-AD Multicenter Trial: Prazosin for Disruptive Agitation in Alzheimer's Disease in 186 long-term care residents.