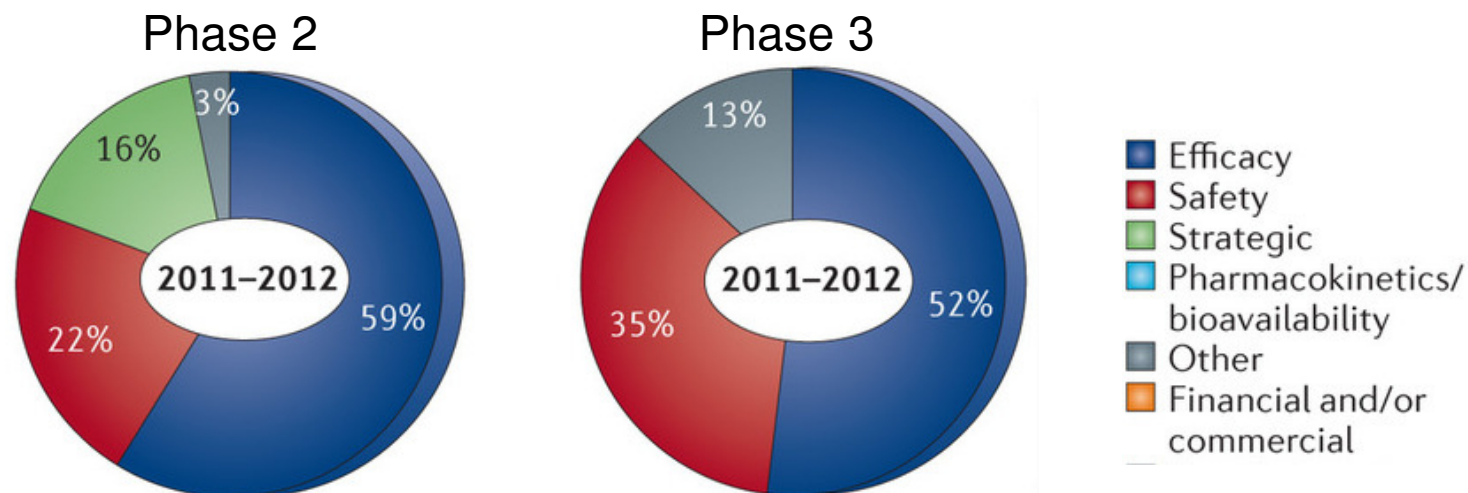


# Using Non-Human Primates to Build More Predictive Tools for Treating Cognitive Disorders

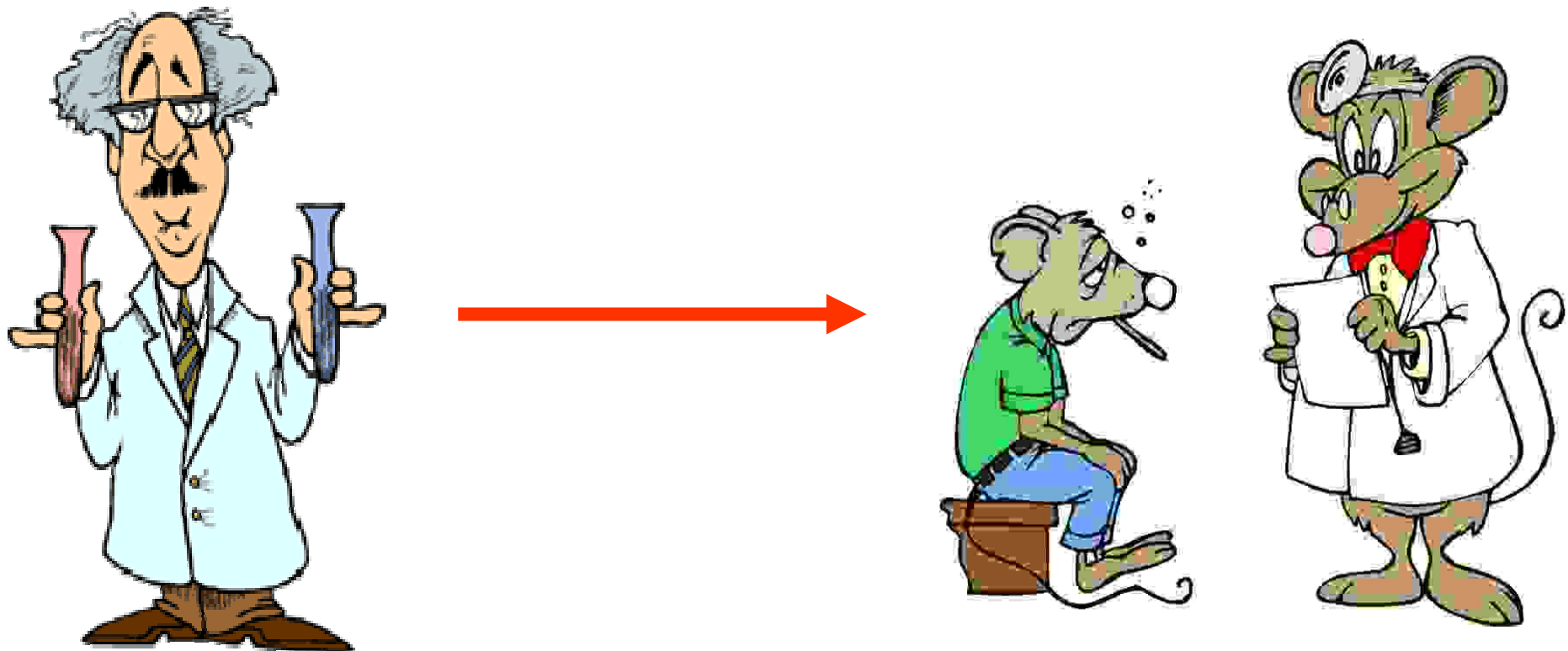
Jason Uslander

# Lack of Efficacy is the Leading Cause of Failure in Phase 2 and 3



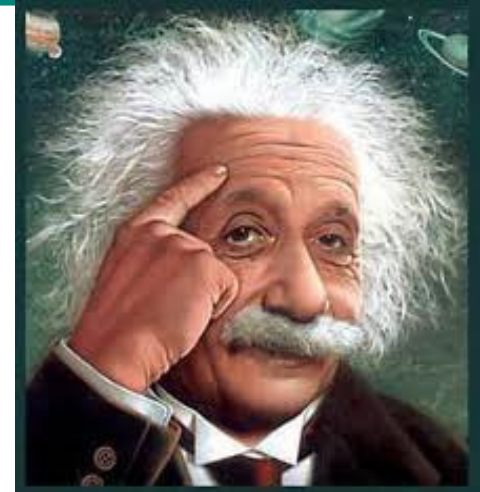
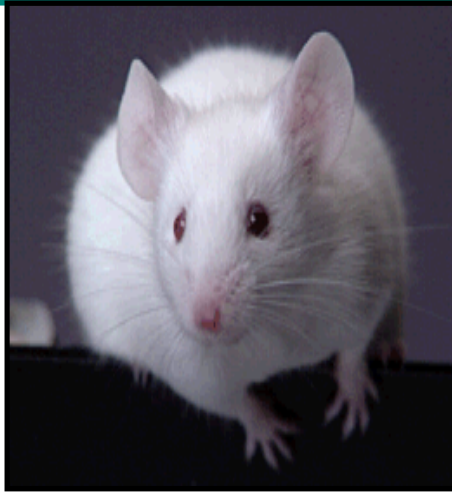
- Potential causes for failure to demonstrate efficacy:
  - Preclinical measurements do not predict clinical efficacy
  - Mechanism of action not appropriately tested
    - Lack of good TE/PD biomarker (i.e. wrong dose)
  - Inability to reliably measure efficacy in clinic

Translational research attempts to connect basic research to patient care... it aims to move research results from "bench to bedside"



# Preclinical Models

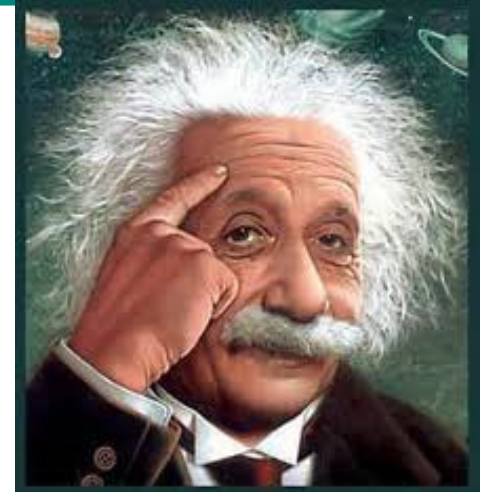
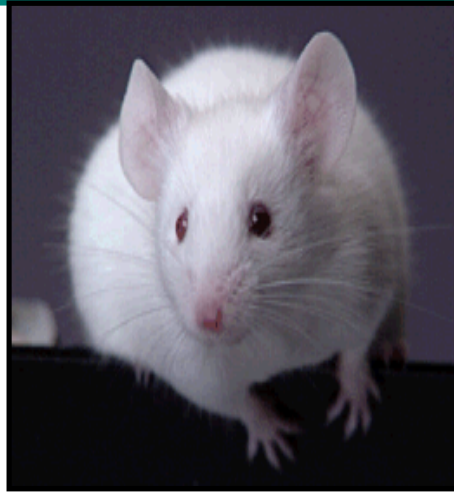
## Traditional Approach: Rodent to Man



- **Relatively Inexpensive**
- **Low compound requirement**
- **High Throughput**
- **Rich History**
- **More amenable to MOA studies**
- **Concerns**
  - **Complex Behavior**
  - **Tolerability**
  - **Translatable Biomarkers**

# Preclinical Models

## Translational Approach: Rodent to NHP to Man



- Relatively Inexpensive
- Low compound requirement
- High Throughput
- Rich History
- More amenable to MOA studies
- Concerns
  - Complex Behavior
  - Species specific AEs
  - Translatable Biomarkers

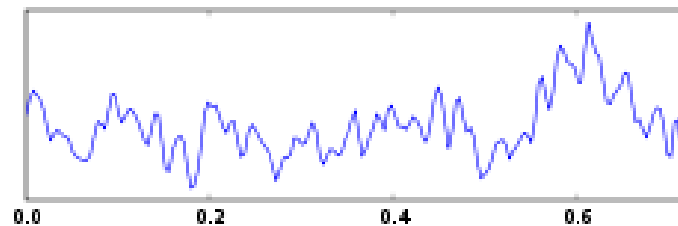
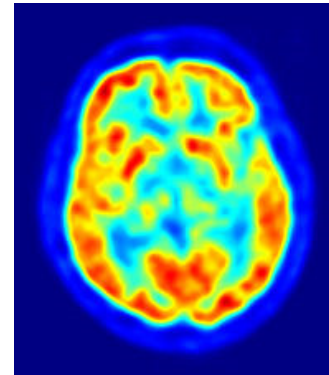
- Complex Behavior
- More comparable AEs
- Variety of Translatable Biomarkers
- Concerns
  - More expensive
  - High compound requirement
  - Lower Throughput
  - Short History

# Increasing POS Through Convergence

Efficacy across species  
and endpoint of interest

Domain	Rodent	NHP	Human
Attention	✓	✓	✓
Working Memory	✓	✓	✓
Episodic-like memory	✓	✓	✓
Executive Function		✓	✓

Relationship  
Between Biomarker  
and Efficacy

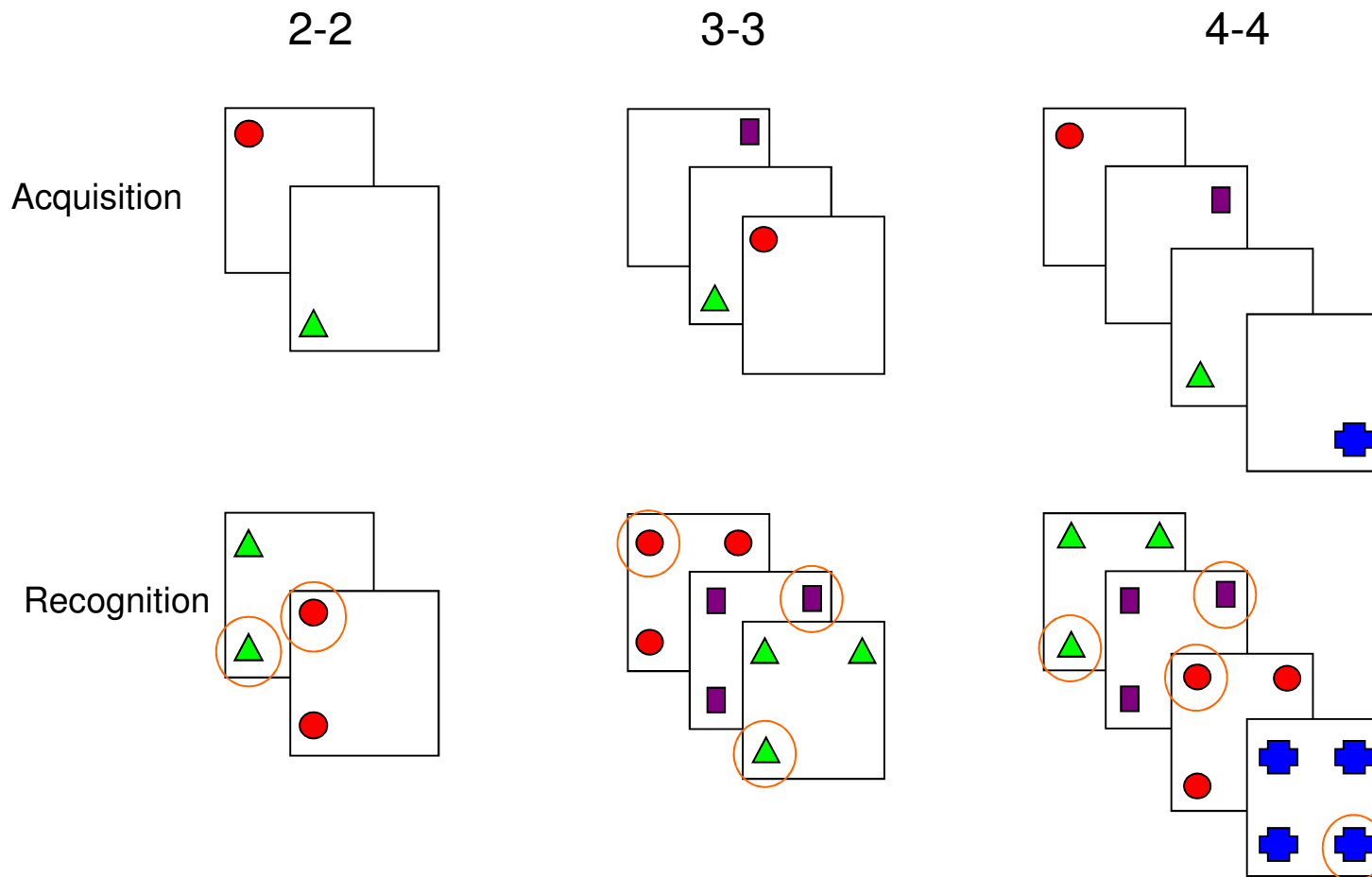


Differentiation

We can't only be  
efficacious, but  
need to be  
better than the  
competition!

Data Convergence (or lack of) drives Go-No Go Decisions

# An Example: Paired Associates Learning



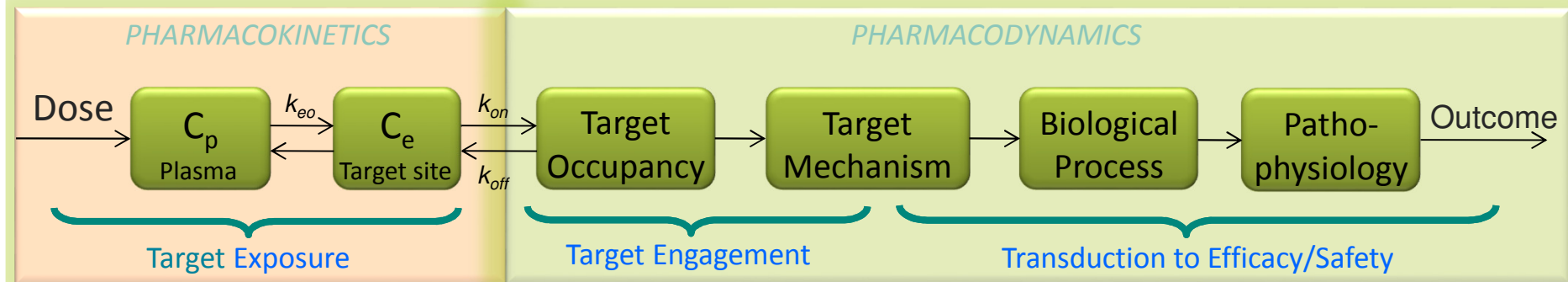
- Test of *What* and *Where*
- Heavily dependent on hippocampus
- Predicts transition from MCI to AD

# An Example: Paired Associates Learning

Paired-Associates Learning in  
Rhesus Monkeys



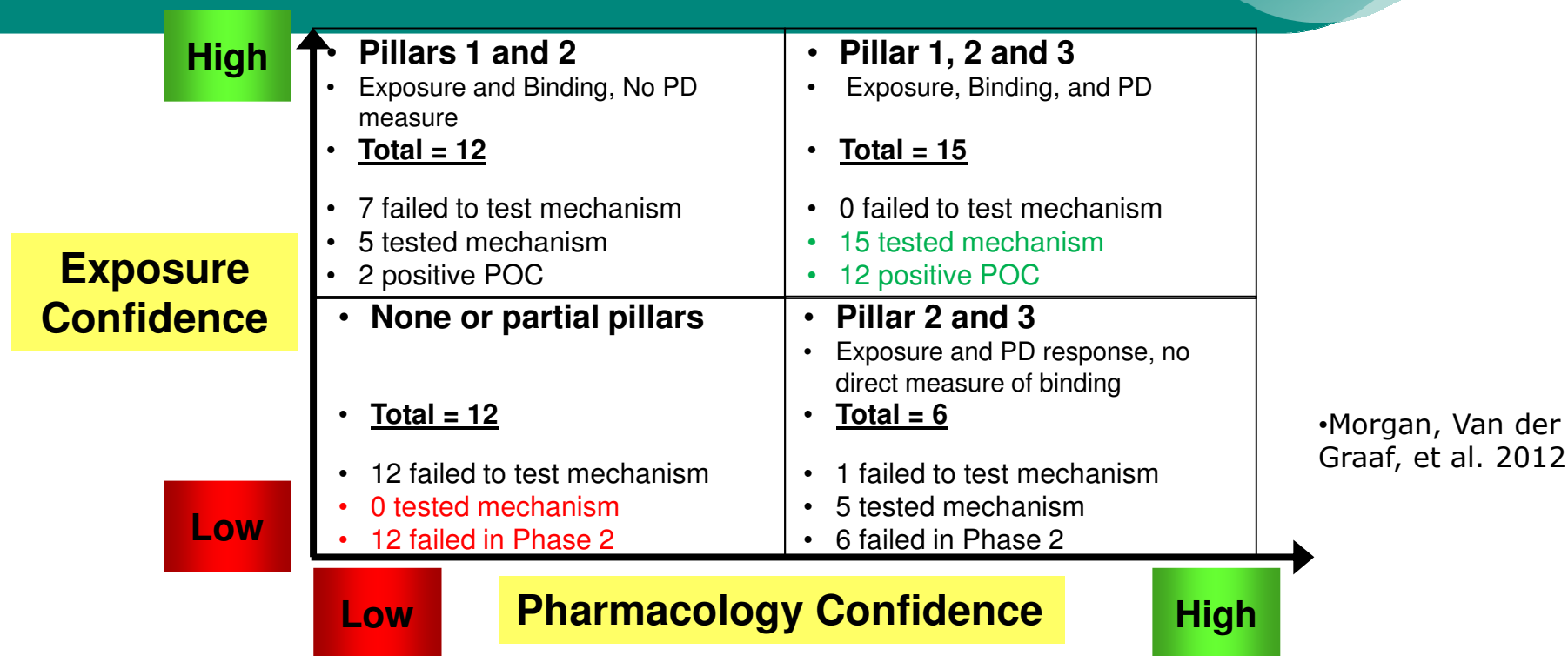
# Increasing POS through Translational Pharmacokinetics/Pharmacodynamics (TPKPD)



*We can increase confidence in human translation and lower overall risk in our Discovery portfolio by:*

- 1. Putting in place the most translatable and informative research operating plans.*
- 2. Using and studying molecules/comparators having human data.*
- 3. Understanding the assumptions and impact on translation*
- 4. Bridging gaps and integrating all PK-PD knowledge with quantitative/model-informed approaches.*

# Pfizer Analysis: Application of TPKPD Increases Clinical POS



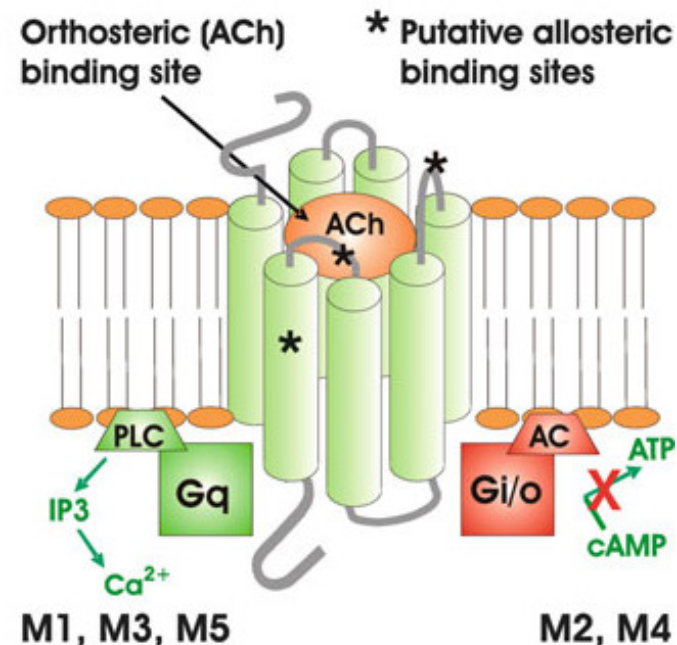
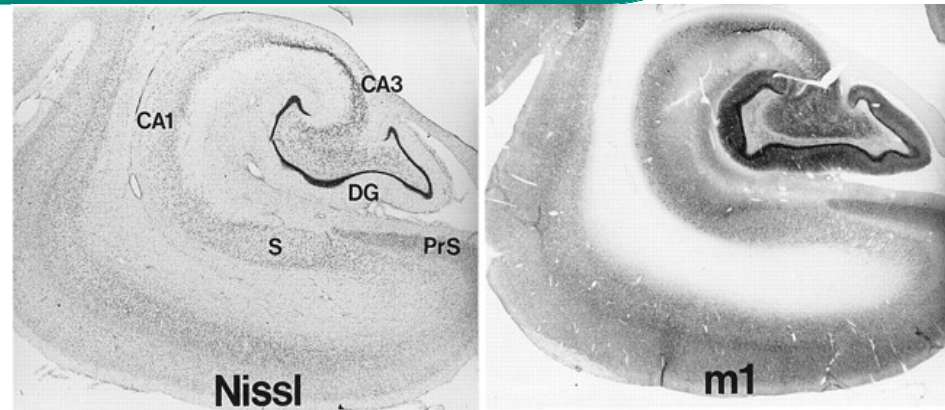
- “3 pillars of survival”
  1. Exposure at target site of action over desired period of time
  2. Binding to the pharmacological target
  3. Expression of pharmacological activity

## Examples Of How This Approach Has Been Implemented at Merck

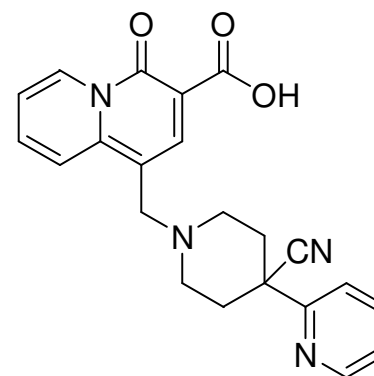
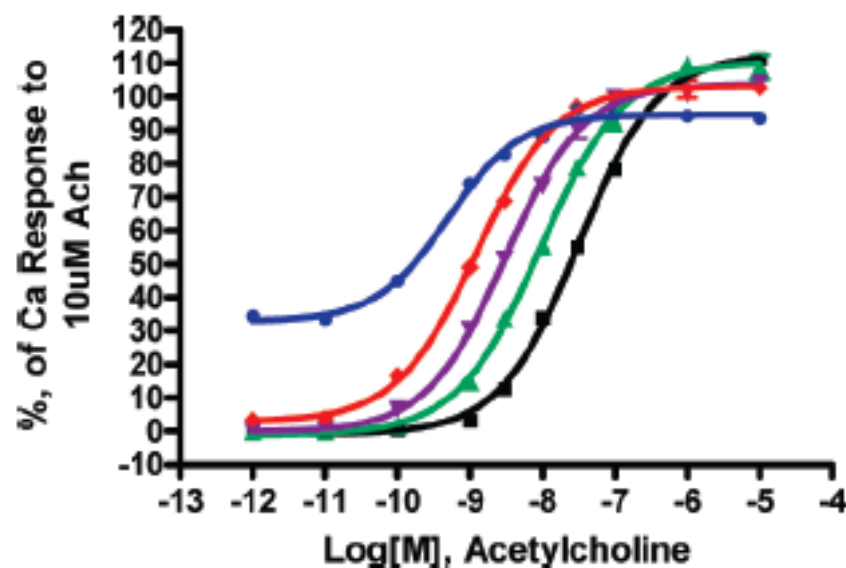
- M1 positive allosteric modulator for Alzheimer's disease
- PDE10 inhibitor for schizophrenia
- Dual Orexin Receptor Antagonist for insomnia

# M1 Muscarinic Positive Allosteric Modulator

- AChEI's (acetylcholinesterase inhibitors): boost ACh (nonselectively) and indirectly increase muscarinic receptor activity
- Xanomeline (non-selective muscarinic agonist) showed efficacy in clinical studies
  - Poor PK and poor tolerability (only moderate selectivity)
- **Hypothesis: a compound with high selectivity for M1 and modulatory mechanism predicted to result in improved efficacy with fewer side effects**
  - Most cholinergic AE's hypothesized to be mediated via M2 & M3
  - M1 (and M4) receptors largely restricted to brain while other muscarinic receptors present throughout periphery



# PQCA is a selective M1 Positive Allosteric Modulator (PAM)



Similar Potencies across species

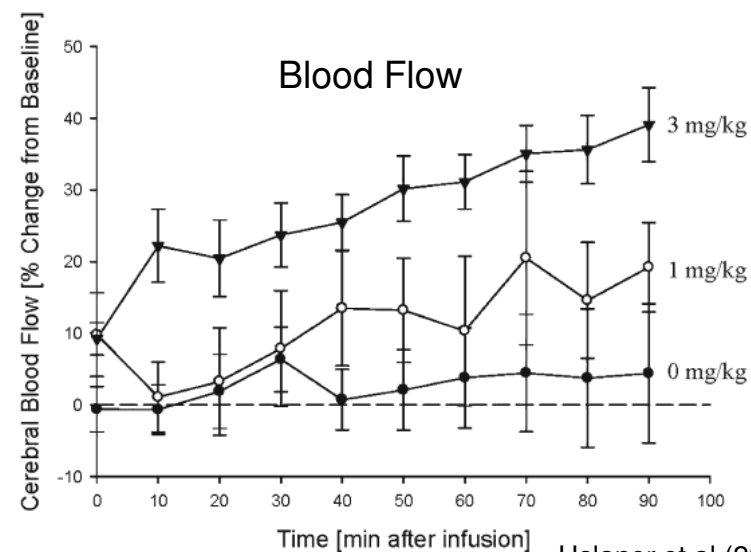
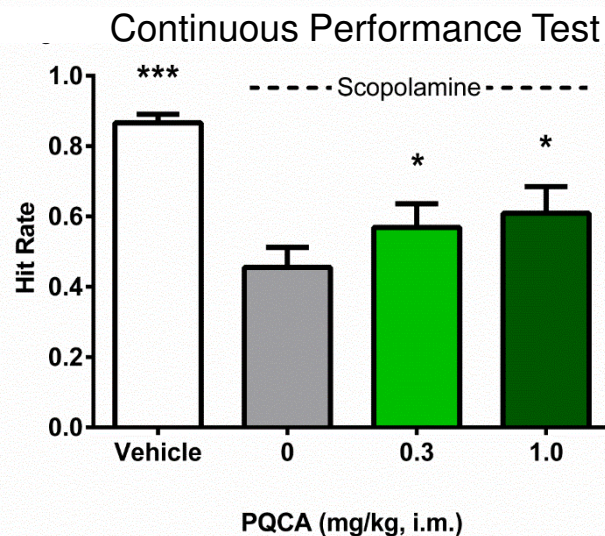
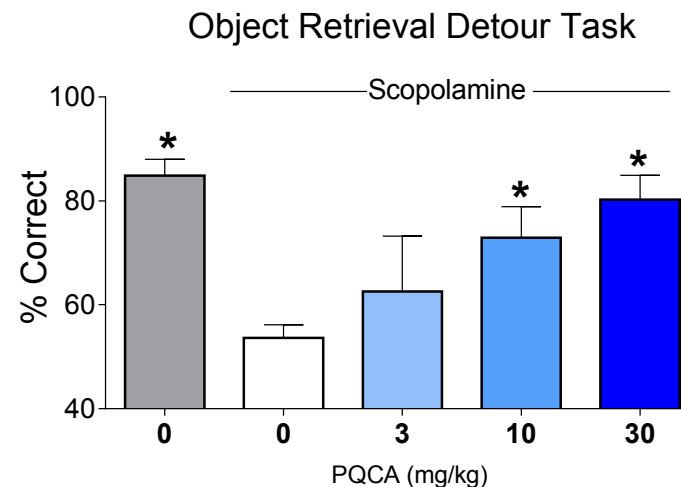
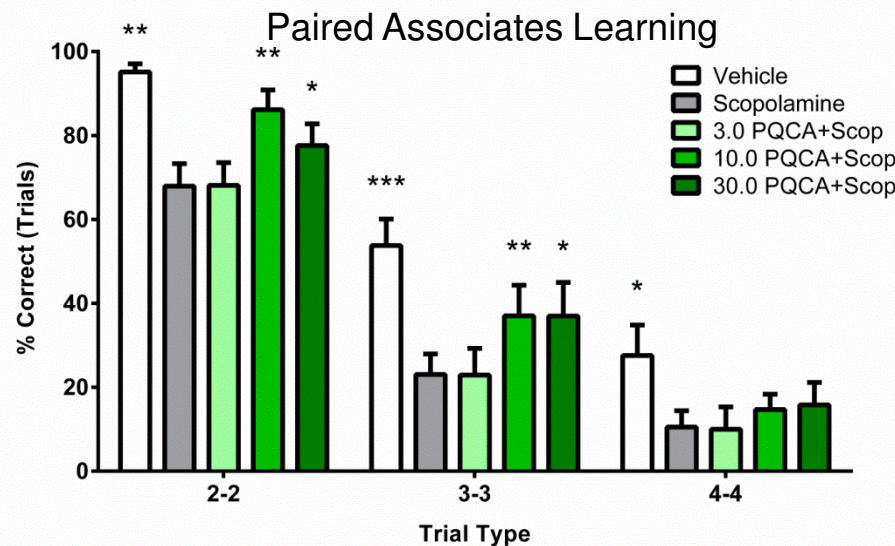
Species	Potentiation IP* (nM)
Human	135
Rhesus	49
Dog	100
Rat	81
Mouse	69

**>1000-fold selective over other Ms**

No activity up to 30 μM in Panlabs

~30% free in plasma, not a PGP substrate

# Convergence across assays and species at equivalent free drug concentrations...

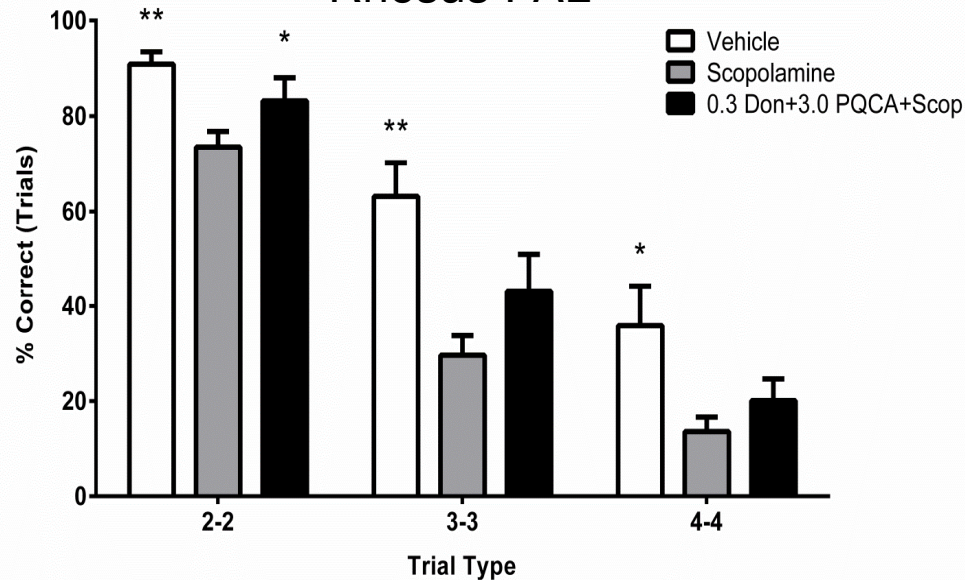


Uslaner et al (2013)  
Lange et al (2015)

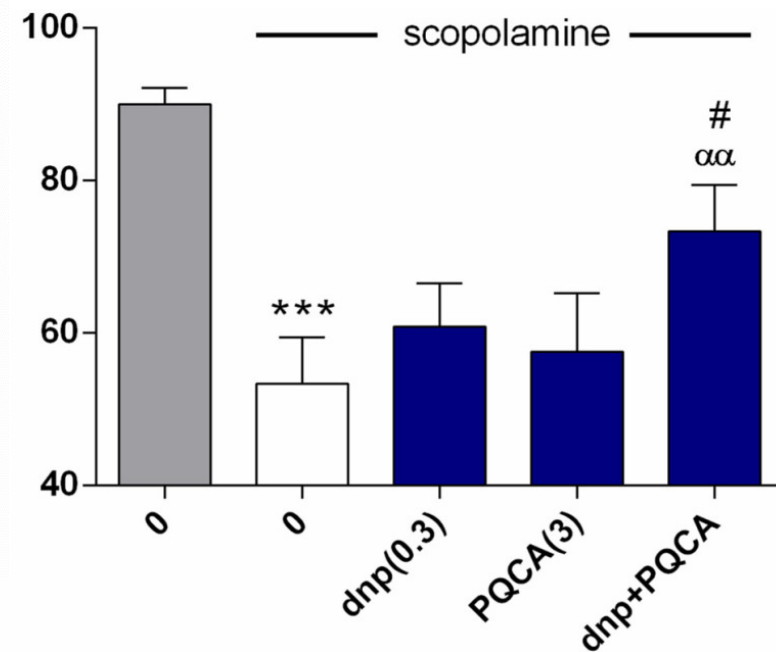


# M1 PAMs Can Be Combined With Standard of Care (SOC)

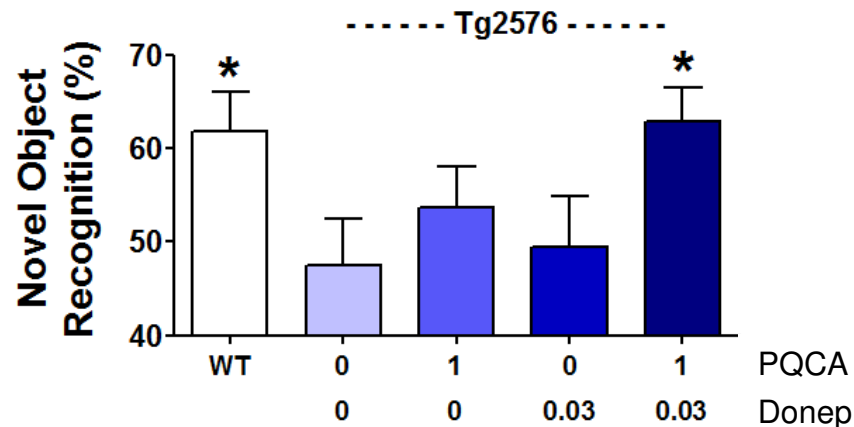
Rhesus PAL



Rhesus OR



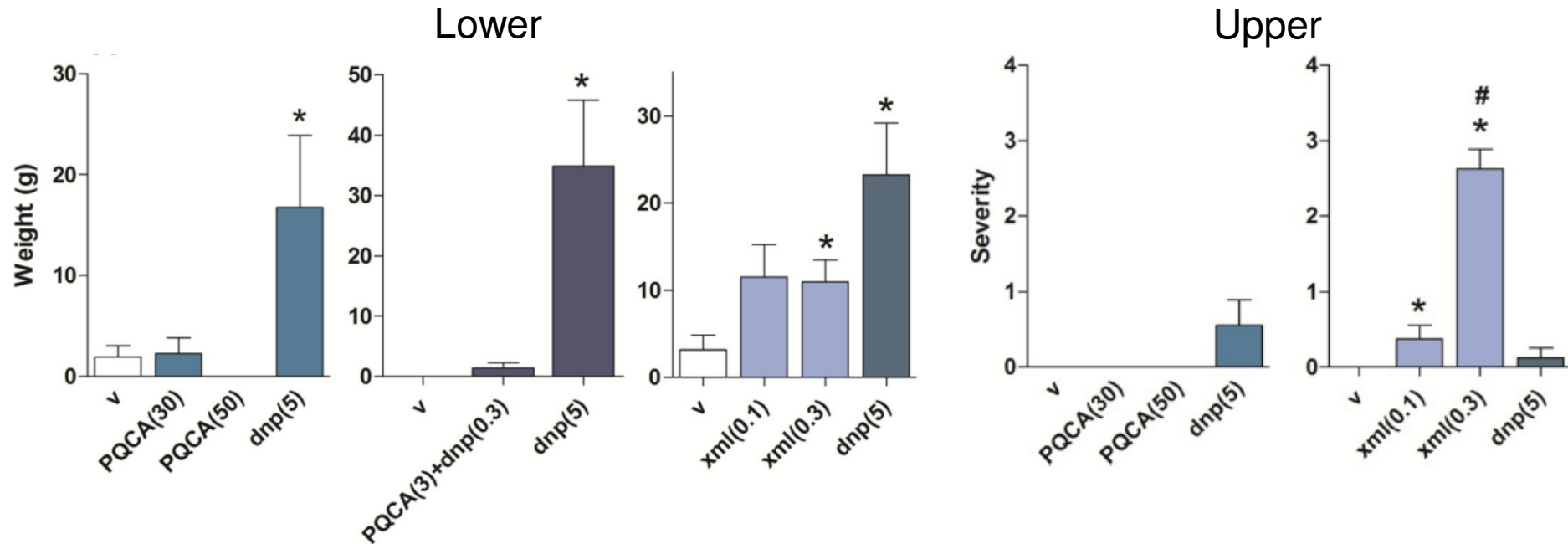
Mouse NOR



Puri et al (2015)  
Vardigan et al (2015)  
Lange et al (2015)

# M1 PAMs Demonstrate Improved Tolerability vs. SOC and Xanomeline

## GI Tolerability



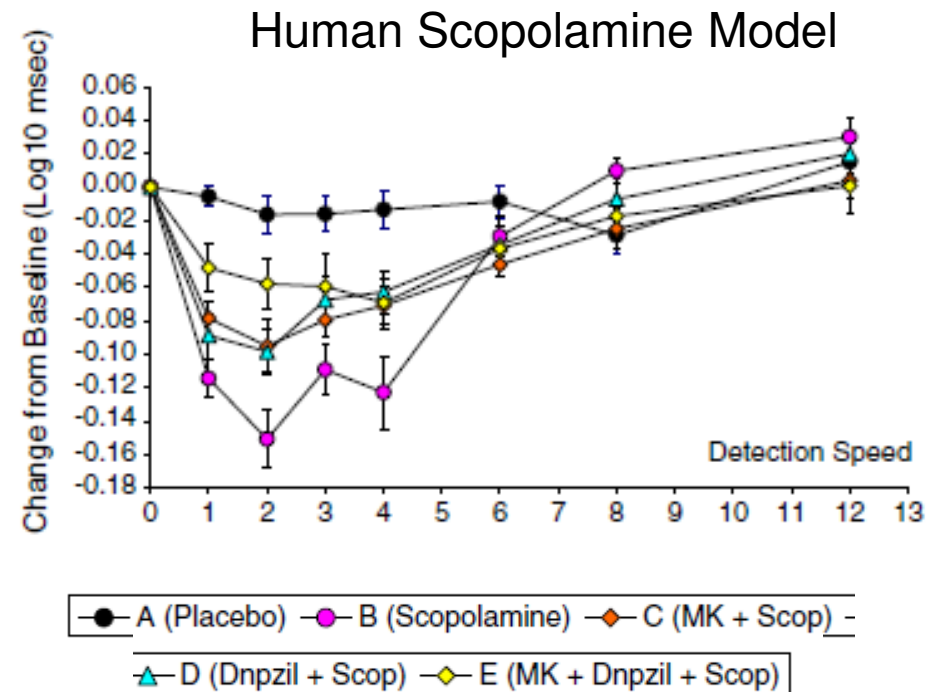
Main liability with SOC are profound GI effects, limiting dose



# Increasing POS Through Convergence

Efficacy across species and endpoint of interest

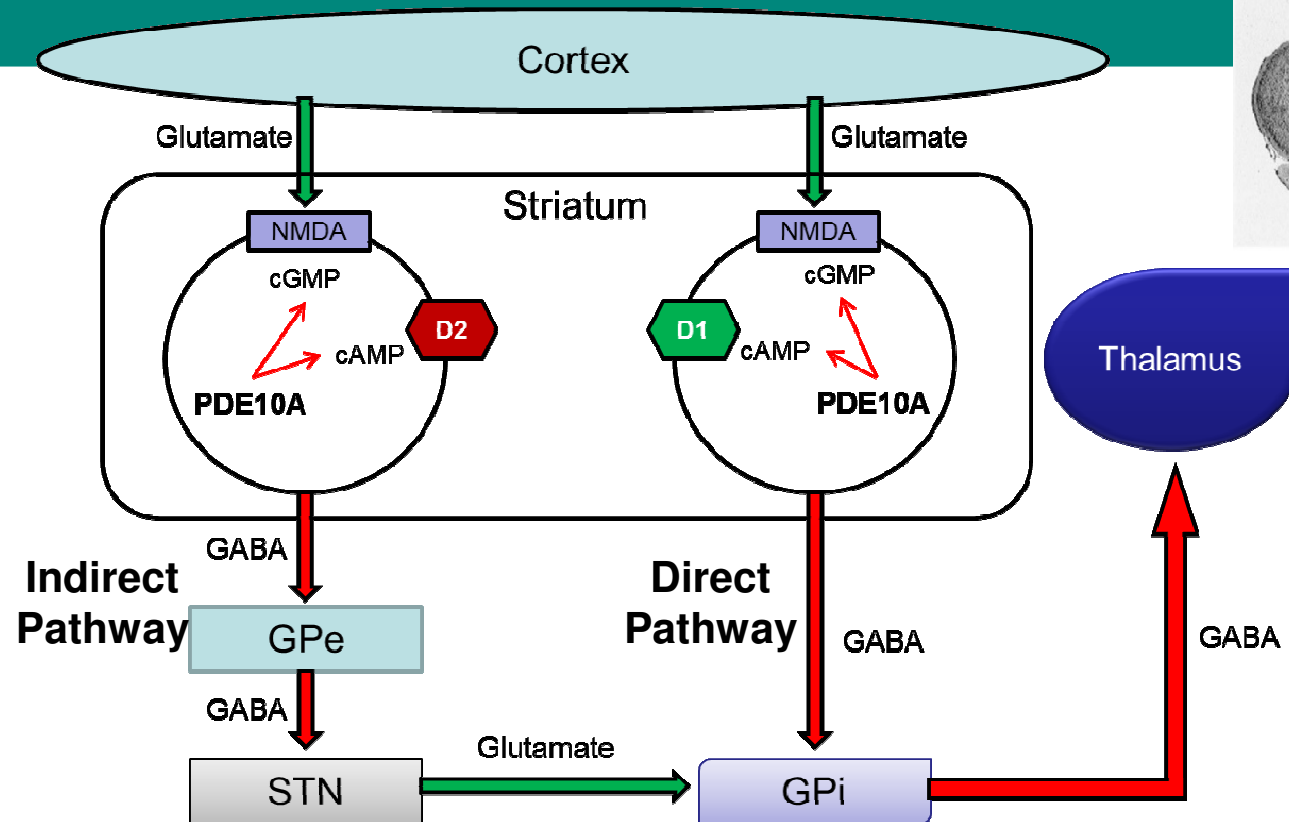
Domain	Rodent	NHP	Human
Attention	✓	✓	✓
Working Memory	✓	✓	✓
Episodic-like memory	✓	✓	✓
Executive Function		✓	✓



Cho et al., 2011

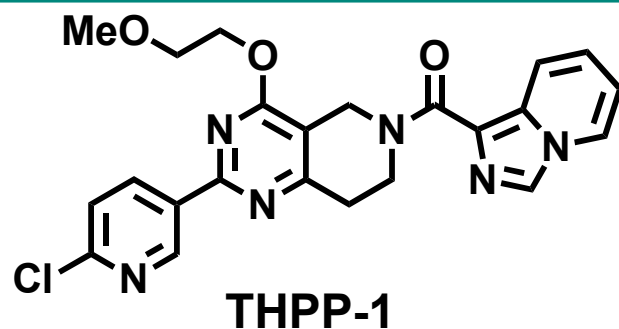
Data Convergence (or lack of) drives Go-No Go Decisions

# PDE10A is a Novel Therapeutic Target for Psychosis



- **Program Rationale:** PDE10A inhibition in the striatum will result in increased cAMP/cGMP signaling and striatal output, restoring behavioral inhibition that is impaired in schizophrenia

# THPP-1: Novel PDE10A Inhibitor



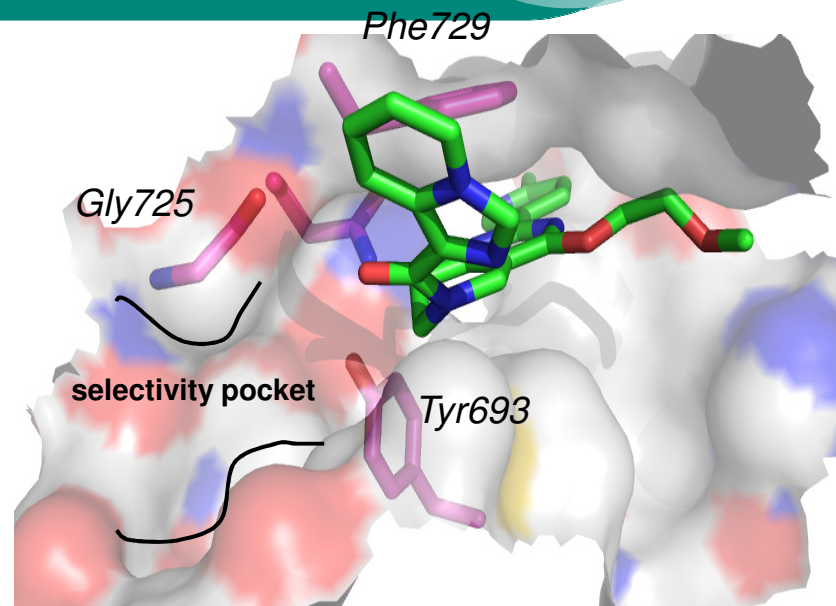
**PDE10  $K_i$  = 1.0 nM**

**PDE selectivity:**

>1000x PDEs 1-4, 7-9

~300x PDE 11

~100x PDE 5 & 6



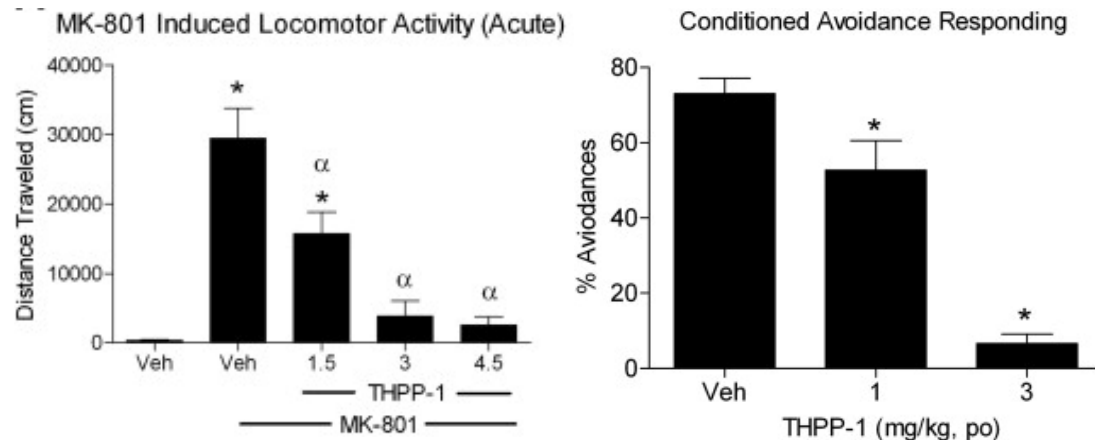
*Raheem et al. Bioorg. Med. Chem. Lett. (2012)*

## **Pharmacokinetics:**

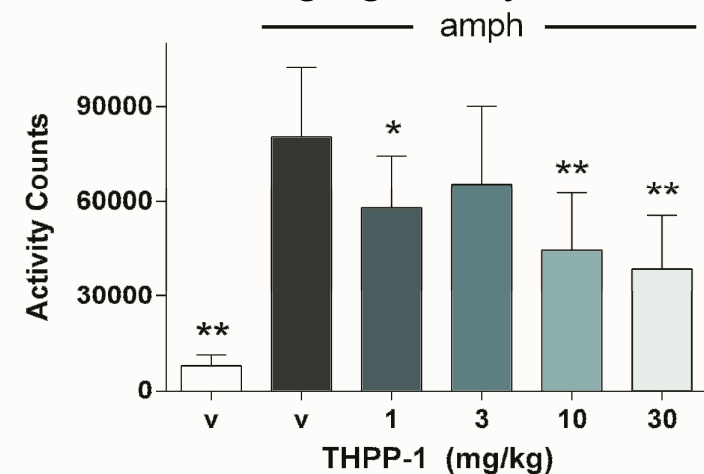
Species	Plasma Protein Bound (%)	Clearance (mL/min/kg)	Bioavailability (%)
rat	98.2	6	47
dog	97	3.8	79
rhesus	98.8	7.7	31

# Convergence across assays and species at equivalent free drug concentrations...

## Traditional Rodent Efficacy Assays

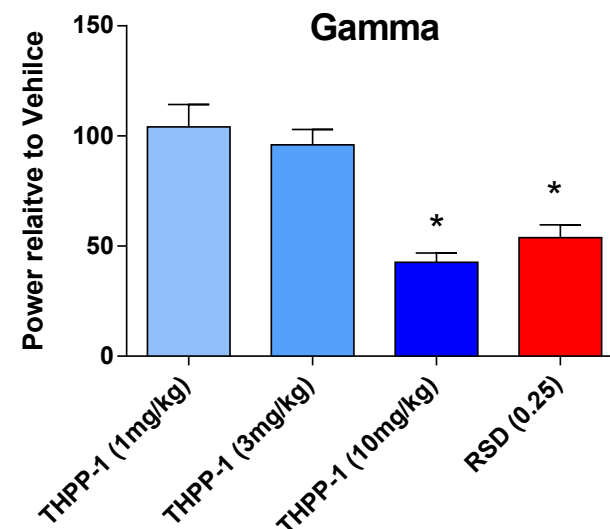
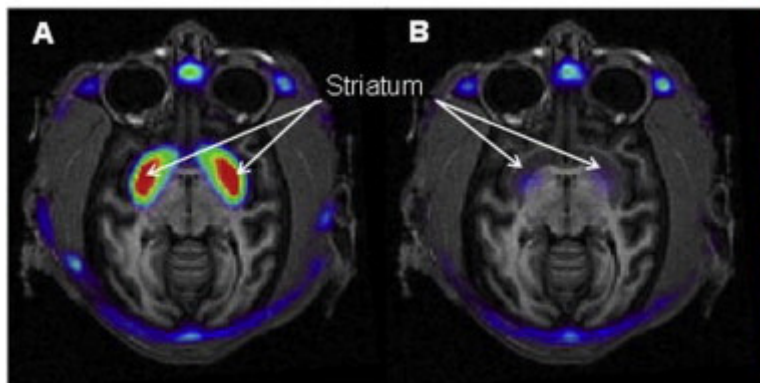


## Bridging Assay to NHP



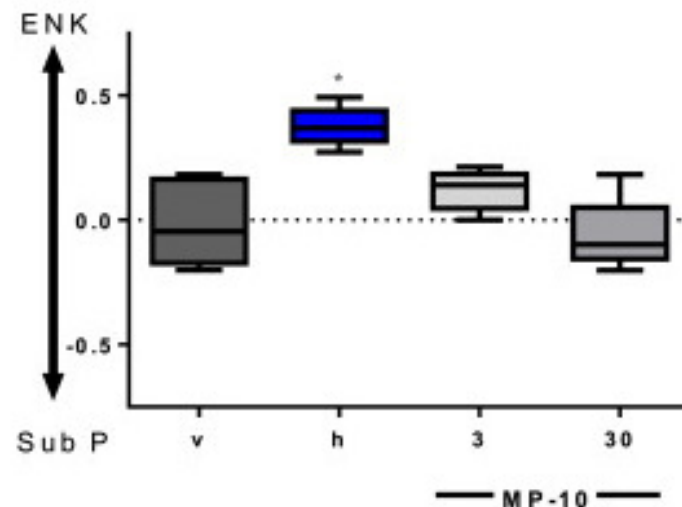
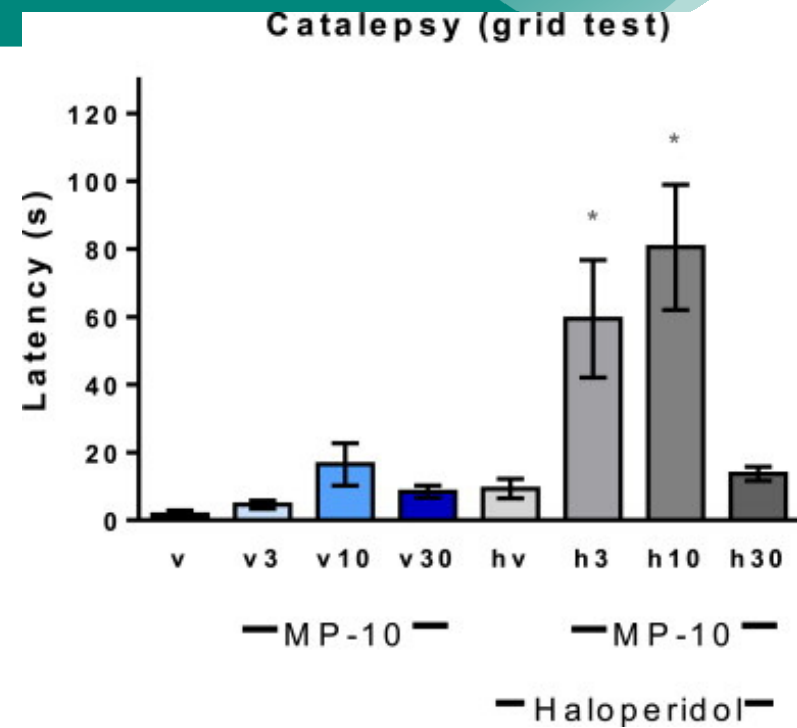
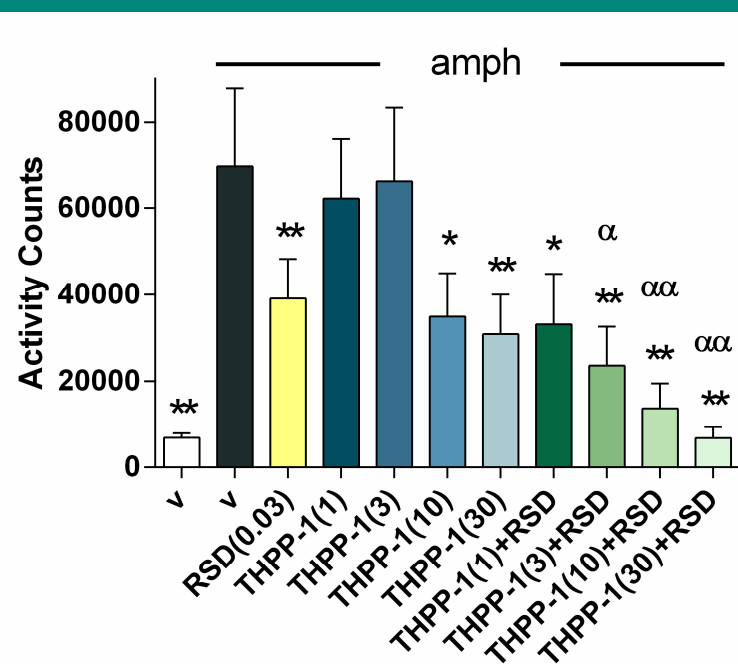
## PD Biomarker: qEEG

## TE Biomarker: Receptor Occupancy



Cox et al. (2015)  
Smith\*, Uslaner\* et al.,  
2013  
Vardigan et al  
(Submitted)

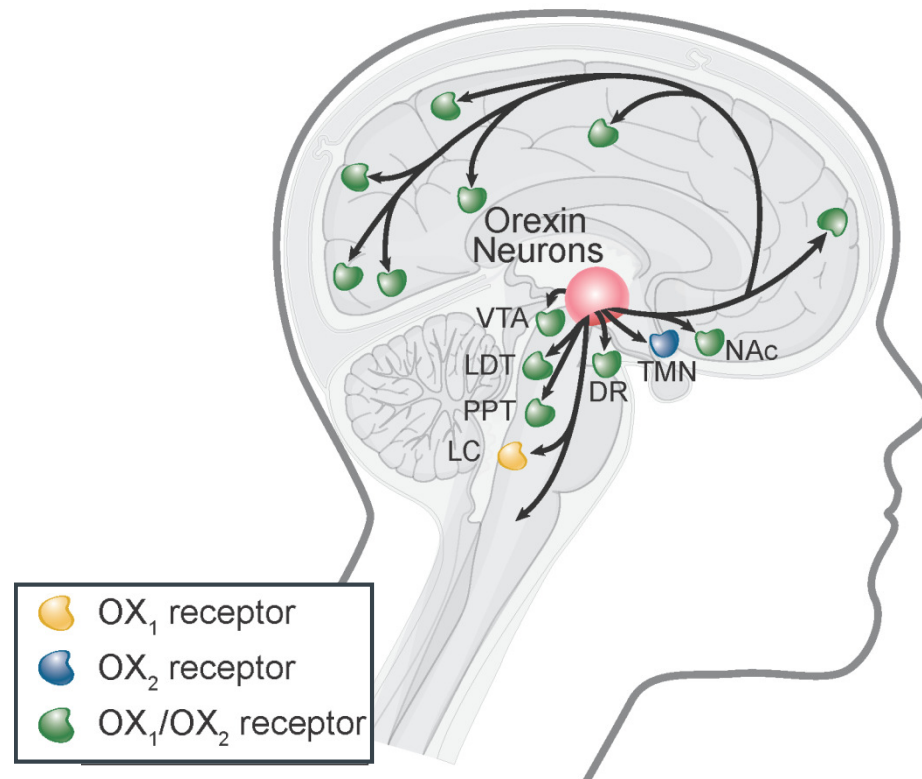
# Additivity with SOC and differentiation



Vardigan et al (submitted)  
Gentzel et al (2015)

# Dual Orexin Receptor Antagonists (DORAs): A More Targeted Approach for the Treatment of Insomnia

- ▶ Leading therapies target GABA receptors which are widely distributed throughout various brain regions
  - Not only the parts that help you sleep, but also parts of the brain integral to cognition, motor control, etc.
- ▶ In contrast, orexin neurons originate in one discrete area of the brain (LH), and selectively target the brain's arousal system
- ▶ This targeted approach provides the potential to address liabilities of current therapies such as cognition disturbances, physical and psychological dependence, and motor deficits.



Winrow et al. 2012 Drug Disc. Psych.Dis.

# DORA-22 in vitro profile

hOX2R  $K_i$  = 0.62 nM

hOX1R  $K_i$  = 10 nM

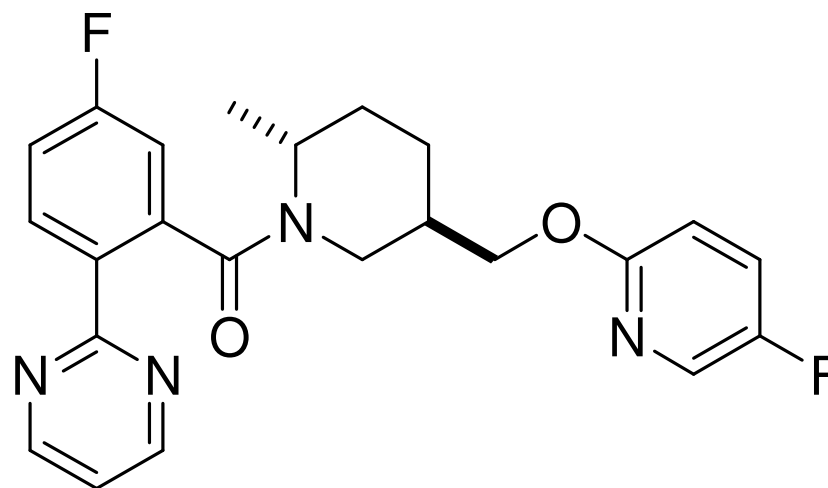
hOX2R  $FI$  = 11 nM

hOX1R  $FI$  = 32 nM

Similar across species. Data shown  
= human

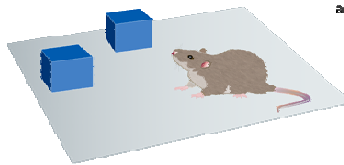
Pgp: 0.6 (h), 0.8 (r)

PPB: 4% (h), 3.5% (r)

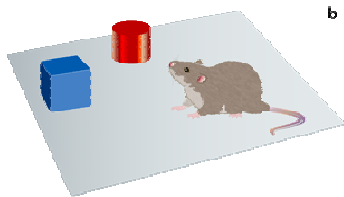


# Tests Used To Evaluate a Range of Cognitive Performance

## Novel Object Recognition

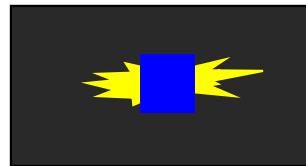


Delay Period (1h)



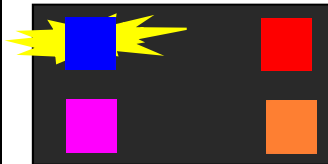
- Dependent on hippocampus and perirhinal cortex
- Measure of long term memory

## Delay Match to Sample



Sample image presented and touched

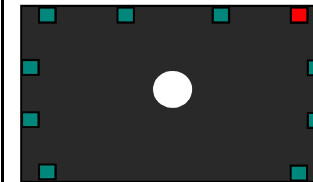
Delay Period (Variable)



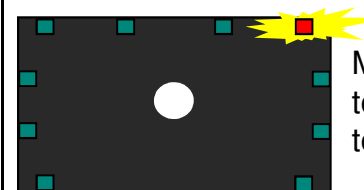
Monkey needs to remember image previously exposed to.

- Prefrontal /medial-temporal cortex-dependent task
- Measure of working memory

## Serial Choice Reaction



Centering response required until cue of variable duration (0.4-4 sec) presented.

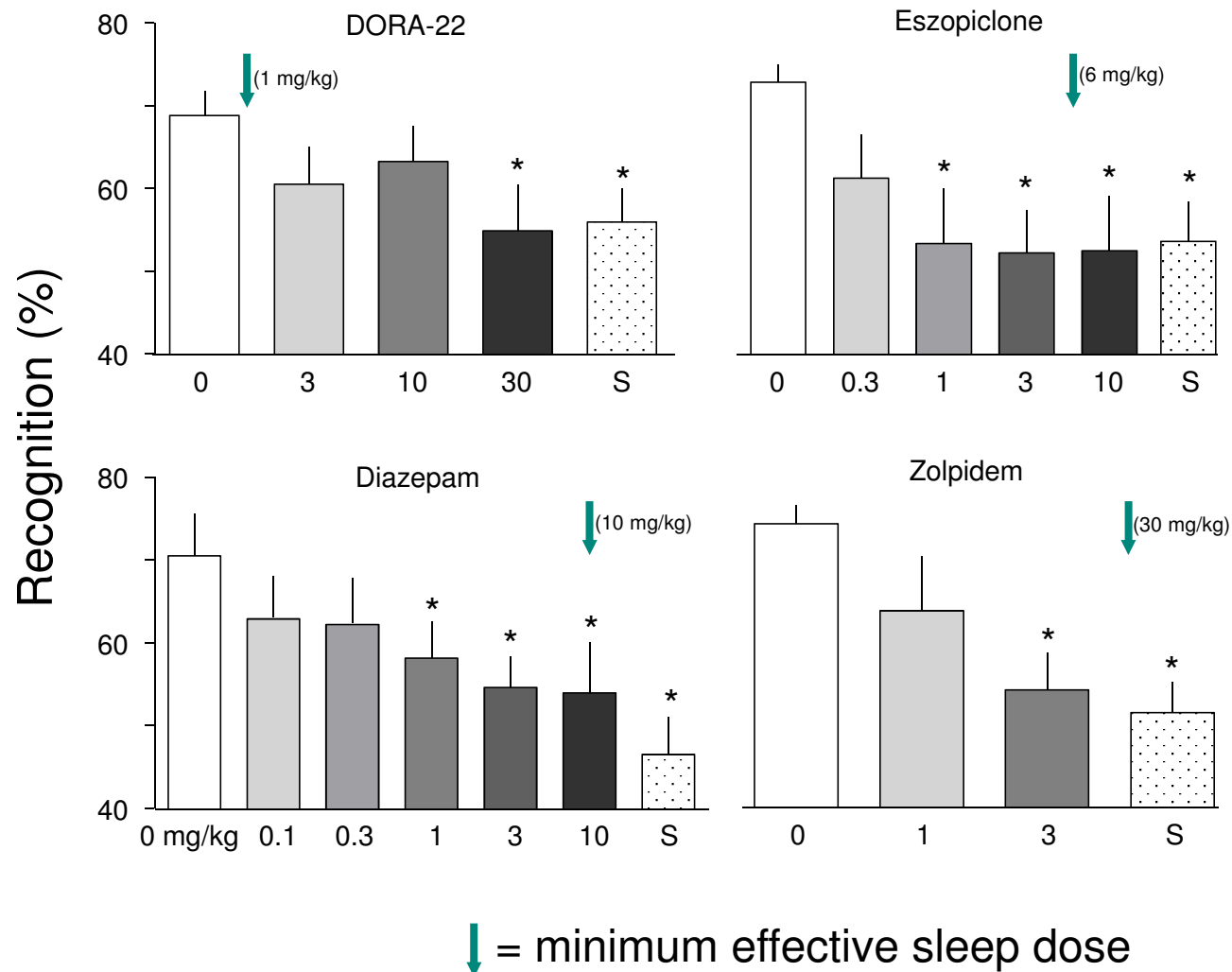


Monkey needs to touch cued location to receive reward.

- Prefrontal cortex-dependent task
- Measure of sustained divided attention



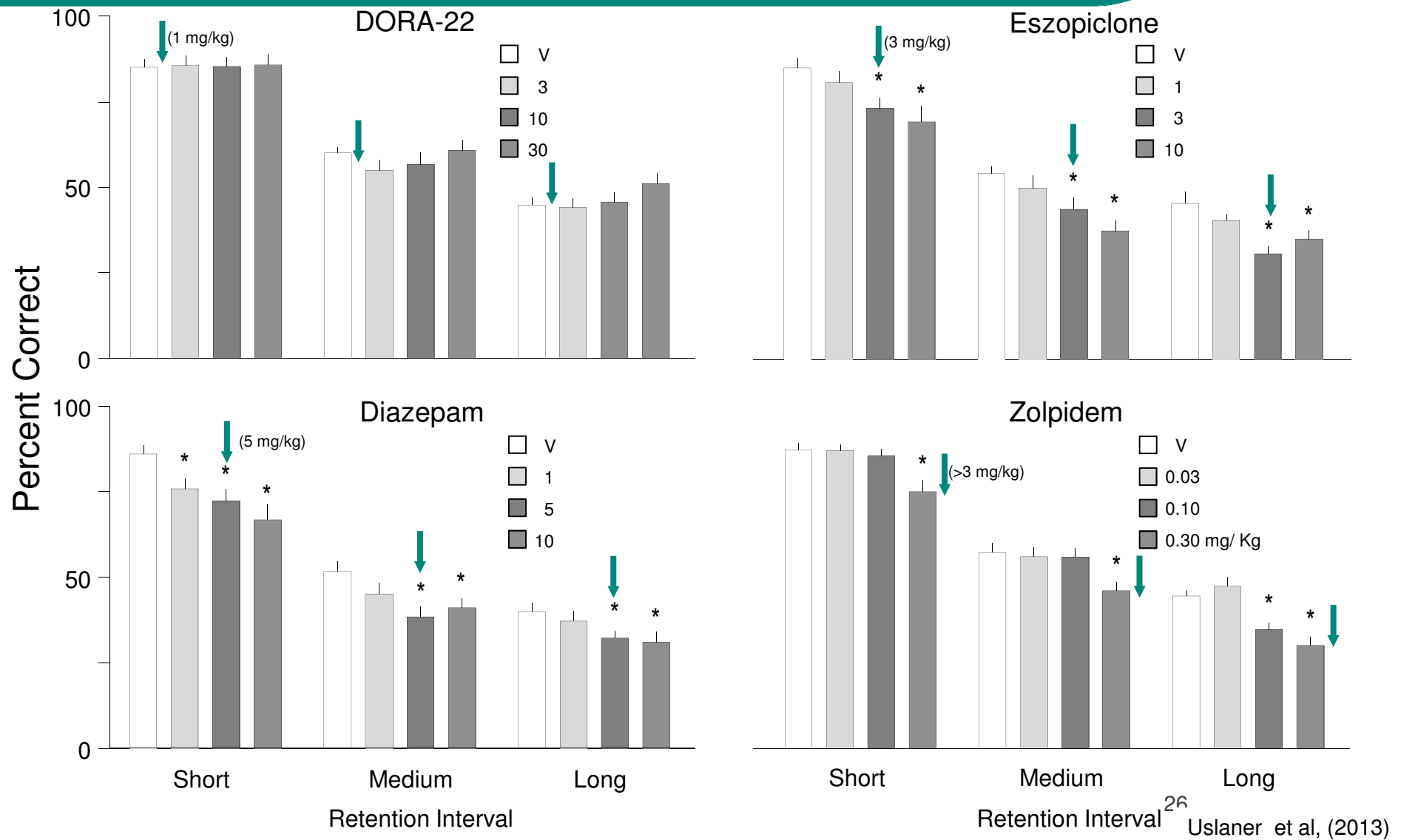
# Novel Object Recognition



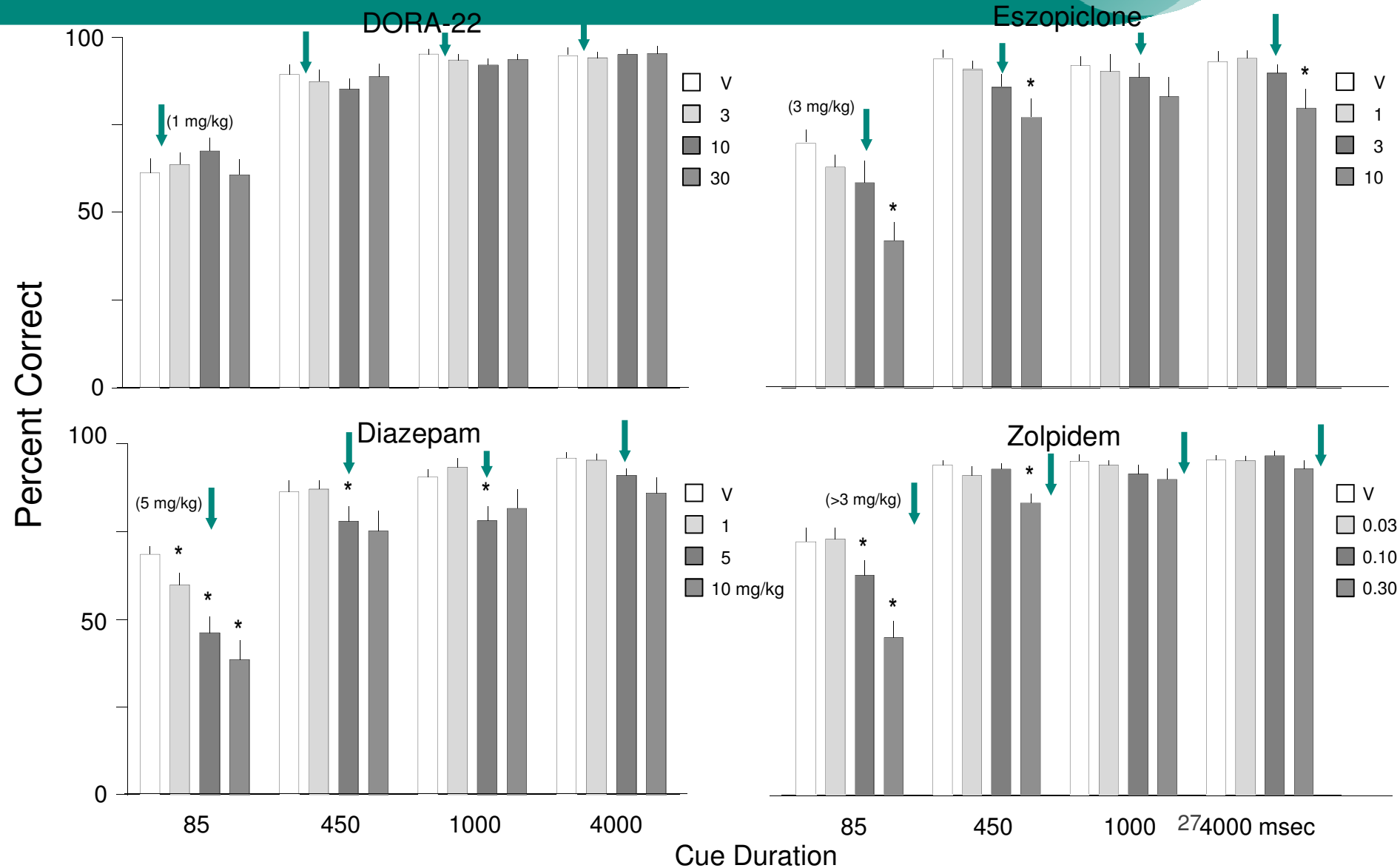
50% Recognition is equal to chance; S = scopolamine 1 mg/kg; \* indicates significantly lower than vehicle.

Uslaner et al, (2013)

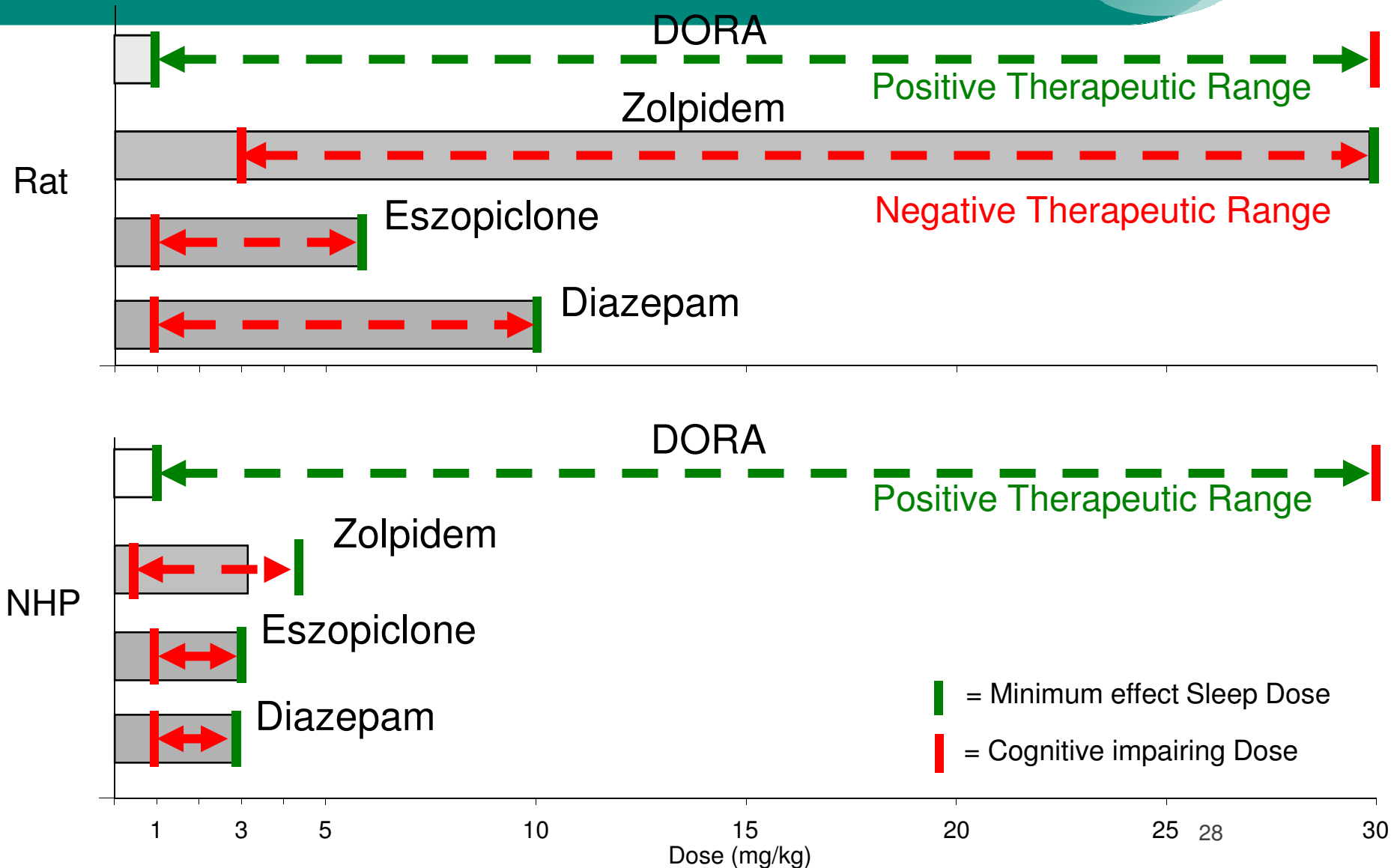
# Delayed Match To Sample



# Serial Choice Reaction Time



# Index of Therapeutic vs. Adverse Cognitive Effects in Rat and NHP models



# Summary

- Translational methodologies in NHPs and TPKPD best practices have been employed Merck neuroscience to improve POS in the clinic
- Merck continues to invest in order to establish novel translatable biomarkers to increase POS in various other CNS disease areas
  - Psychosis
  - Pain
  - Movement Disorders
  - Disease Modifiers

# Acknowledgements

Chris Cannon  
Jason Drott  
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Renee Gentzel  
Eric Hostetler

Andrea Houghton  
John Renger  
Chris Winrow  
Paul Coleman  
Scott Kuduk  
Many members from  
SALAR  
Darryle Schoepp  
Richard Hargreaves  
John Hunter

# Brief muscarinic review

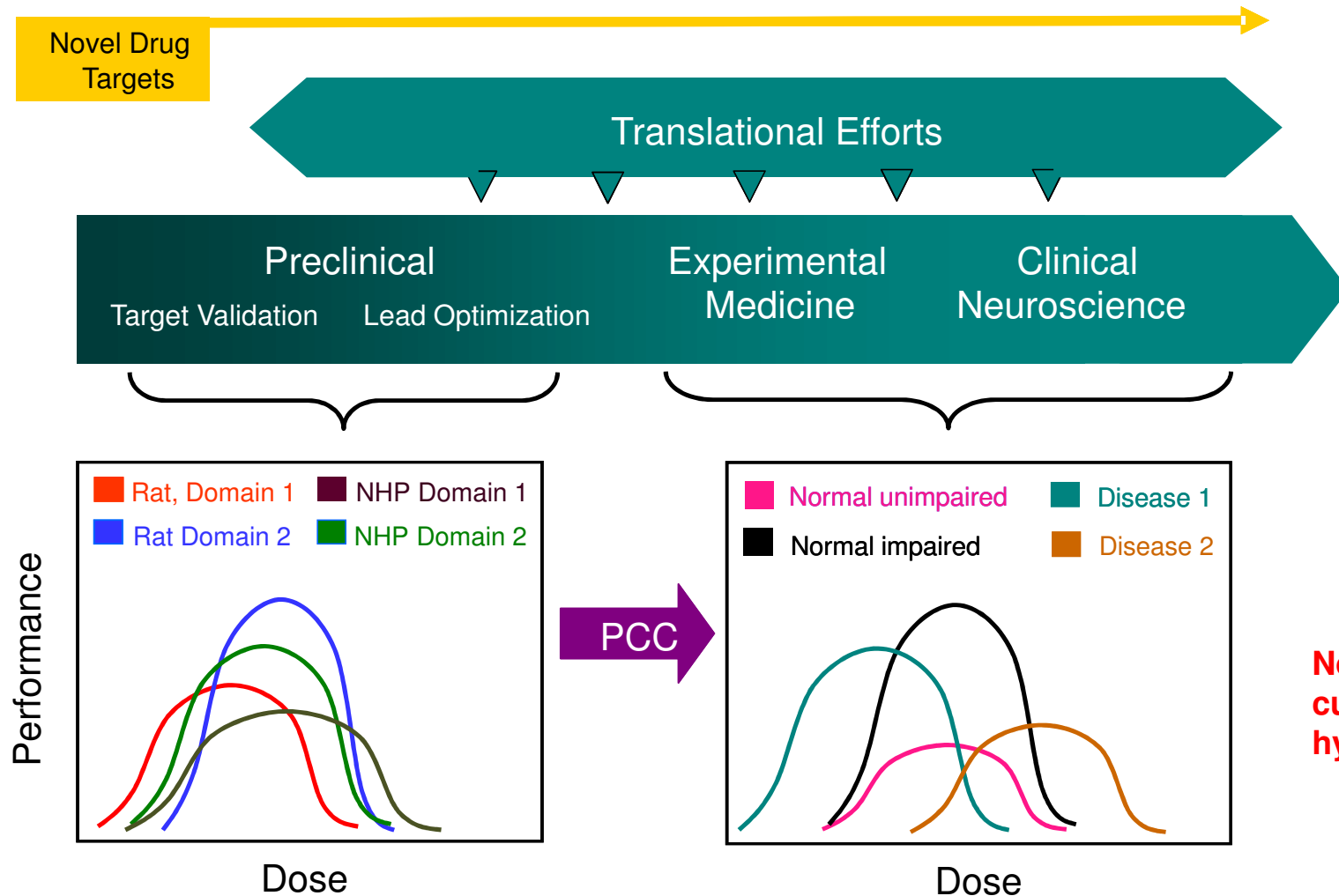
- Selective targeting of M1 muscarinic receptor could provide additional benefit in improving cognition in AD without substantially increasing **adverse effects** from **nonspecific** cholinergic stimulation
  - M1 expression in periphery relatively limited

What	mAChR's involved	Implication for M <sub>1</sub> -selective SAMM
Peptic ulcer	M <sub>3</sub> > M <sub>5</sub> → acid secretion	SAMM should not increase gastric acid
GI motility	M <sub>2</sub> and M <sub>3</sub> → increased GI motility	SAMM should not have an effect on GI motility
Salivation	M <sub>3</sub> > M <sub>1</sub> stimulate salivation	SAMM may increase salivation, although not as much as nonselective muscarinic agonist
Overactive bladder	M <sub>3</sub> inhibition helps incontinence	SAMM should not worsen incontinence
COPD/bronchial asthma	M <sub>3</sub> > M <sub>2</sub> → bronchoconstriction M <sub>1</sub> → bronchodilation	SAMM should not worsen COPD or asthma
Heart rate	M <sub>2</sub> → vagal bradycardia	SAMM should not cause bradycardia

Data from mouse KO studies

# The Conundrum Of Drug Development For CNS Diseases

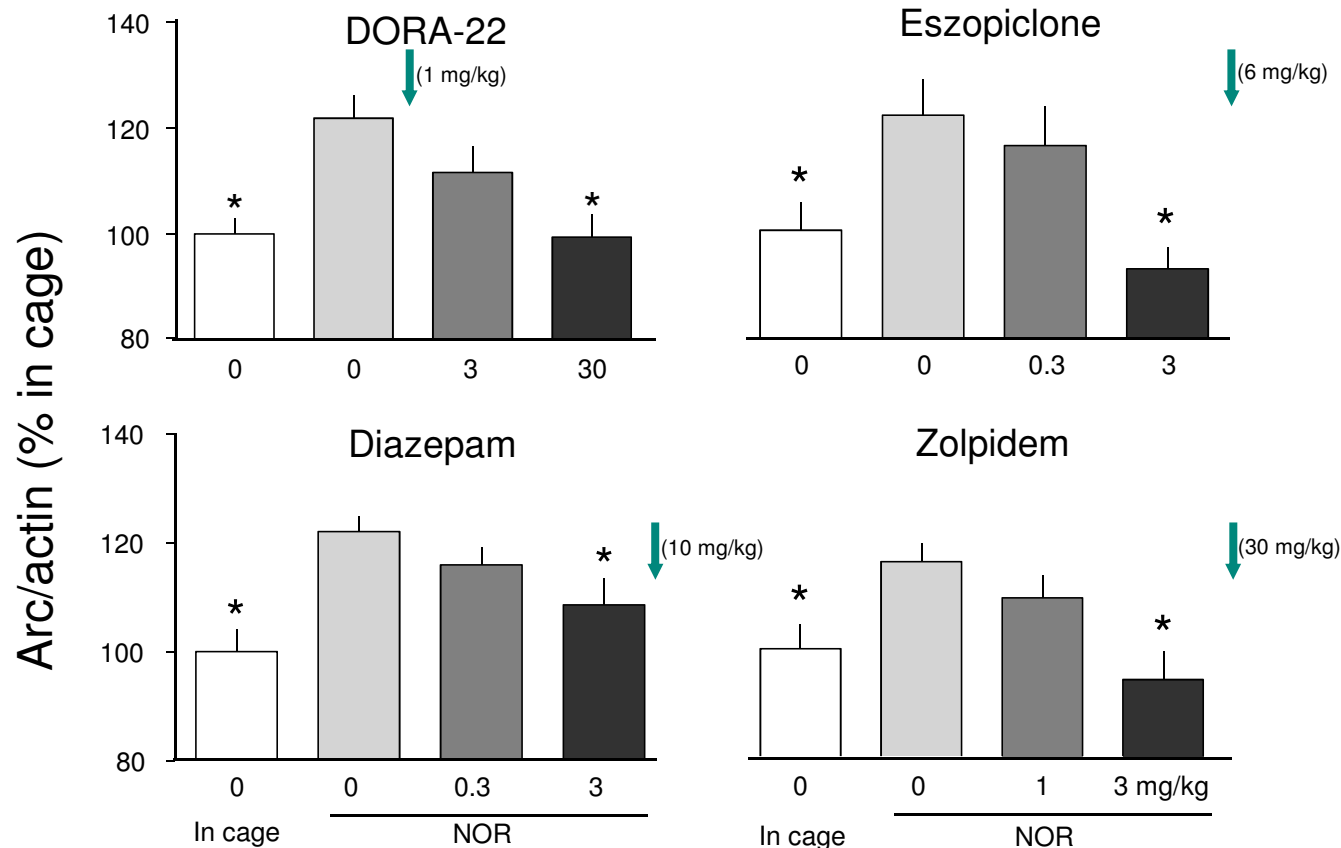
## Translation From Lab To Clinic



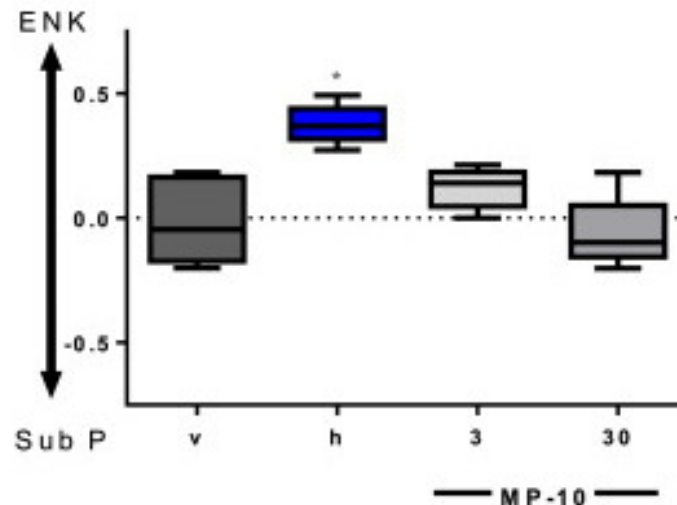
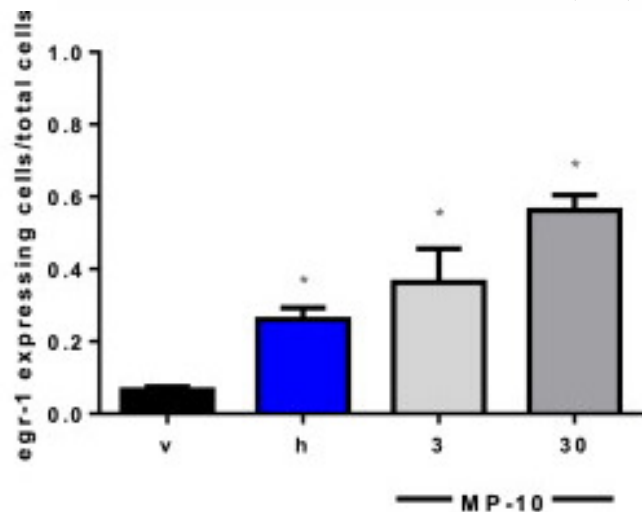
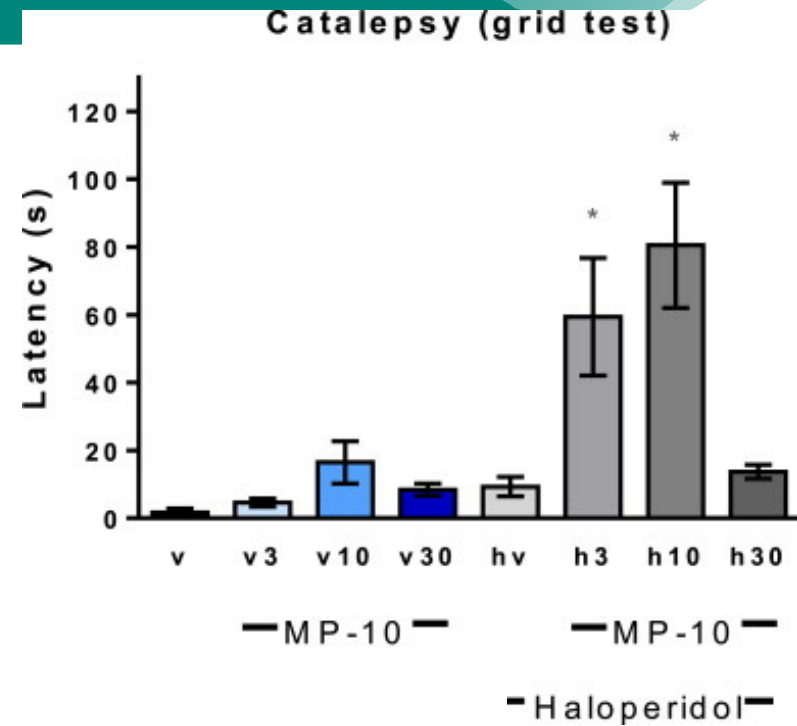
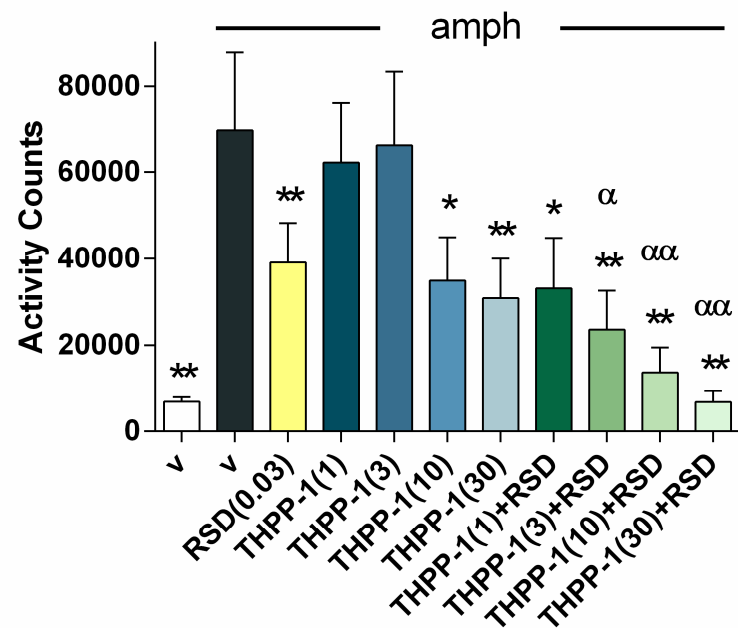


# Cellular Evidence That Supports Cognitive Effects

DORA-22, Eszopiclone, Diazepam, And Zolpidem Reduce Arc Protein Levels In Hippocampus Of Rat At Doses Which Impair Cognition

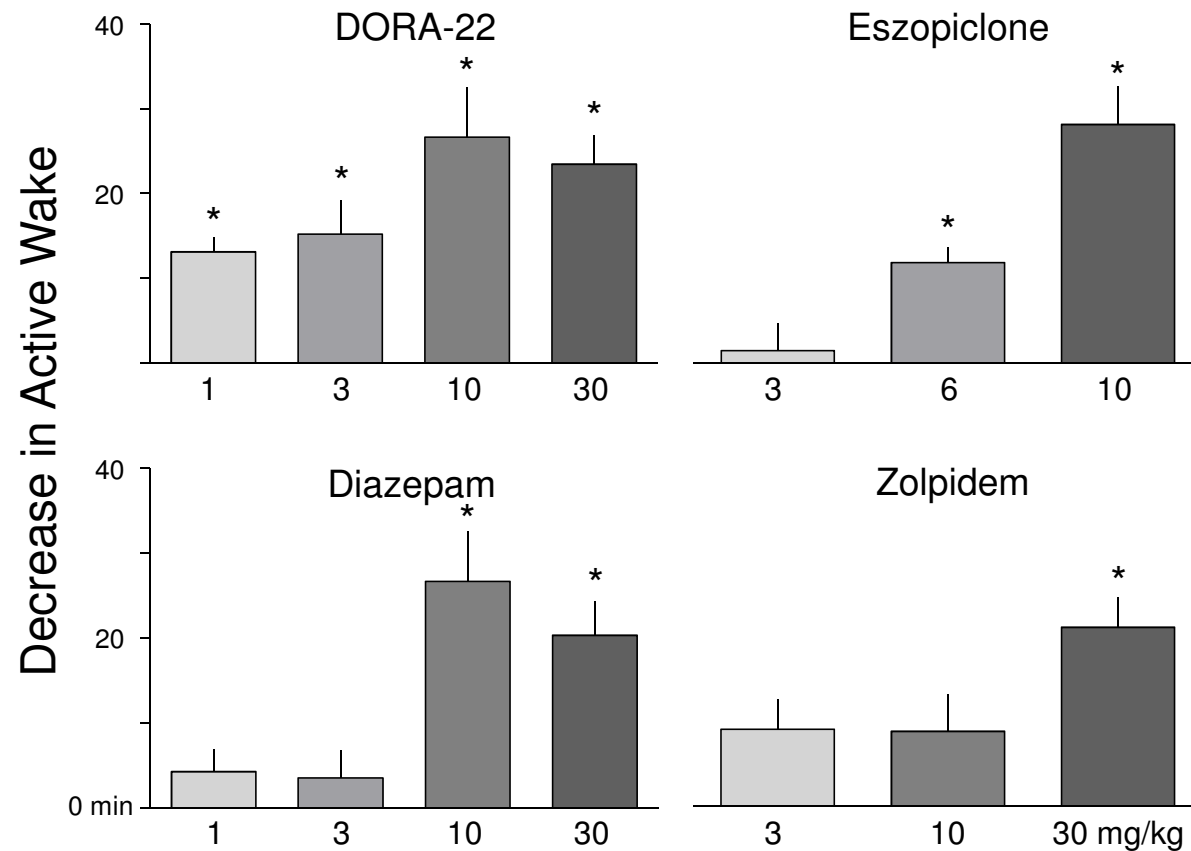


# Additivity with SOC and differentiation

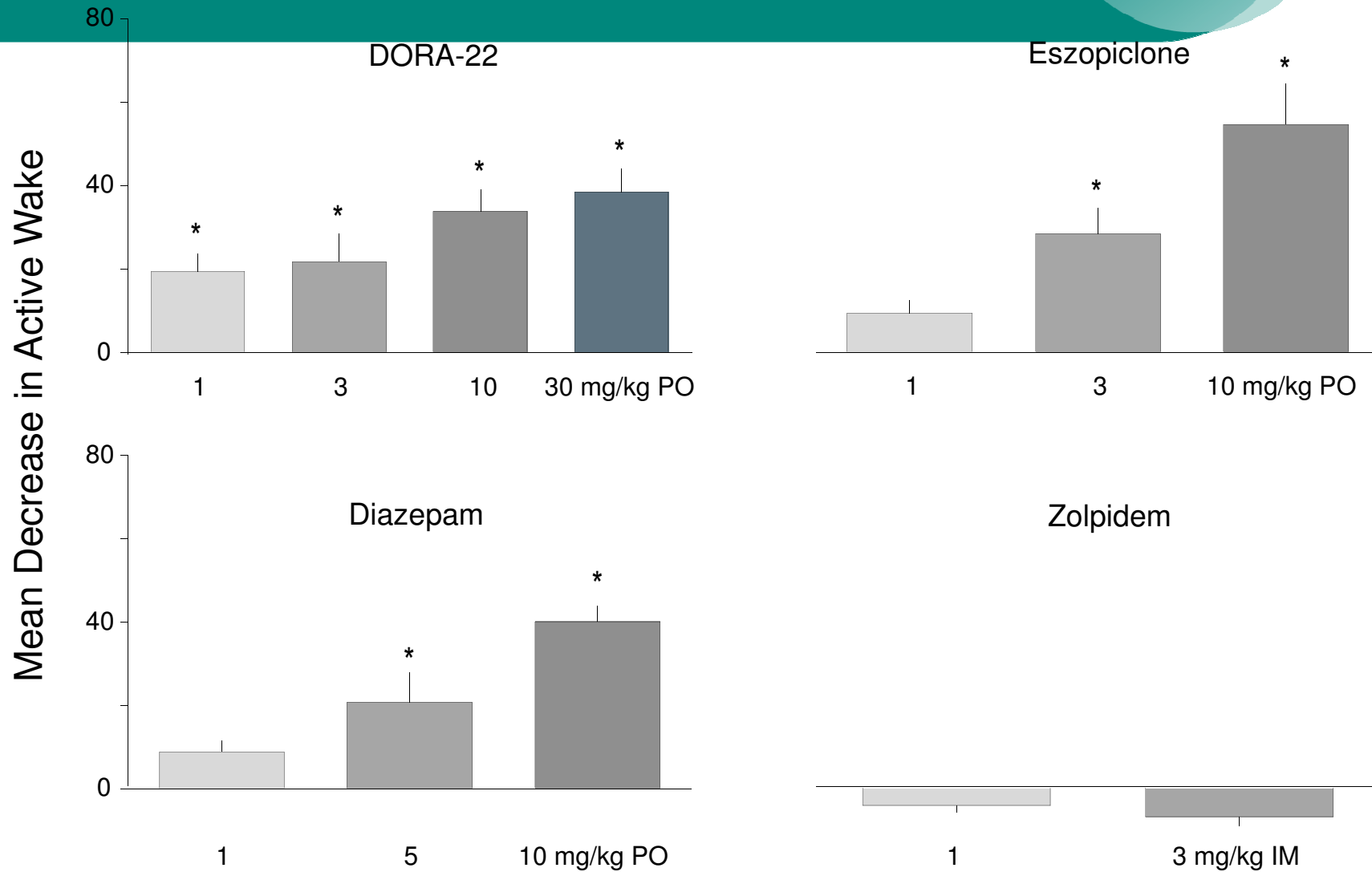


Vardigan et al (submitted)  
Gentzel et al (2015)

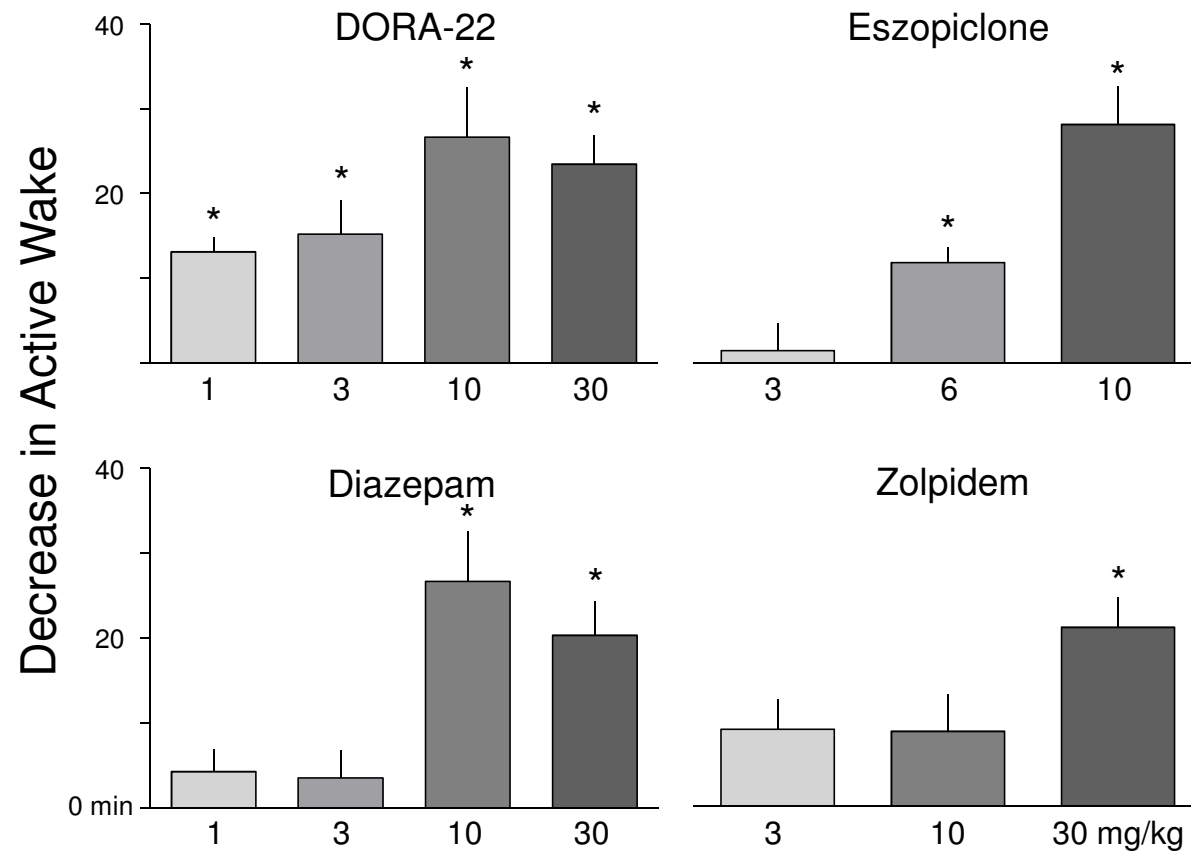
# Compounds Matched for Sleep Time in Rat



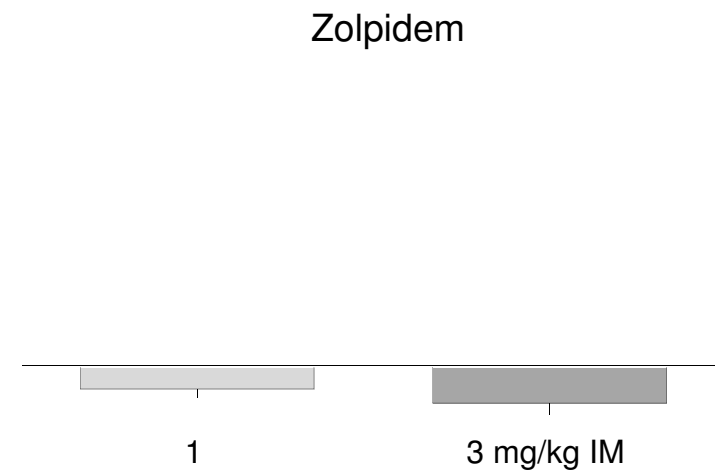
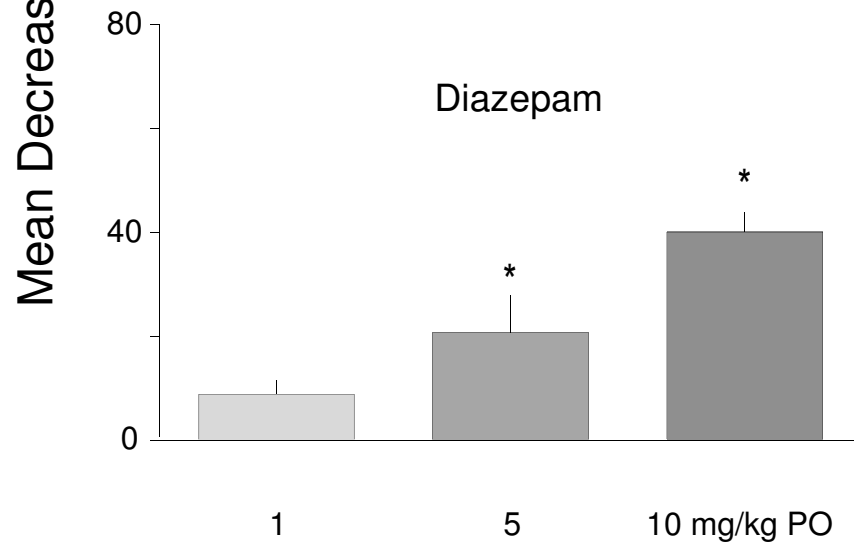
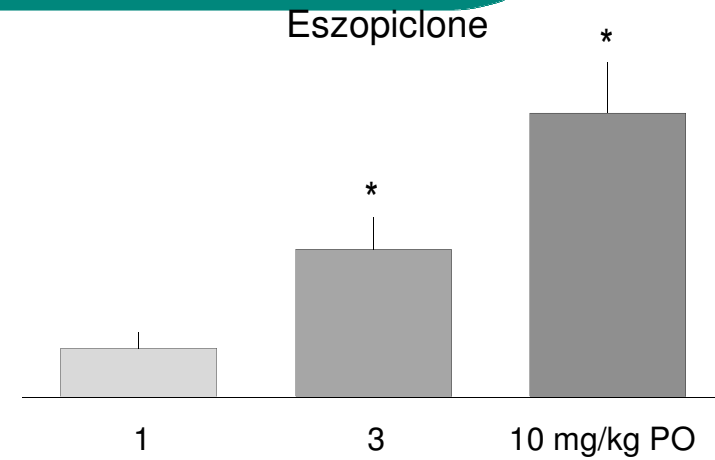
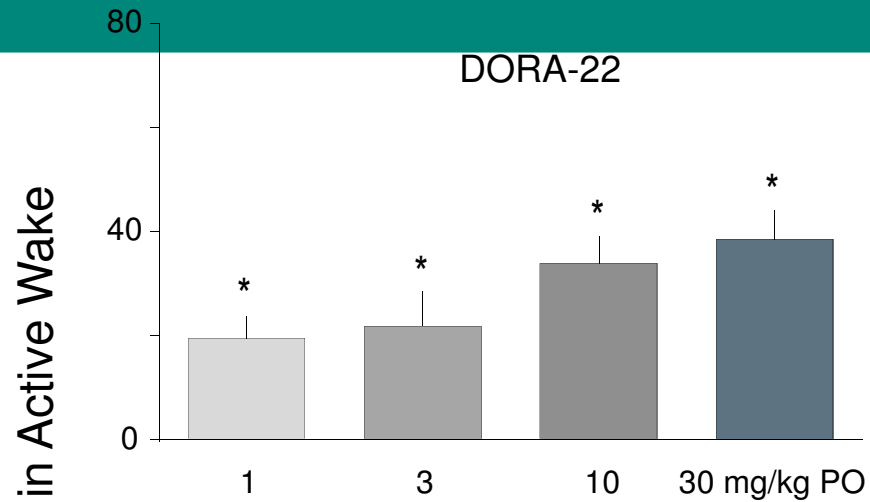
# Compounds Matched for Sleep Time in NHP



# Compounds Matched for Sleep Time in Rat



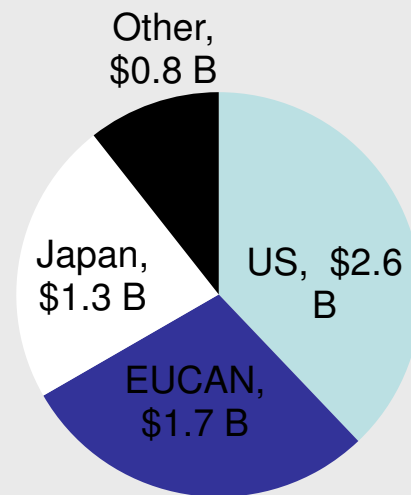
# Compounds Matched for Sleep Time in NHP



# Alzheimer's: an area of critical unmet need

- Most common form of dementia, affecting 1 out of every 8 people >65 years of age
- Acetylcholinesterase inhibitors (current lead therapy class) and NMDA antagonists only modestly effective
  - AChEIs exhibit tolerability issues related to non-specific cholinergic activity

## \$6.4 B Global Market



Source: N7D Anti-Alzheimer's Products IMS Sales Data MAT 2Q13

## • Current Market is Symptomatic Treatments Only:

- Acetylcholinesterase inhibitors (AChEIs) are the leading class with 69% of sales, and NMDA receptor antagonists capture the remaining 31%
- Three approved AD therapies reached blockbuster status despite modest efficacy
  - ARICEPT (donepezil/AChEI/Pfizer): \$4.4B peak sales
  - NAMENDA (memantine/NMDA/Forest): \$1.4B 2012 sales, 75% concomitant use with AChEIs
  - EXELON (rivastigmine/AChEI/Novartis): \$1.1B 2012 sales