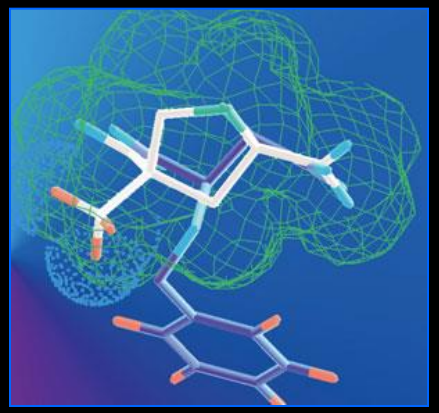
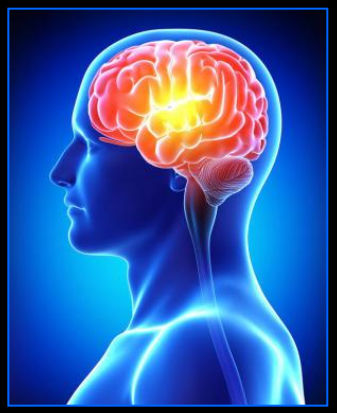


Clinical Trials and Drug Development for Neuropsychiatric Symptoms of Alzheimer's Disease

- Jeffrey Cummings, MD, ScD
- Cleveland Clinic Lou Ruvo Center for Brain Health
- Las Vegas, Nevada; Cleveland, Ohio; Weston, Florida

Cleveland Clinic

Disclosures

Dr. Cummings has provided consultation to Abbott, Acadia, Adamas, Anavex, Astellas, Avanir, Bayer, BMS, Eisai, EnVivo, Forest, Genentech, GSK, Lundbeck, Neuronetrix, Novartis, Otsuka, Pfizer, Prana, QR, Sanofi-Aventis, Signum, Takeda and Toyama pharmaceutical companies.

Dr. Cummings has provided consultation to MedAvante, Neurotrax, Avid, ExonHit, GE Healthcare, and UBC assessment companies.

Dr. Cummings owns the copyright of the Neuropsychiatric Inventory

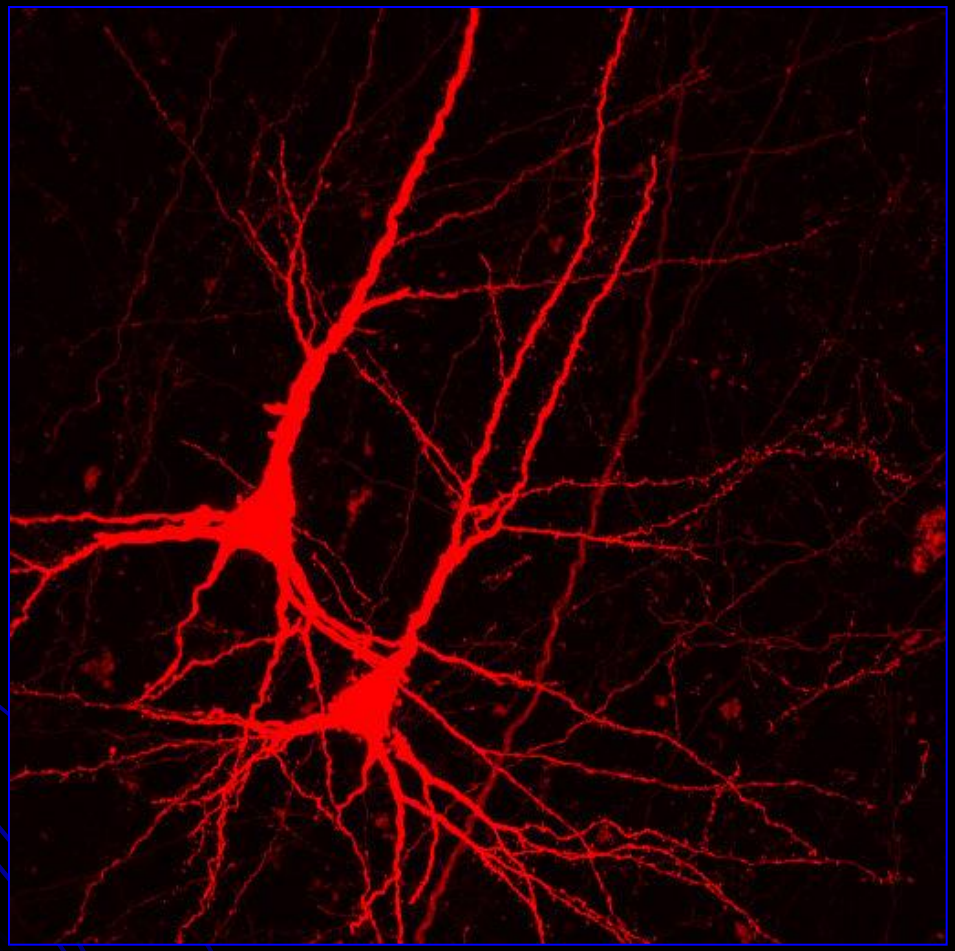
Dr. Cummings has stock options in Prana, Neurokos, ADAMAS, MedAvante, QR pharma

Dr. Cummings will discuss the off-label use of drugs in development

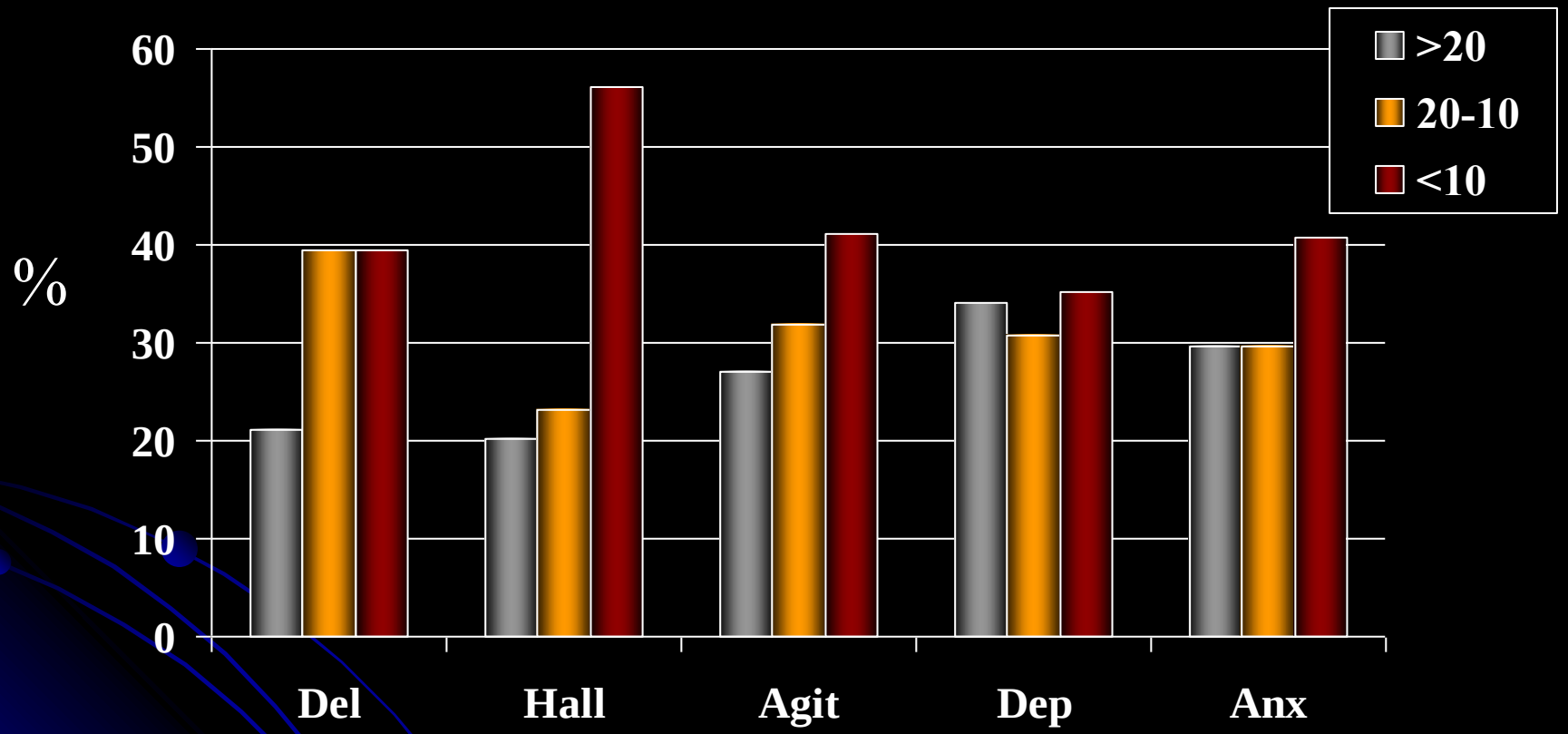
Drug Development for AD NPS

- NPS in AD
  - Frequency, severity
- Biology of NPS in AD
- Progress in definitions
- Trial design challenges and responses
- Review of drug development for AD NPS and current pipeline

NPS in Alzheimer's Disease



NP Sx in AD: Mild, Mod, Severe



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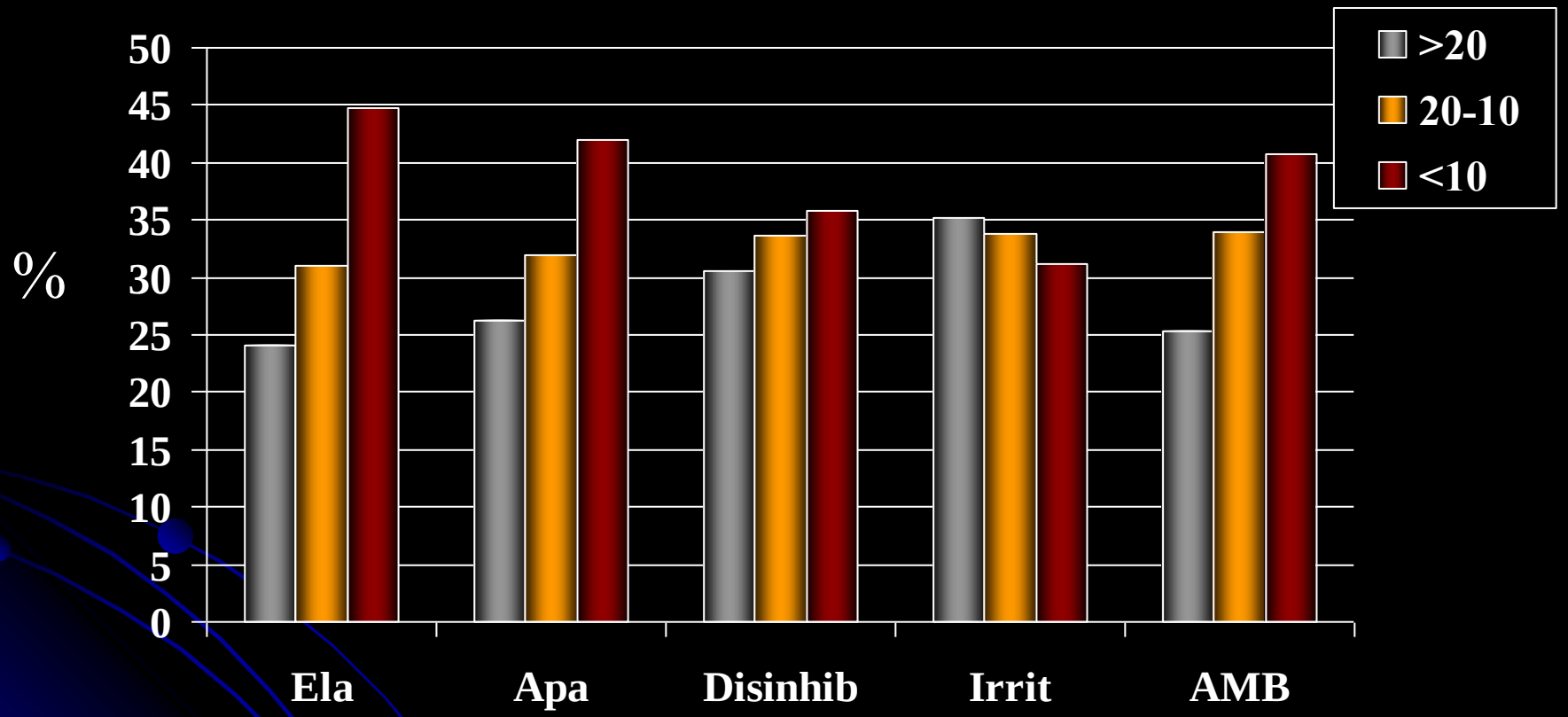
(Craig D, et al. Am J Geriatric Psychiatry 2005; 13: 460-468)

NP Sx in AD: Mild, Mod, Severe



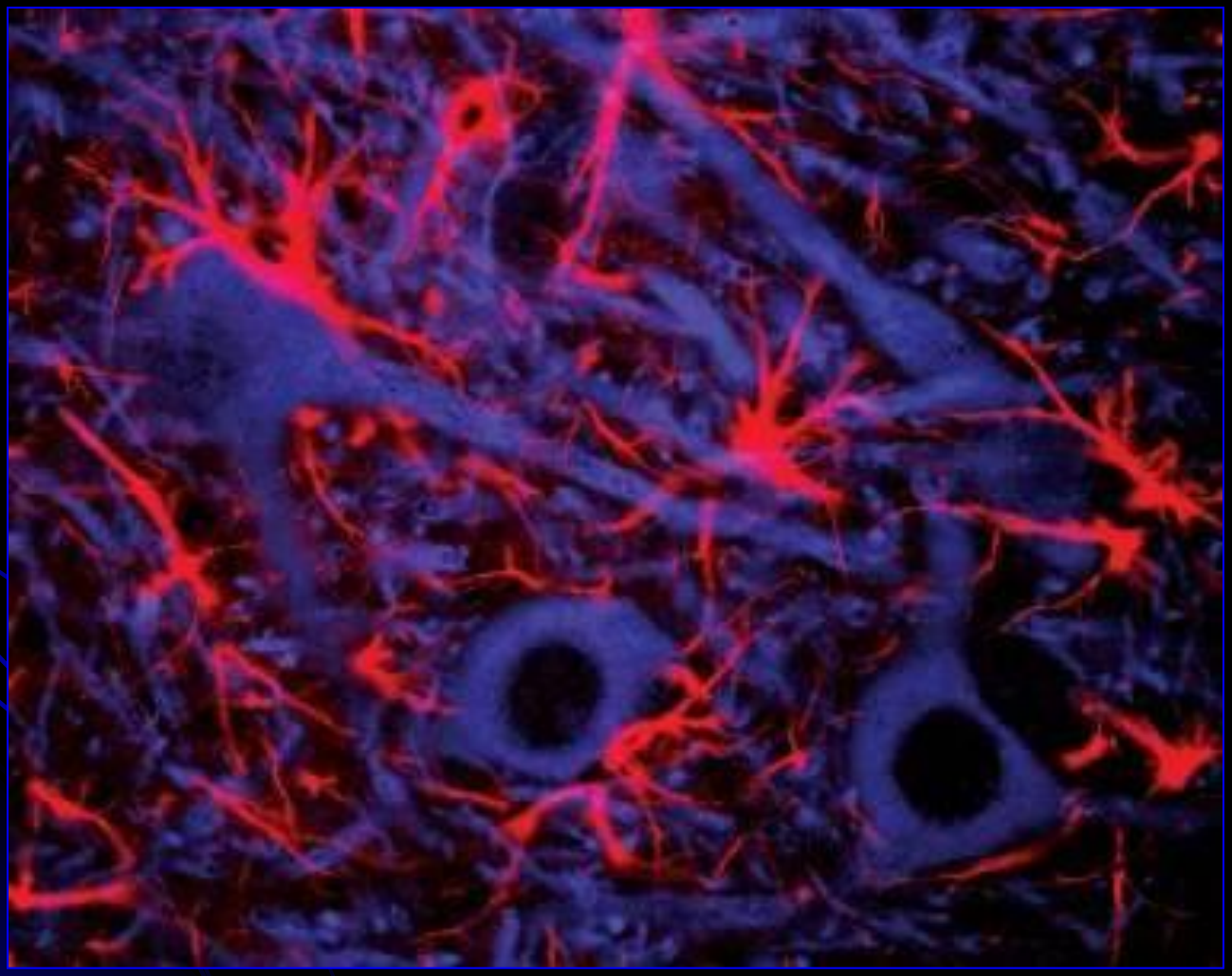
<10=162
20-10=125
>20=119

(Craig D, et al. Am J Geriatric Psychiatry 2005; 13: 460-468)

NPS in Alzheimer's Disease

- NPS are common
- Clinically meaningful
  - Increase cost
  - Increase institutionalization
  - Decrease quality of life (patients, partner)
- Symptoms tend to co-occur
  - Patient could meet criteria for an agitation trial or a depression trial

Biology of NPS in AD



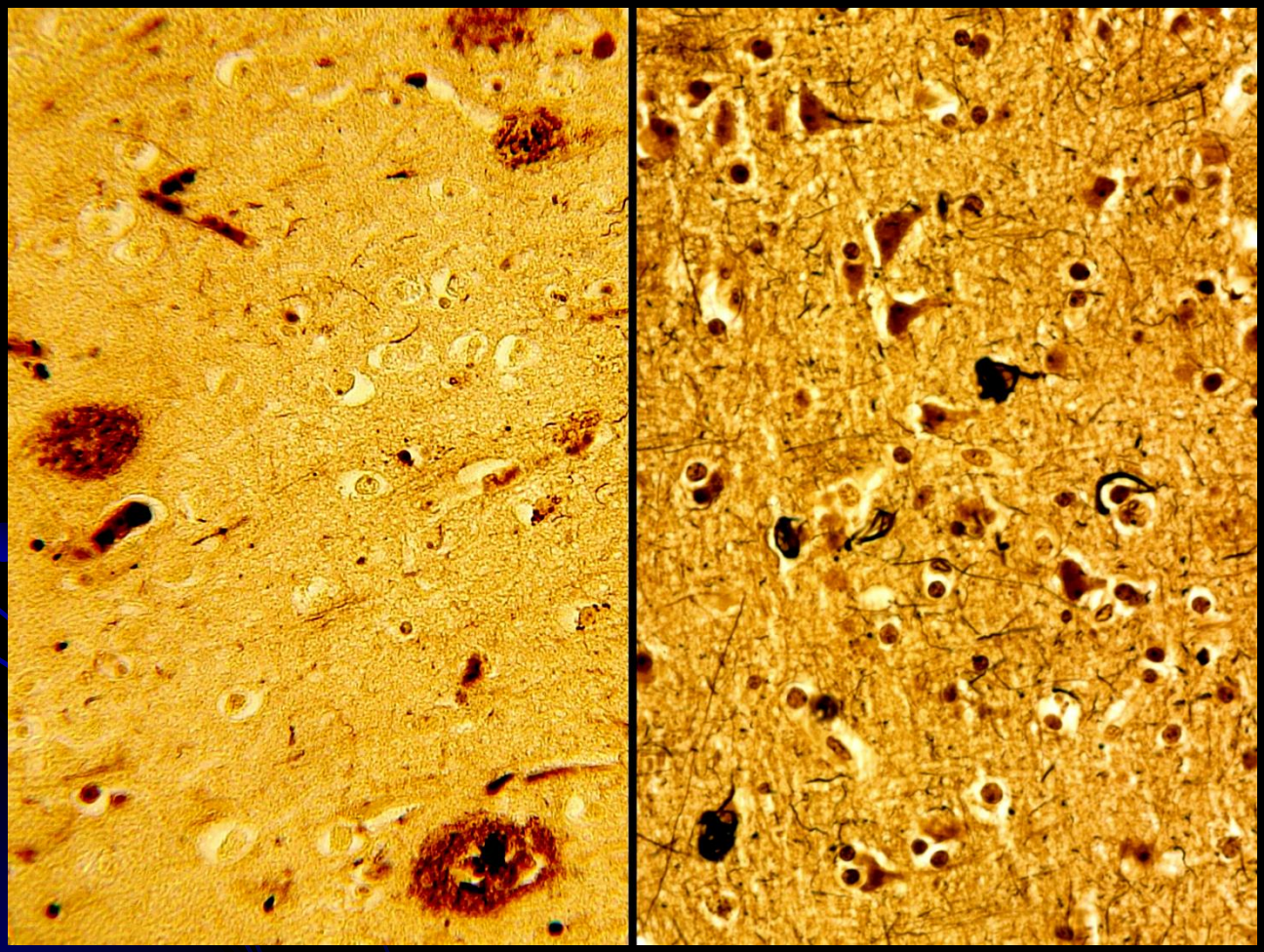
Biology of NPS in AD

- Biology of NPS incompletely understood
- Tau burden (autopsy)
  - Agitation
  - Psychosis
- Imaging biomarkers
  - FDG PET
  - SPECT

Agitated Patients Have More Neurofibrillary Tangles in the Frontal Cortex

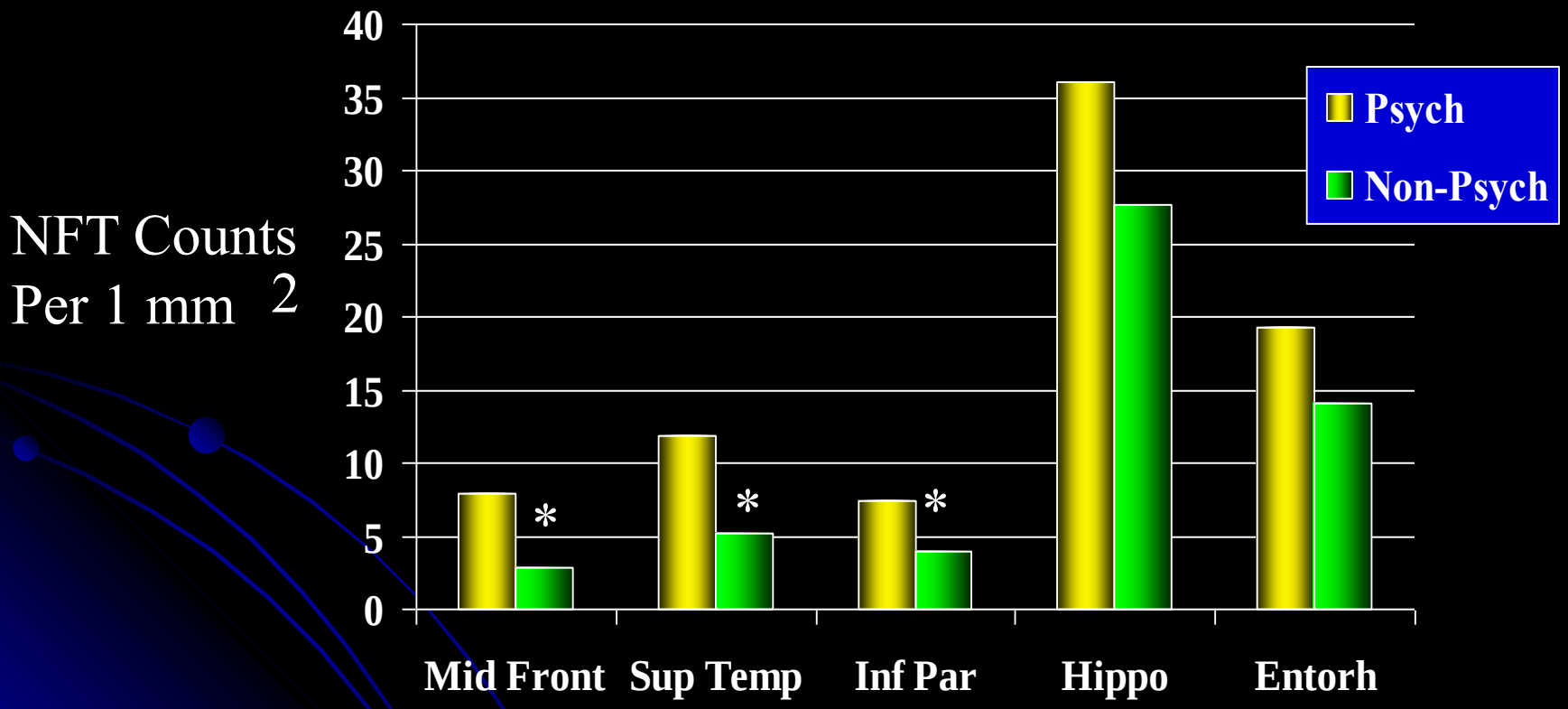
Without Agitation

With Agitation



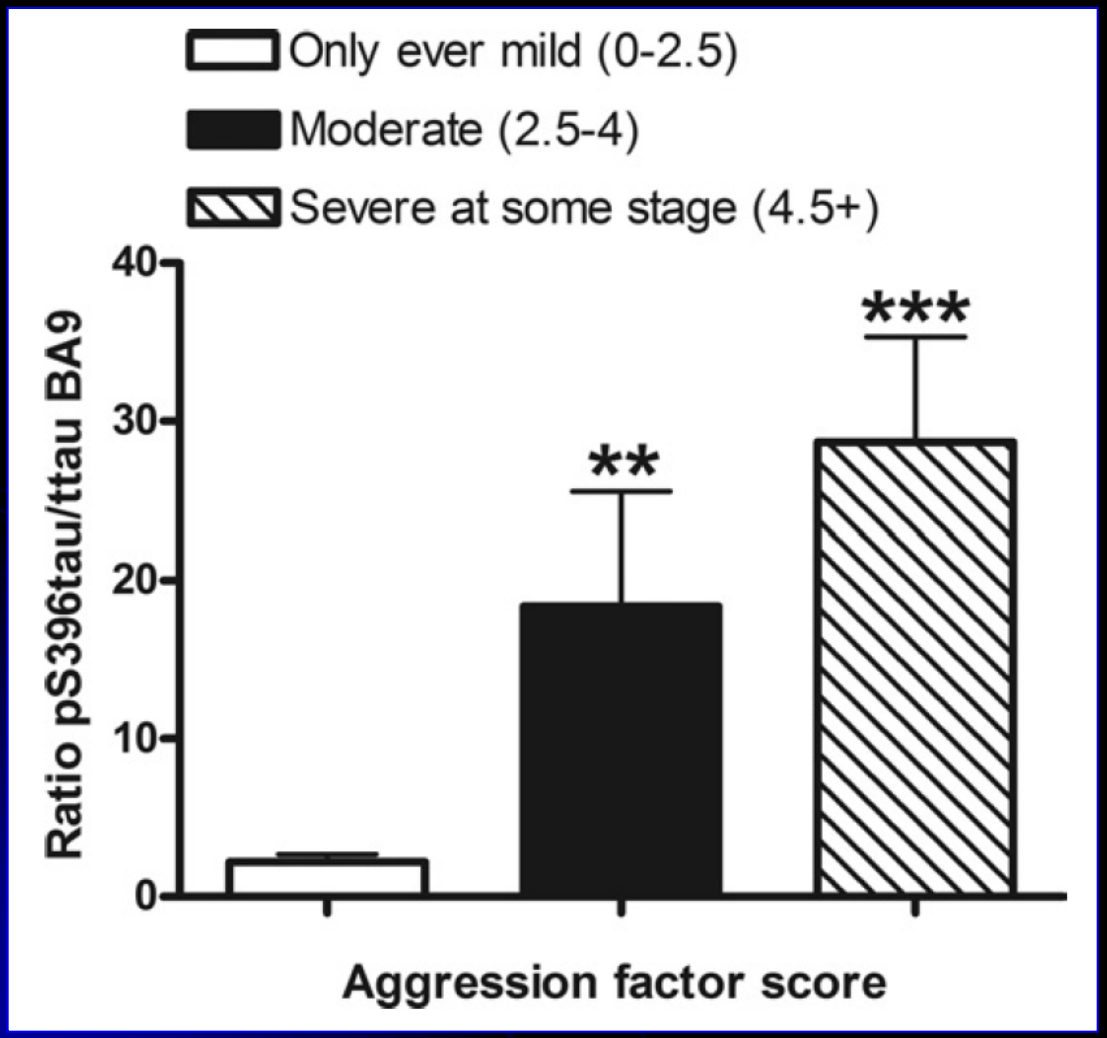
(Tekin et al, Ann Neurol 2001; 49: 355-361)

Psychotic AD Patients Had Significantly More NFT in Neocortex



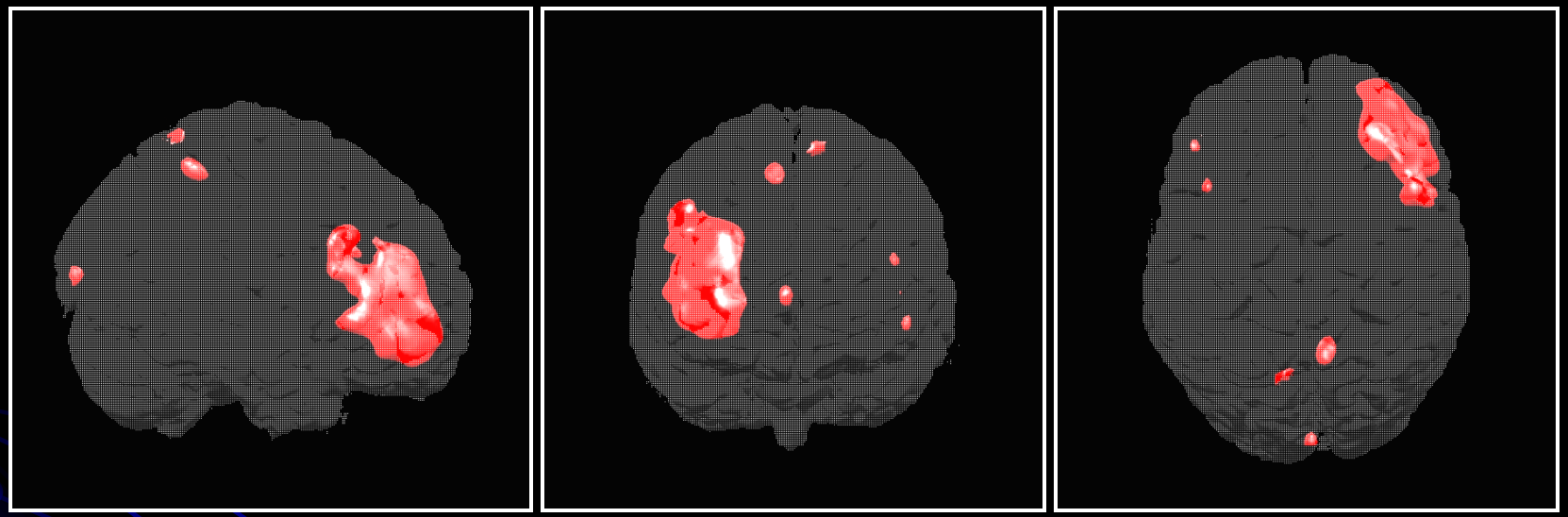
(Farber et al, Arch Gen Psychiatry 2000; 57: 1165-1173)

High P-Tau/Tau Ratio is Associated with Agitation



Guadagna S, et al. Neurobiol Aging 2012; 33: 2798-2806

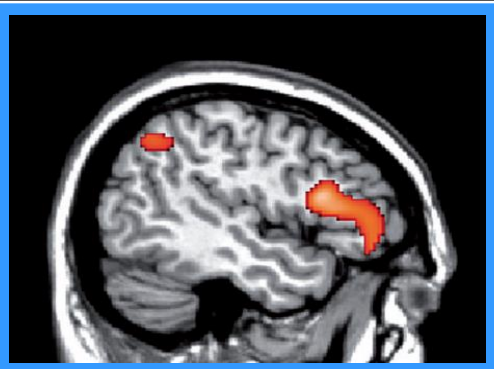
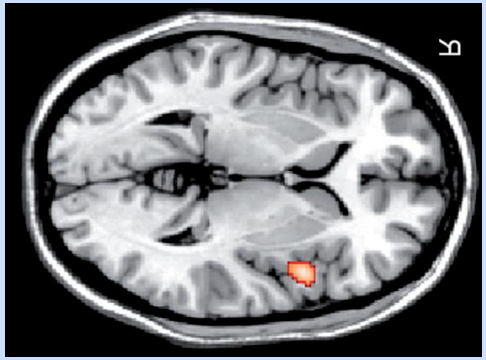
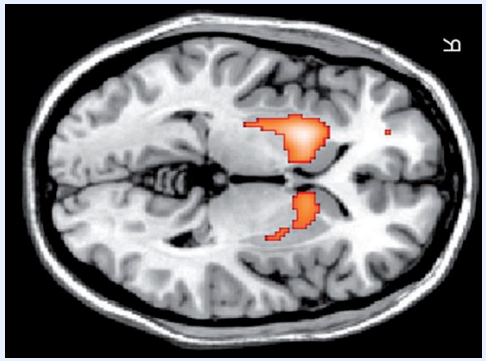
FDG PET Imaging: AD with Delusions



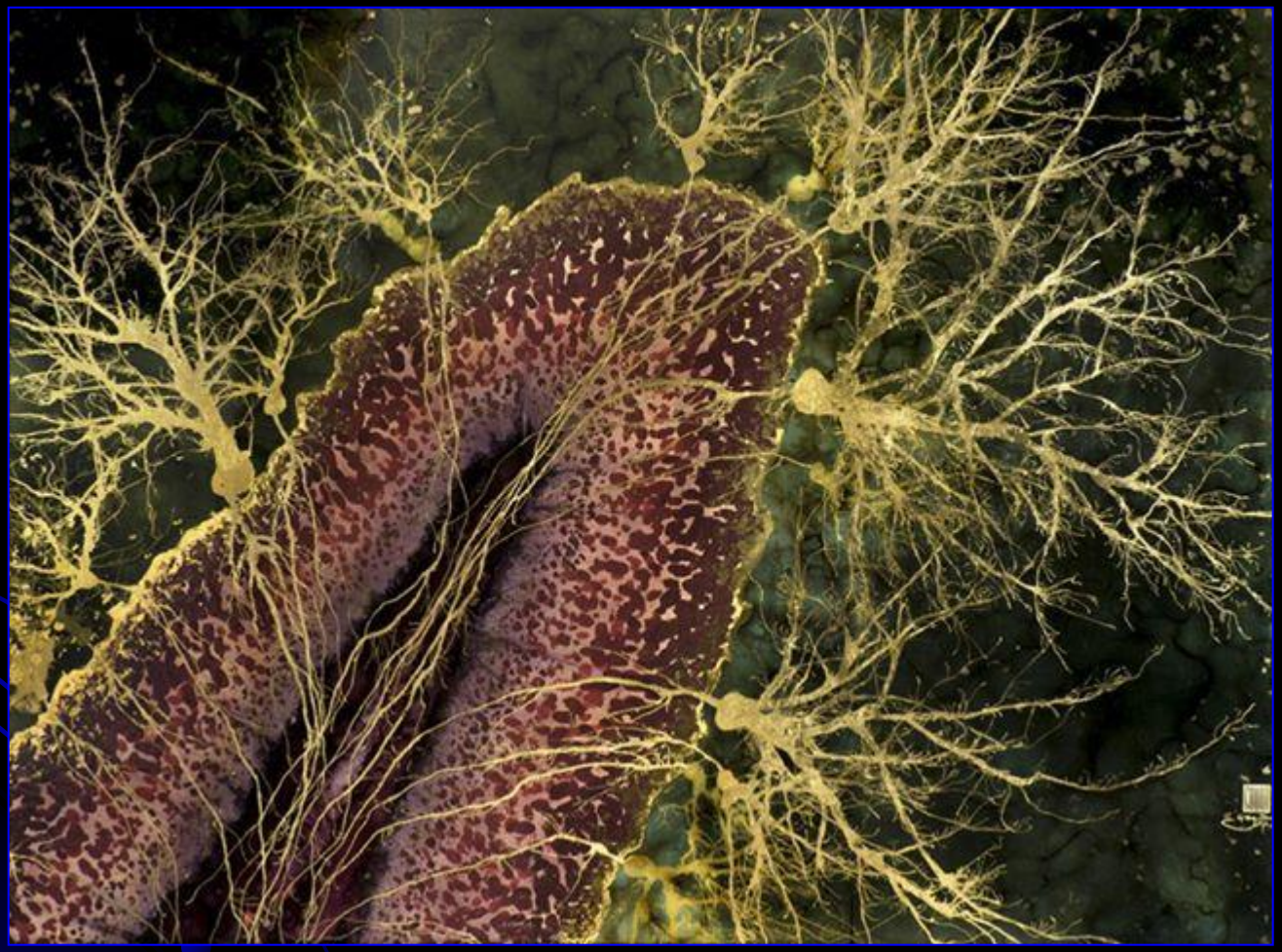
SPM2 Analysis
Non-delusional vs delusional
Two-sample t test, $P < .01$

(Sultzer DL. UCLA, 2005).

NP Sx Tx in AD: Biomarkers

Psychosis	
Agitation	
Apathy Bruen PD et al. Brain 2008; 131: 2455-63	

Progress in Definitions



Definitions

- Trials require
  - Definition to identify the patient population
  - Rating scales to determine severity at baseline and measure improvement
- Definitions
  - Applicable by practitioners to identify the population appropriate for therapy
  - Not dependent on a rating scale

Definitions of NPS in AD

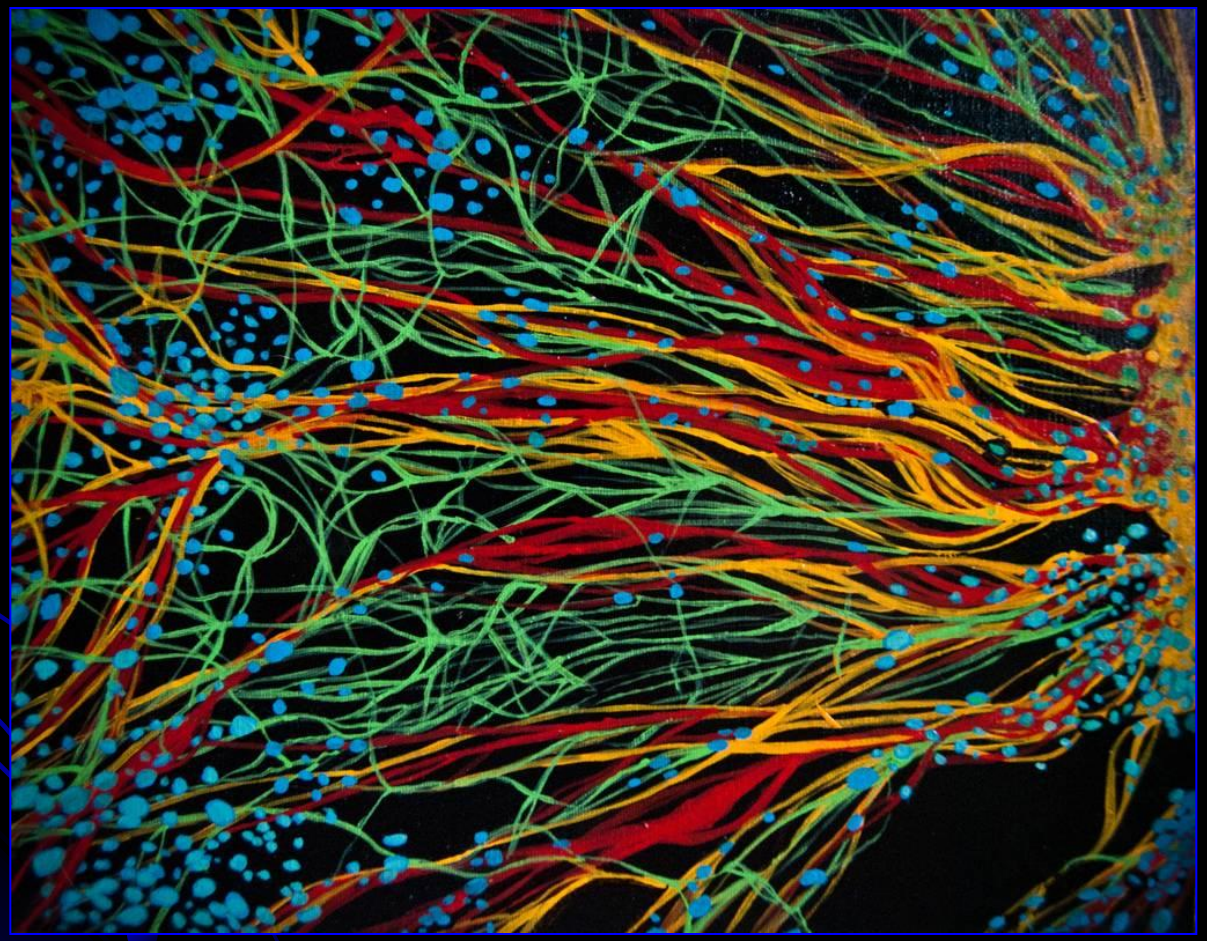
- Psychosis of AD(1)
- Depression of AD(2)
- Agitation of AD(3)
- Apathy(4)

1) Jeste D, Finkle S; 2) Olin J et al; 3) IPA in progress; 4) Robert P et al

Definitions of NPS in AD

- Allow construction of trial populations
- Allow identification of appropriate patients for treatment after approval
- Avoid pseudo-specificity
- Facilitate drug development

Trial Design Challenges and Responses



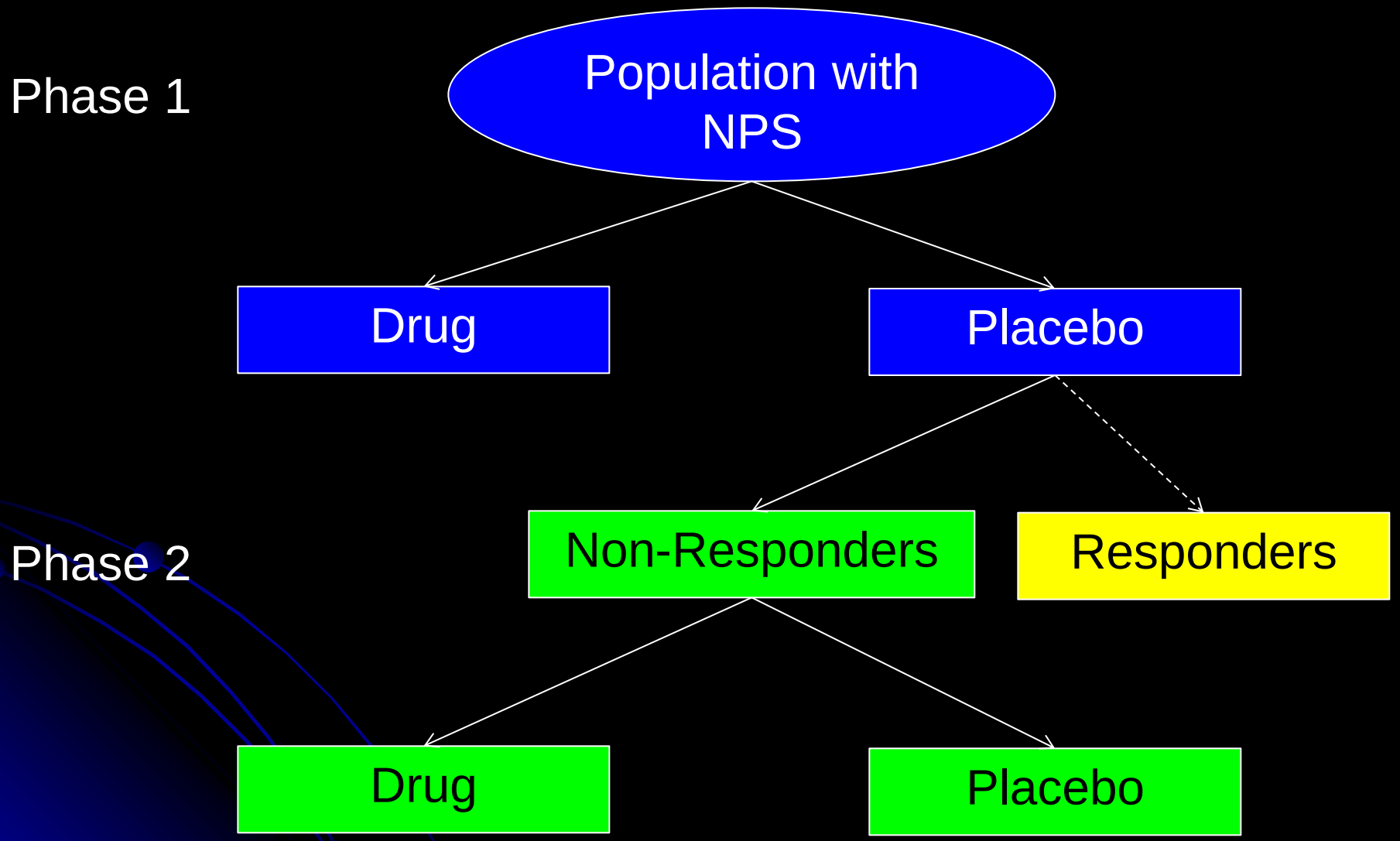
NPS in Alzheimer's Disease

- High frequency may be misleading; may not be severe enough for trial entry
- NPS make trial participation difficult
- NPS often produce urgent desire for resolution
- Off-label use of psychotropics common
- Difficult to recruit

Challenges to AD NPS Trials

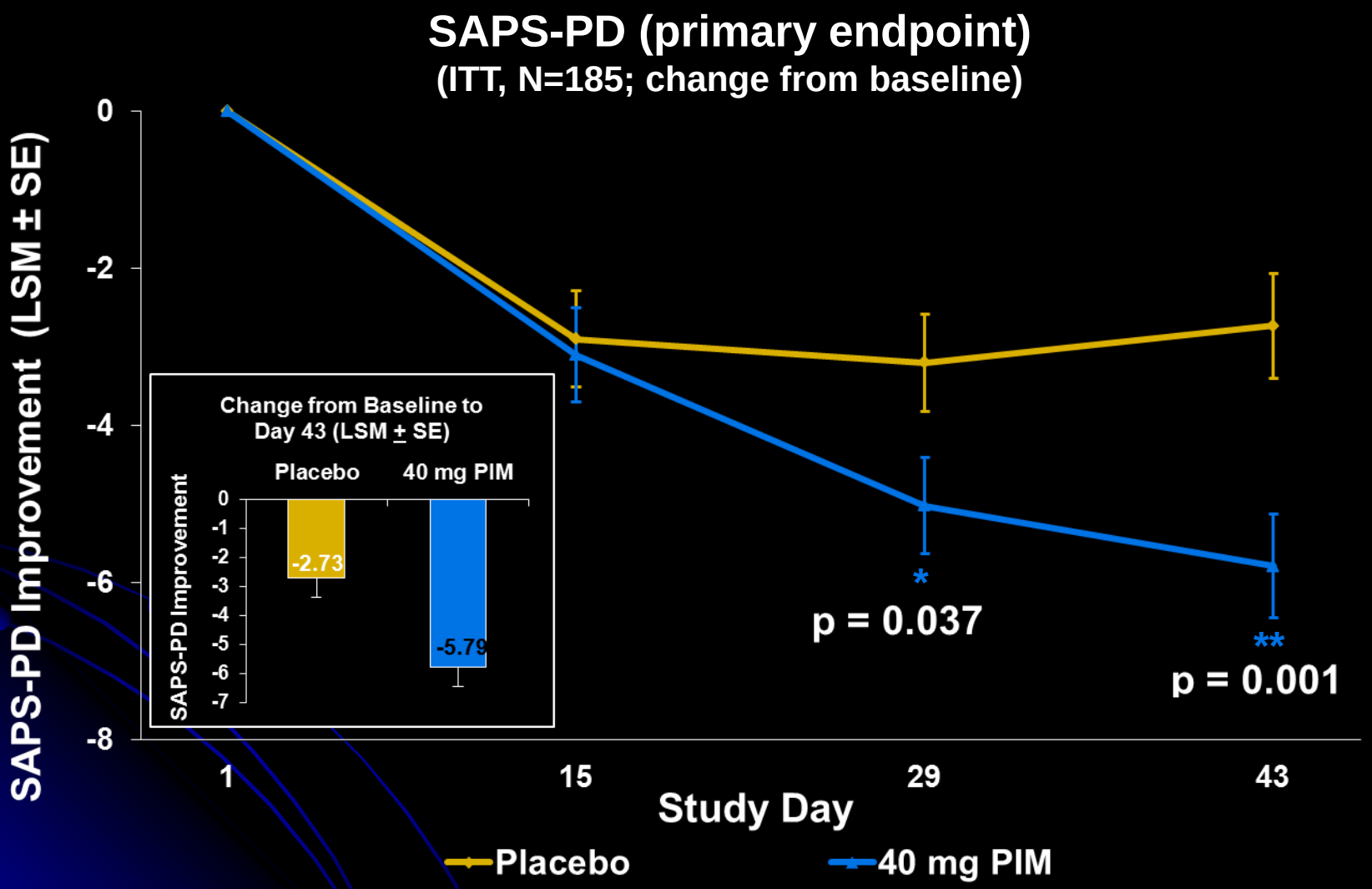
- High rate of trial/placebo response
- High standard deviations on measures
- High measurement variability
- Cultural perceptions differ across global trial locations

Parallel Sequential Comparative Design



(Fava M et al. Psychother Psychosom 2003; 72: 115-127)

Pimavanserin: Antipsychotic Efficacy

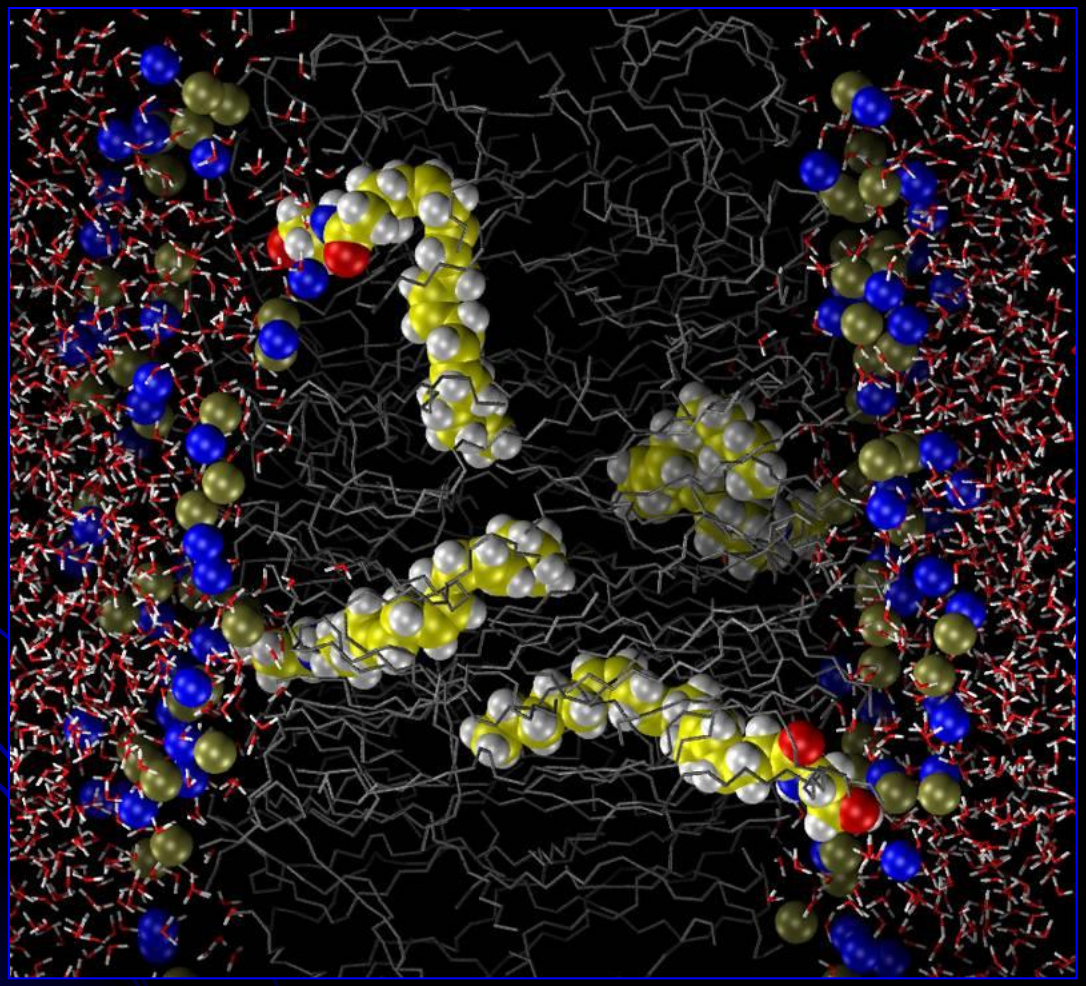


(Cummings J et al. Lancet, 2013)

Pimavanserin in Parkinson's Disease

- Successful trial with drug-placebo difference in primary and secondary outcomes
- 2 week behavioral therapy lead-in
- Centralized blinded rating of primary outcome

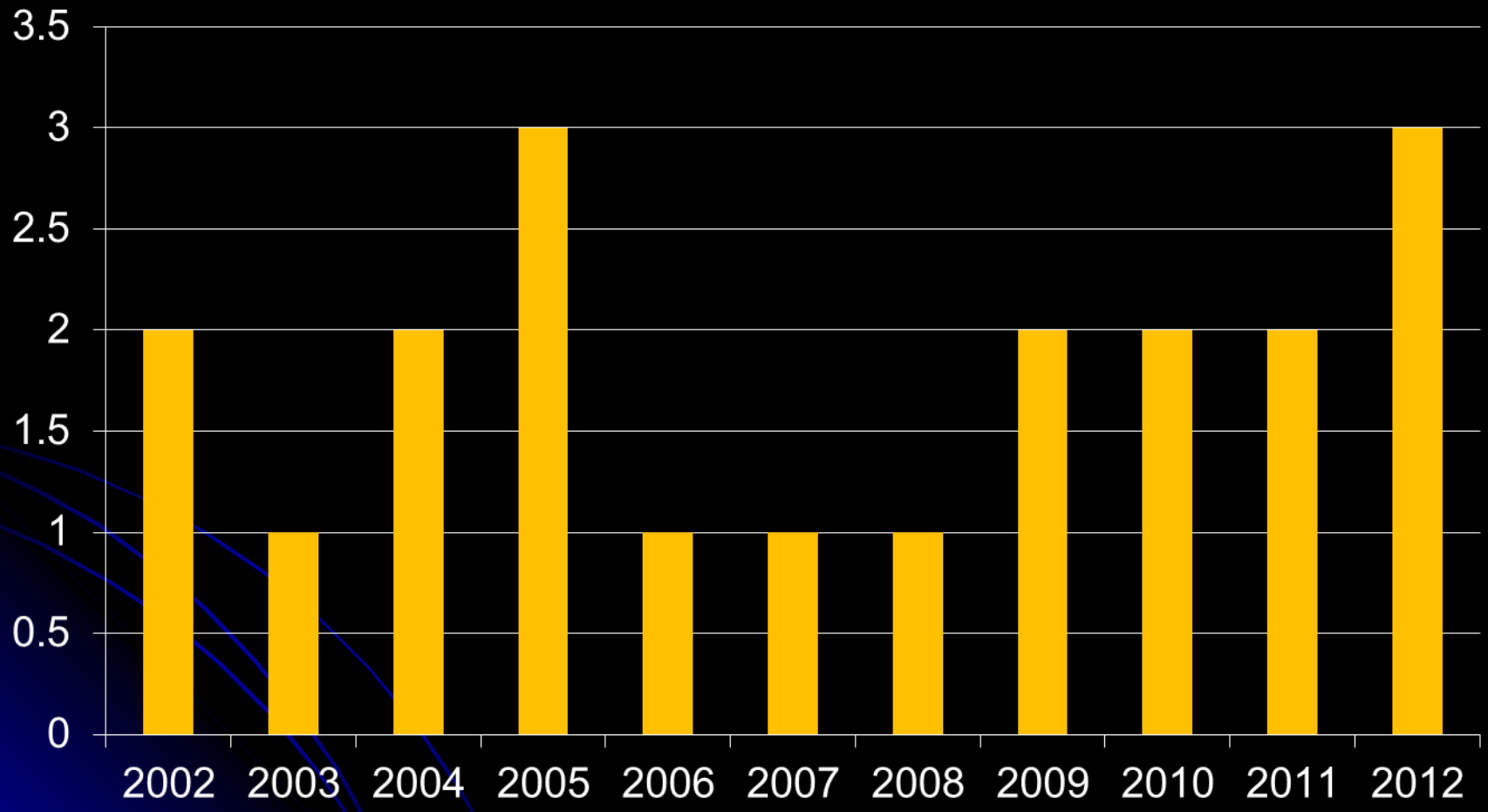
Review of Drug Development for AD NPS and Current Pipeline



Psychotropics for NPS in AD

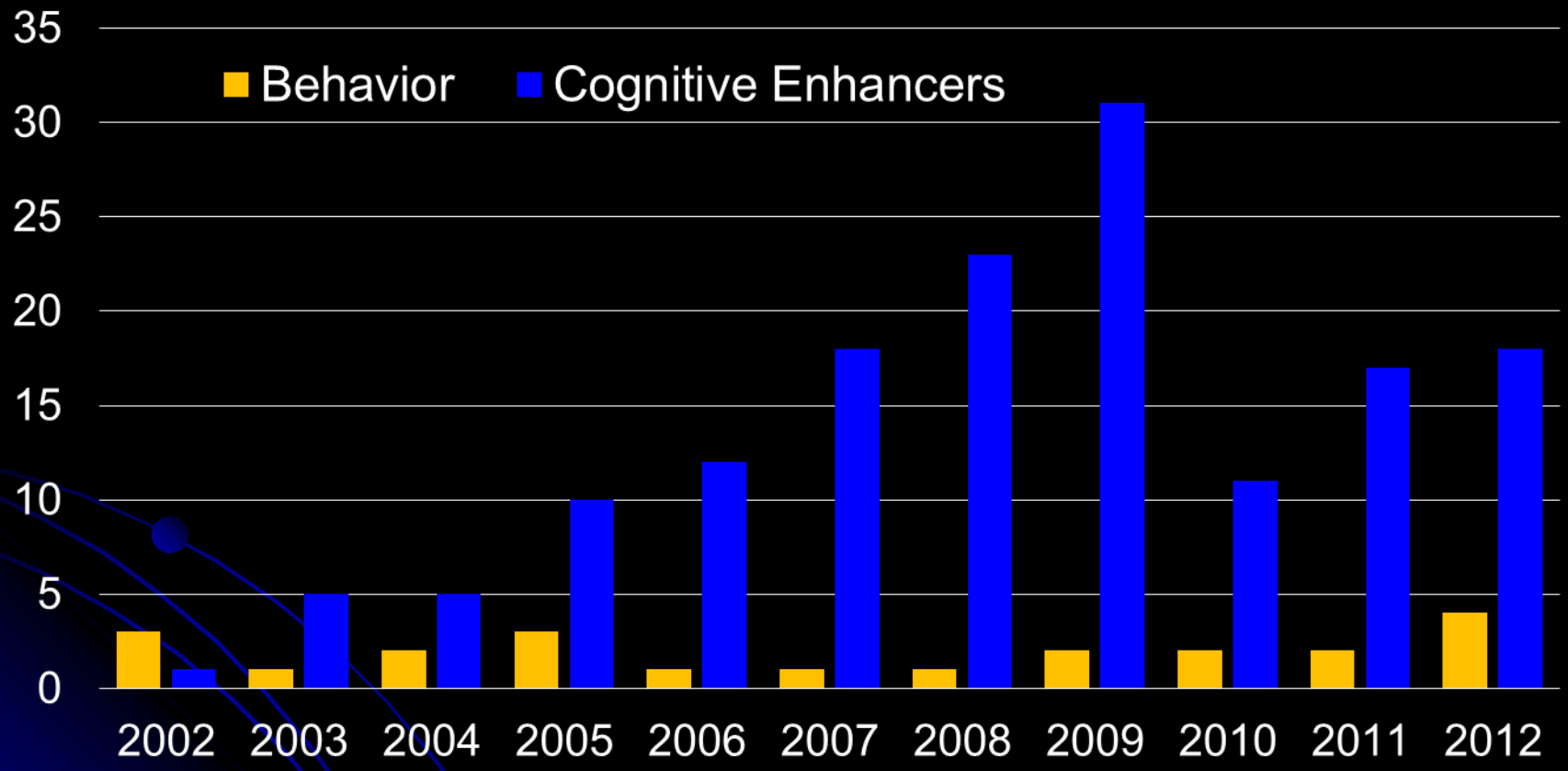
- No agents approved for NPS in AD
- AD patients excluded from trials of psychotropics
- Antipsychotics have “black box” warning for excess mortality
- Anti-epileptic agents, antidepressants have many trials with no drug-placebo difference

Registered Trials: 2002-2012 (Behavioral Agents)



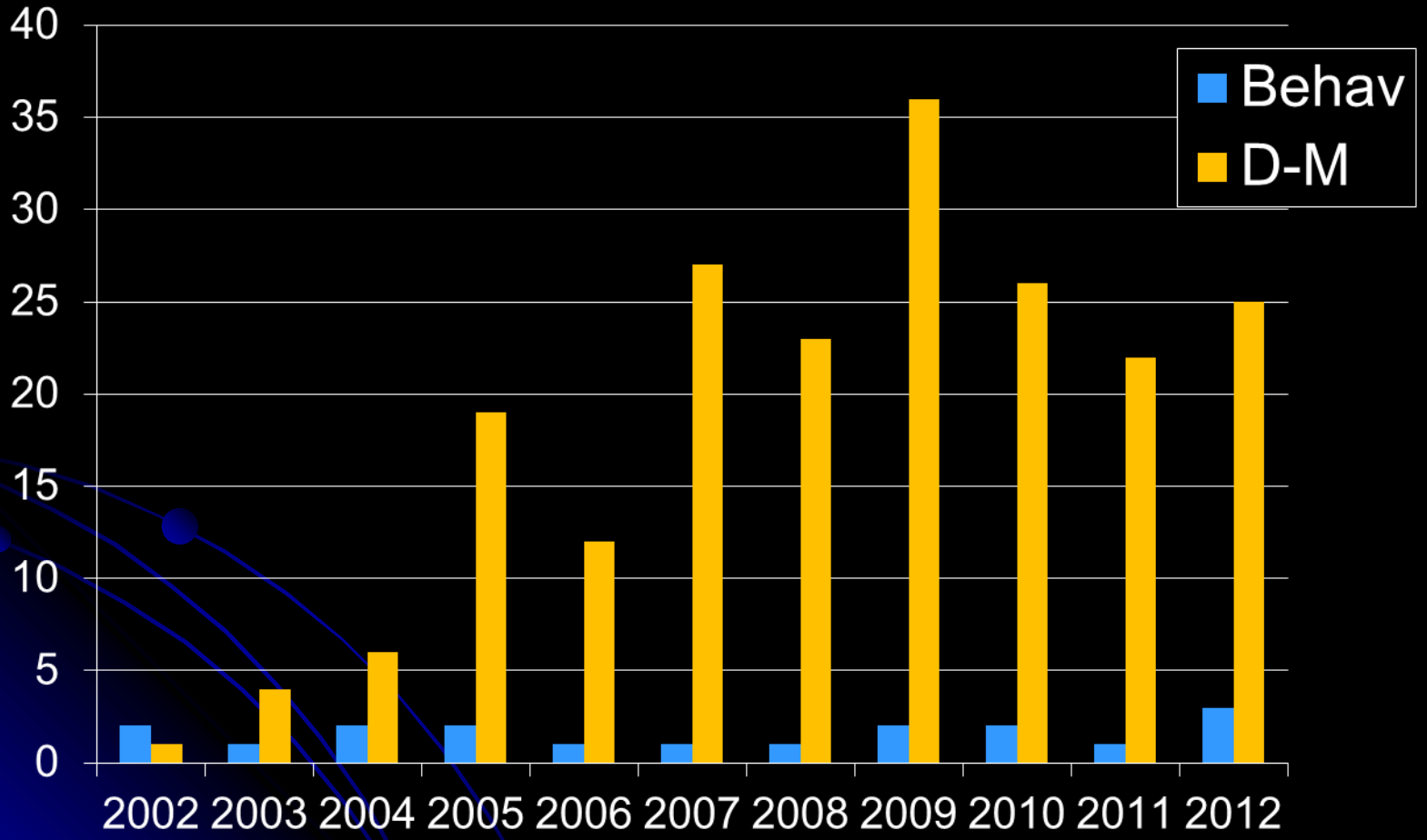
(Cummings J et al, 2013)

Registered Trials: 2002-2012
(Behavioral Agents, Cognitive Enhancers)



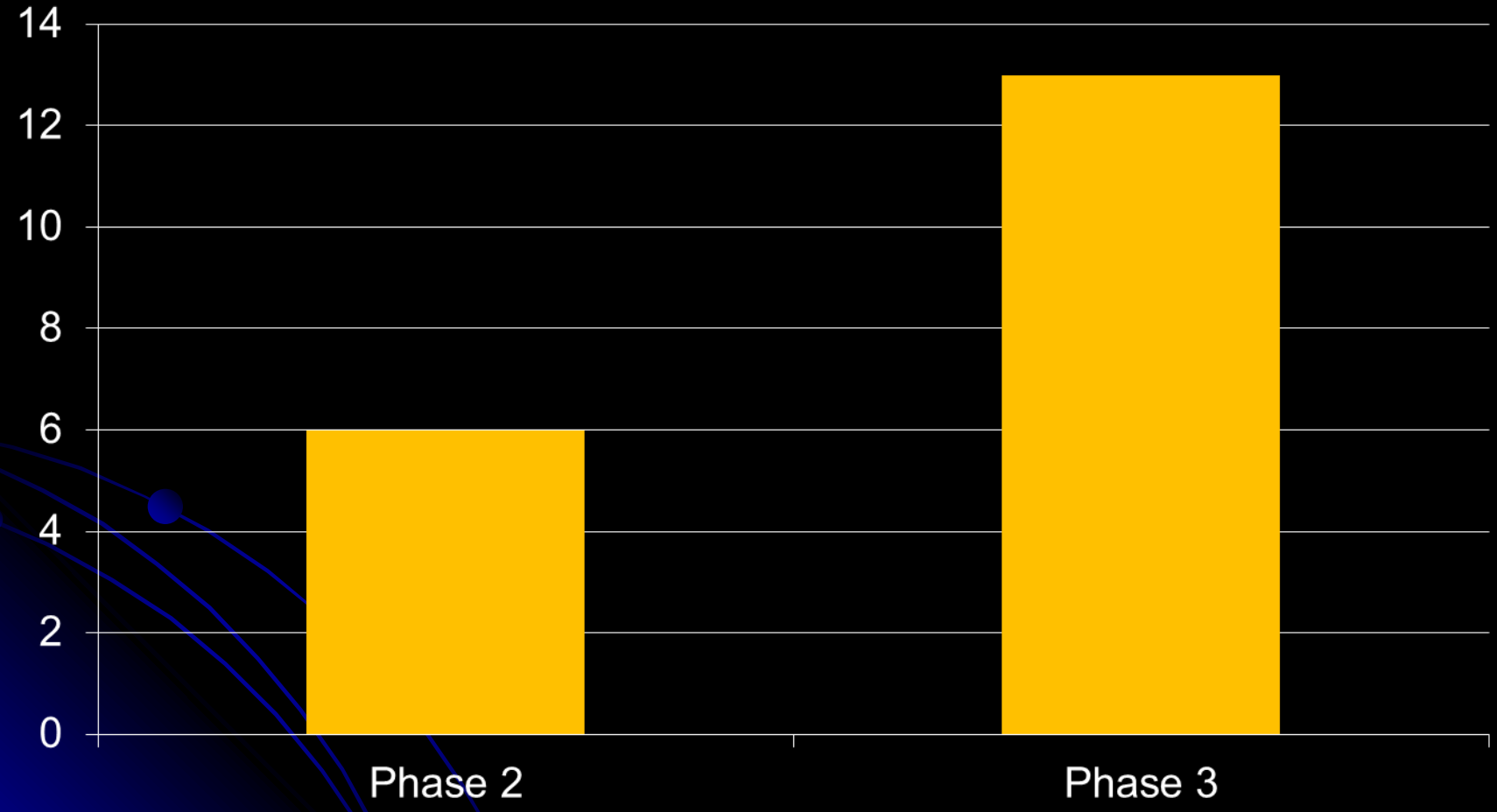
(Cummings J et al, 2013)

Registered Agents: 2002-2012 Behavioral, D-M



(Cummings J et al, 2013)

Psychotropics for NPS in AD: 2002-2012



(Cummings J et al, 2013)

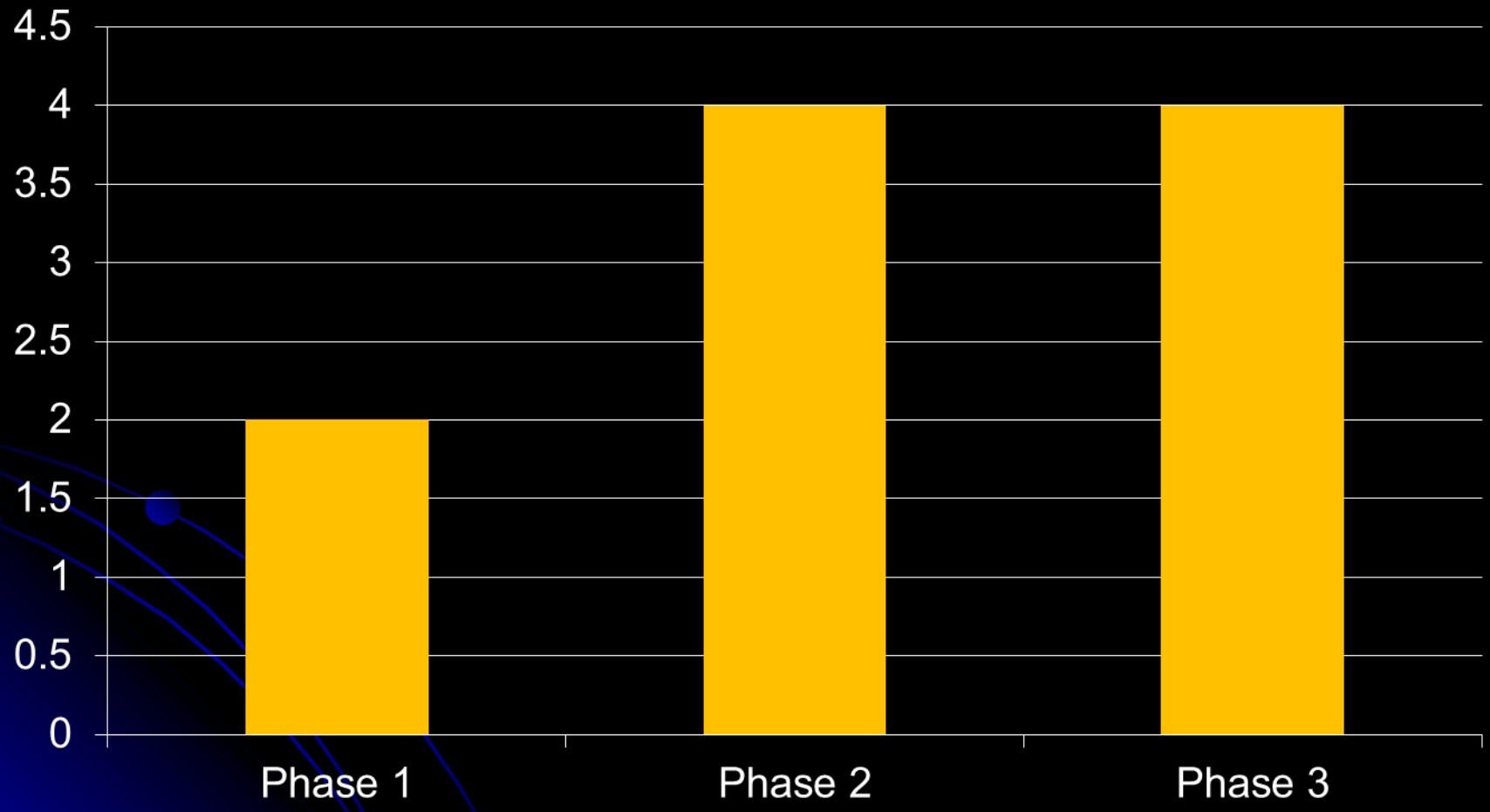
Psychotropics for NPS in AD: 2002-2012

Indication	Number
Psychosis	5
Agitation	6
Depression	2
Sleep	3
Apathy/attention	3
Pain	1

Psychotropics for NPS in AD: 2002-2012

- Relatively few agents tested
- None approved
- No Phase 2 agent moved to Phase 3
- All agents derived from psychiatry approaches

Agents in Current Trials for AD NPS



(Cummings J et al, 2013)

Current Pipeline: Phase 3

Behavioral management agents

Agent	Mechanism	Classification
Bupropion	Anti-depressant	Apathy
Mirtazapine	Hypnotic	Sleep
Citalopram	SSRI	Agitation
Brexpiprazole	Antipsychotic	Agitation

Development of Agents for NPS of AD

- Agitation
  - Scyllo-inositol (ELND005)
  - SSRI (citalopram)
  - Antipsychotic (brexpiprazole)
  - Alpha-1 adrenergic antagonist (prazosin)
  - DM/Q (sigma-1 agonist; NMDA-R antagonist)

Development of Agents for NPS of AD

- Apathy
  - Stimulant (ritalin)
  - H3 antagonists
  - Bupropion

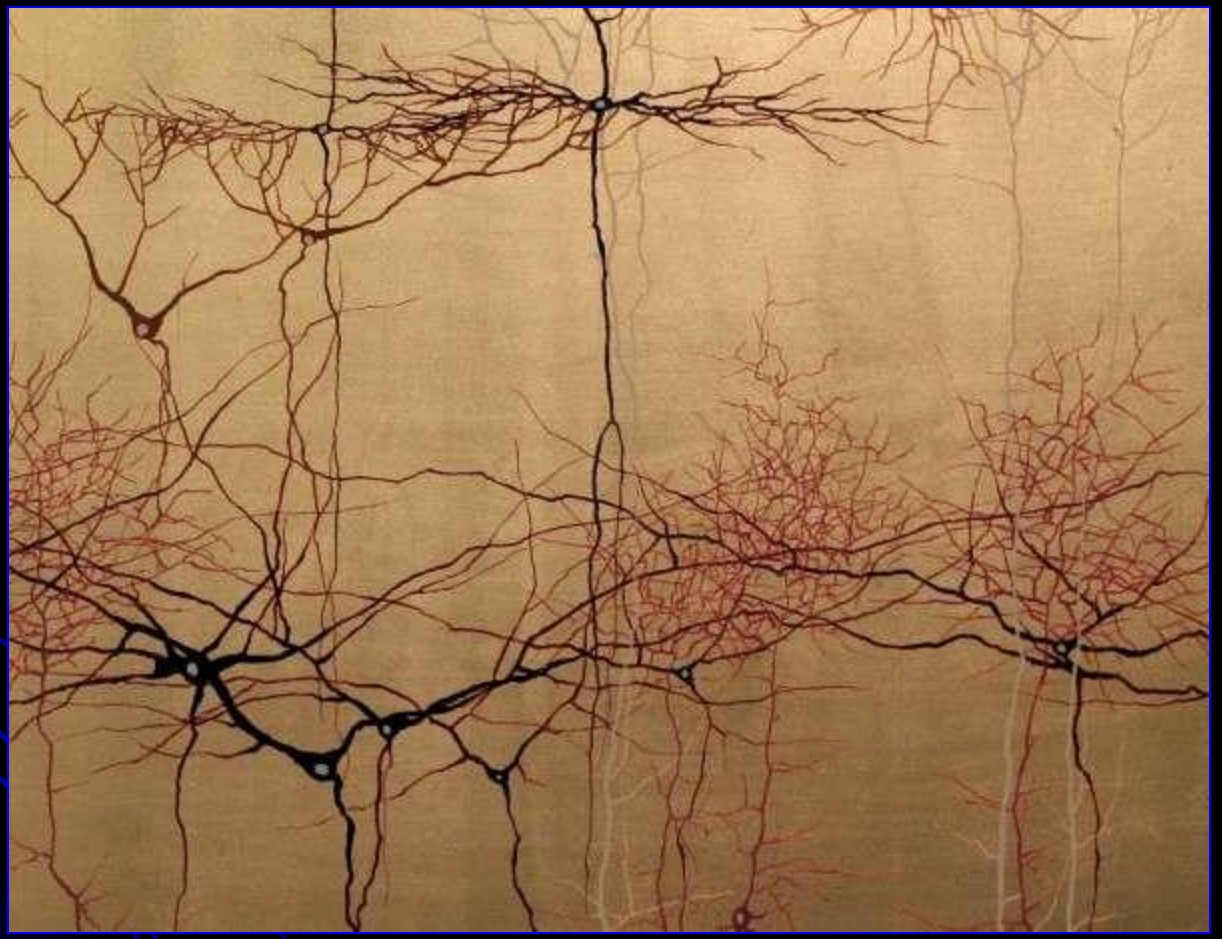
Developmental Pathways for Agents for NPS of AD

- Develop as psychotropic with AD population
- Develop as cognitive enhancing agent with behavioral co-primary (requires regulatory discussion)

Developmental Pathways for Agents for NPS of AD

- Develop as a disease-modifying outcome with reduced emergence of NPS
  - Appropriate design
  - Biomarkers of disease modification
  - Not the primary outcome

Summary



Summary

- NPS are common in AD
- NPS are disabling and reduce quality of life
- Tau biology is closely linked to NPS
- NPS trials are challenging
- There are no approved agents for NPS of AD
- There is a relatively small pipeline of agents in trials for NPS of AD
- The NPS/AD pipeline and trials have increasing novelty