

The Influence of Orexin Antagonist, SB-334867, on Cognitive Flexibility

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Alzheimer's Disease

ALZHEIMER'S DISEASE IS THE
6TH LEADING CAUSE
OF DEATH IN THE UNITED STATES

In 2017, Alzheimer's and other dementias will cost the nation \$259 billion
By 2050, these costs could rise as high as

\$1.1 TRILLION



MORE THAN
5 MILLION
AMERICANS ARE
LIVING WITH
ALZHEIMER'S
BY 2050, THIS
NUMBER COULD
RISE AS HIGH AS
16 MILLION

EVERY



SECONDS

someone in the
United States
develops the disease

35% of caregivers for people with Alzheimer's or another dementia report that their health has gotten worse due to care responsibilities, compared to **19%** of caregivers for older people without dementia



1 IN 3

seniors dies
with Alzheimer's or
another dementia



Since 2000, deaths
from heart disease have
decreased by 14%

while deaths from
Alzheimer's disease have
increased by 89%

MORE
THAN

15 MILLION AMERICANS
provide unpaid care for people with
Alzheimer's or other dementias

IN
2016

these caregivers provided
an estimated
18.2 BILLION HOURS
of care valued at over
\$230 BILLION

**IT KILLS
MORE THAN**
breast cancer
and prostate cancer
COMBINED



Alzheimer's Association, 2017 (<http://www.alz.org>)

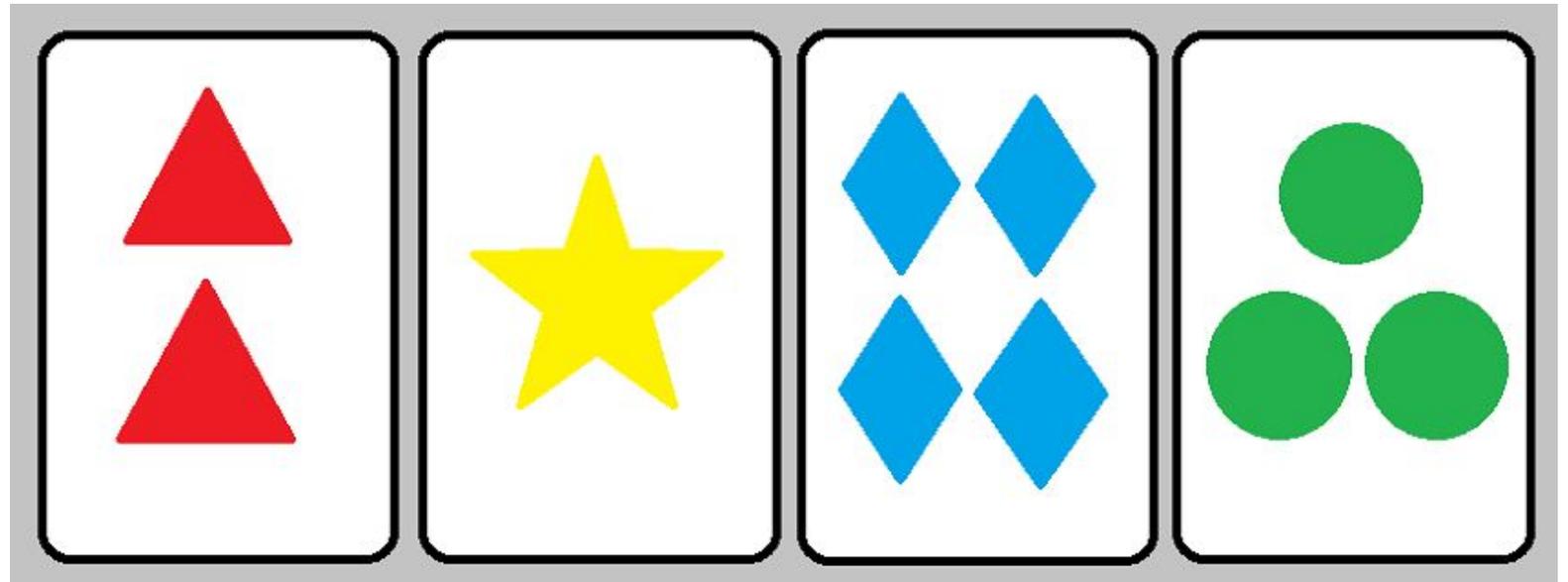
Cognitive Flexibility

The ability for one to adapt to ever-changing situations, which normally has been seen to decline with age. (Brown & Tait, 2016)

Measures of cognitive flexibility:

Human Model

- The Wisconsin Card Sorting Task (Grant & Berg, 1948)



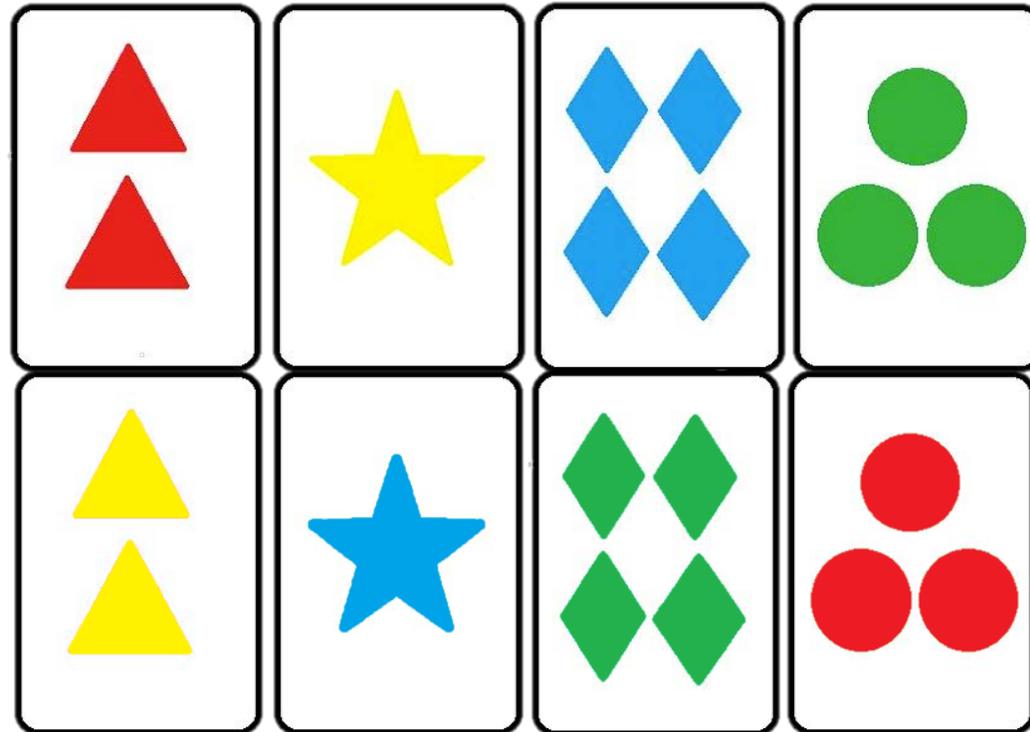
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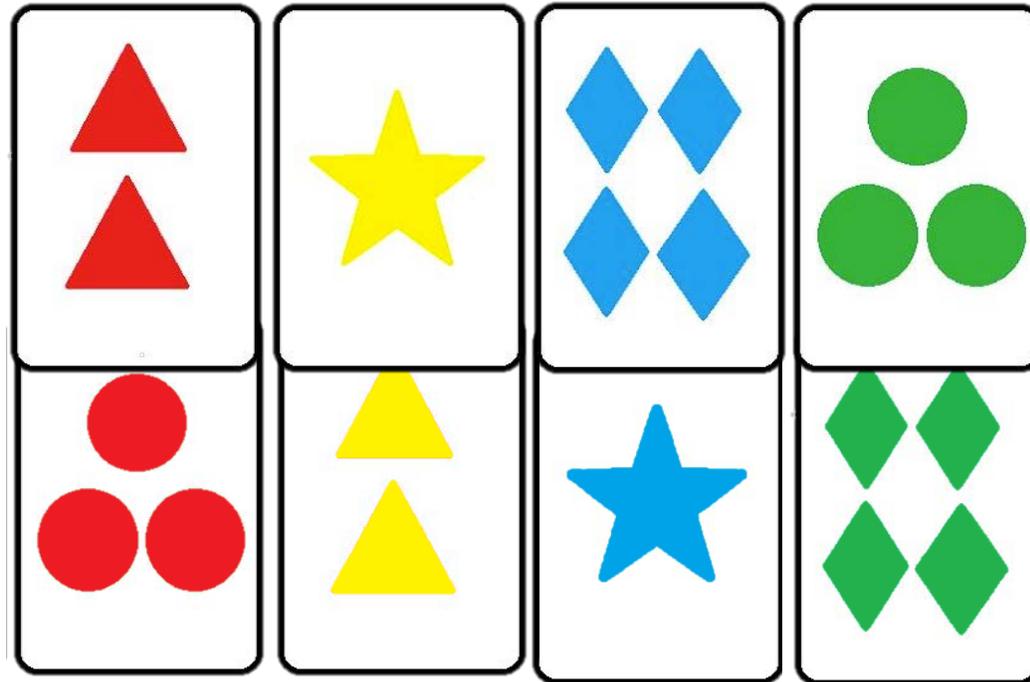
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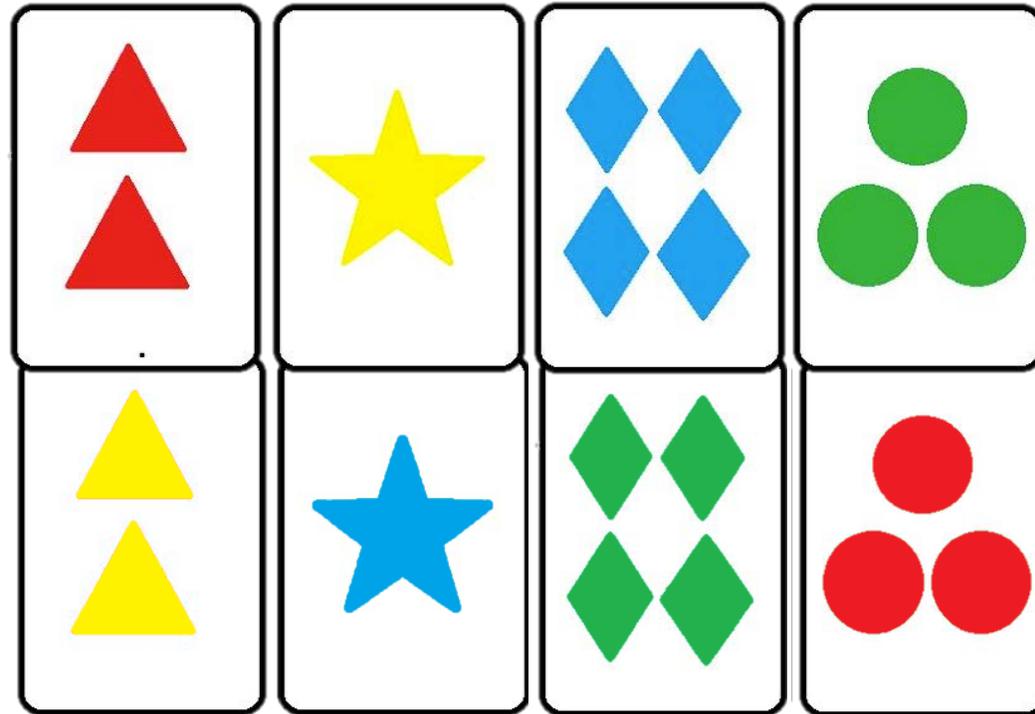
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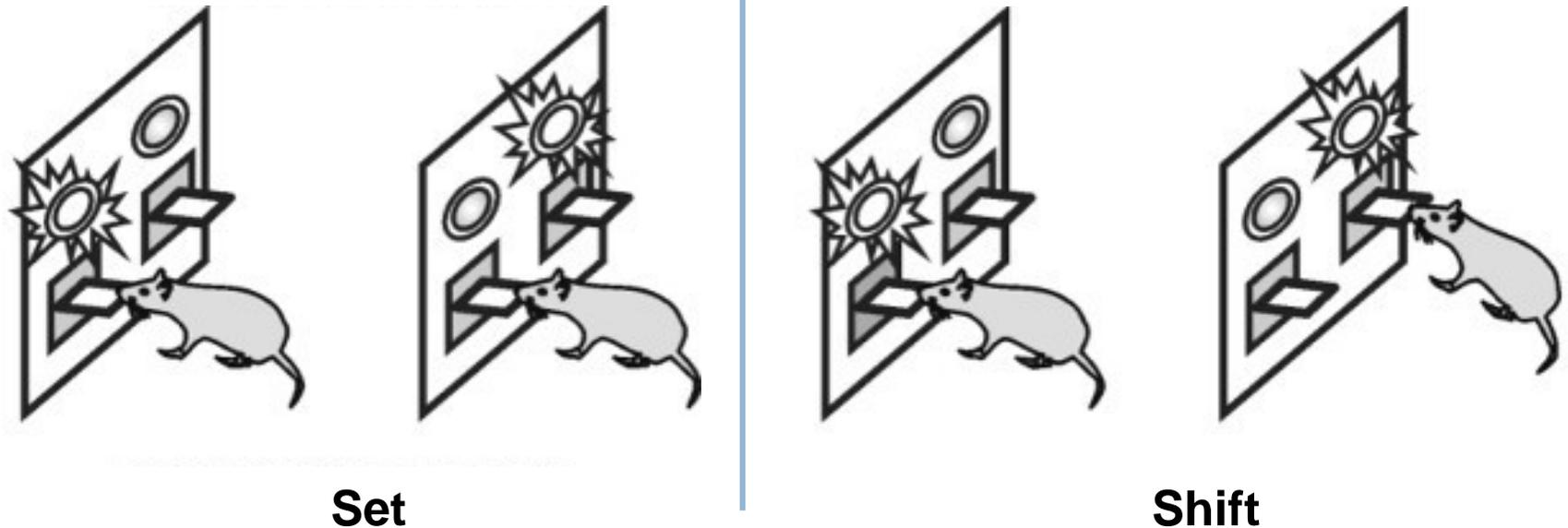
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Measures of cognitive flexibility:

Rodent Model

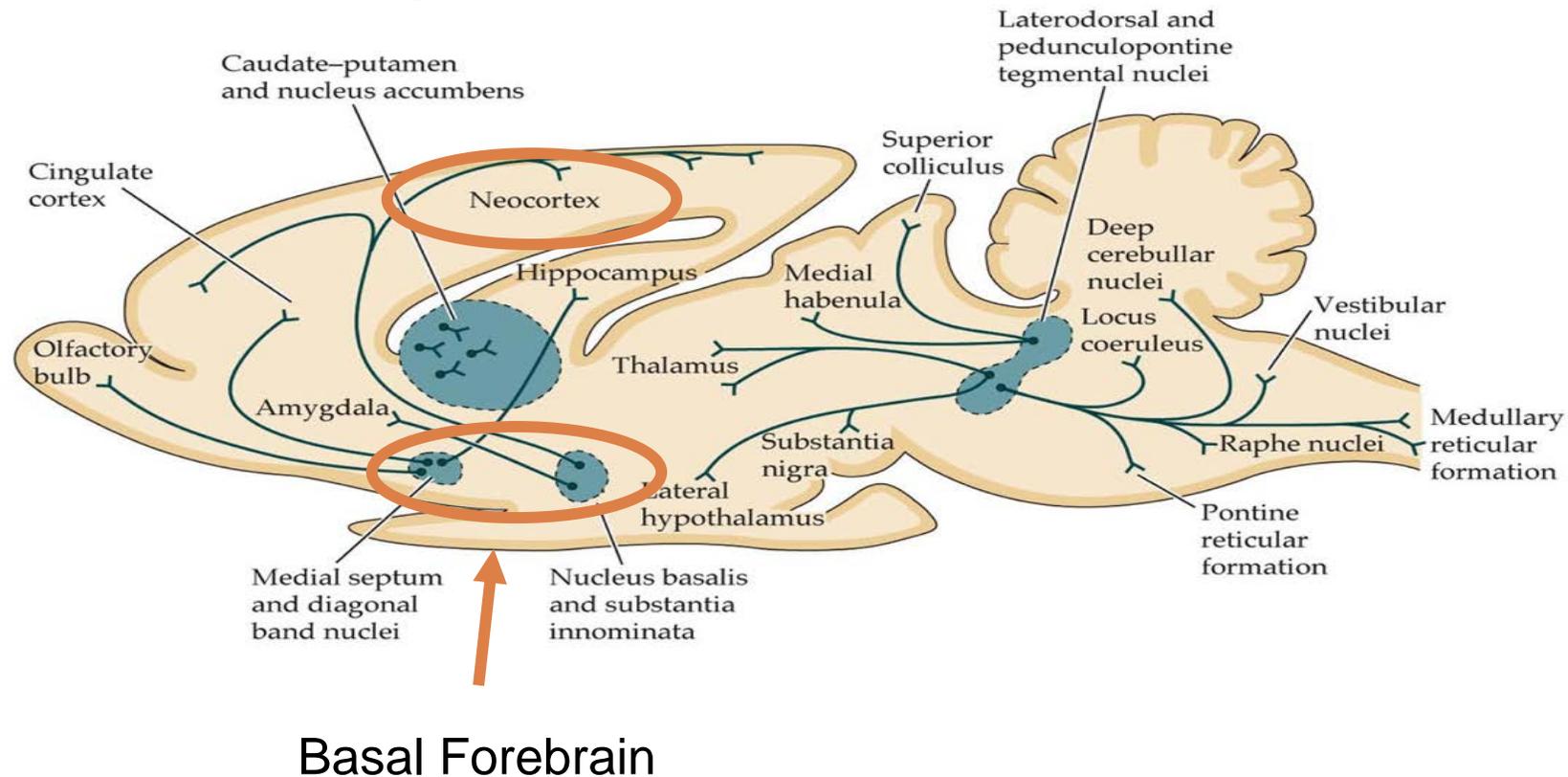
- **Set Shift Task** (Arnold et al., 2002; Brady & Floresco, 2015; Cabrera et al., 2006)



The Cholinergic Hypothesis of Alzheimer's Disease

Acetylcholine transmission to the hippocampus and neocortex from the basal forebrain is disrupted following degeneration of cholinergic neurons. (Bigl, Woolf, & Butcher, 1982)

The Basal Forebrain Cholinergic System



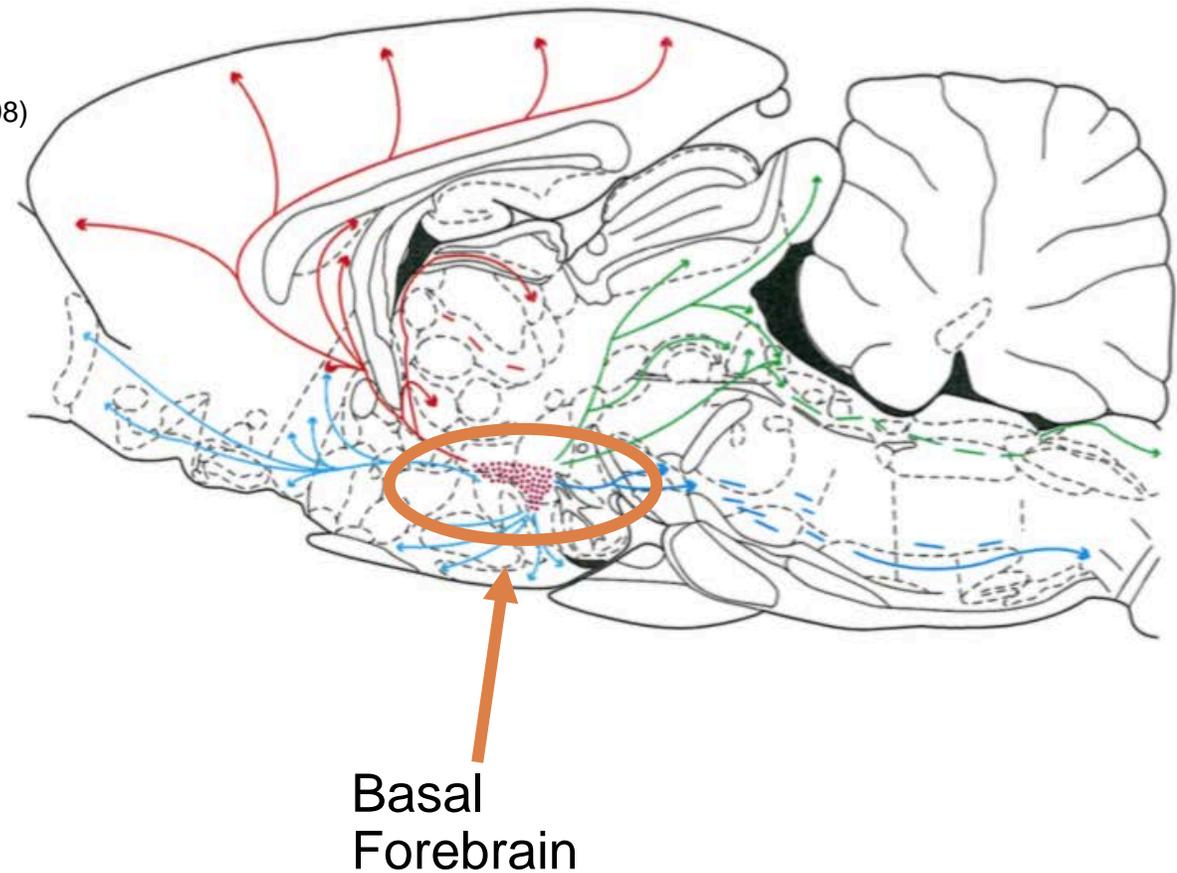
PSYCHOPHARMACOLOGY, Figure 6.7 © 2005 Sinauer Associates, Inc.

Blennow et al., 2006
Grober et al., 2008
Muir, 1997

Figure derived from
Meyer & Quenzer (2nd ed.)

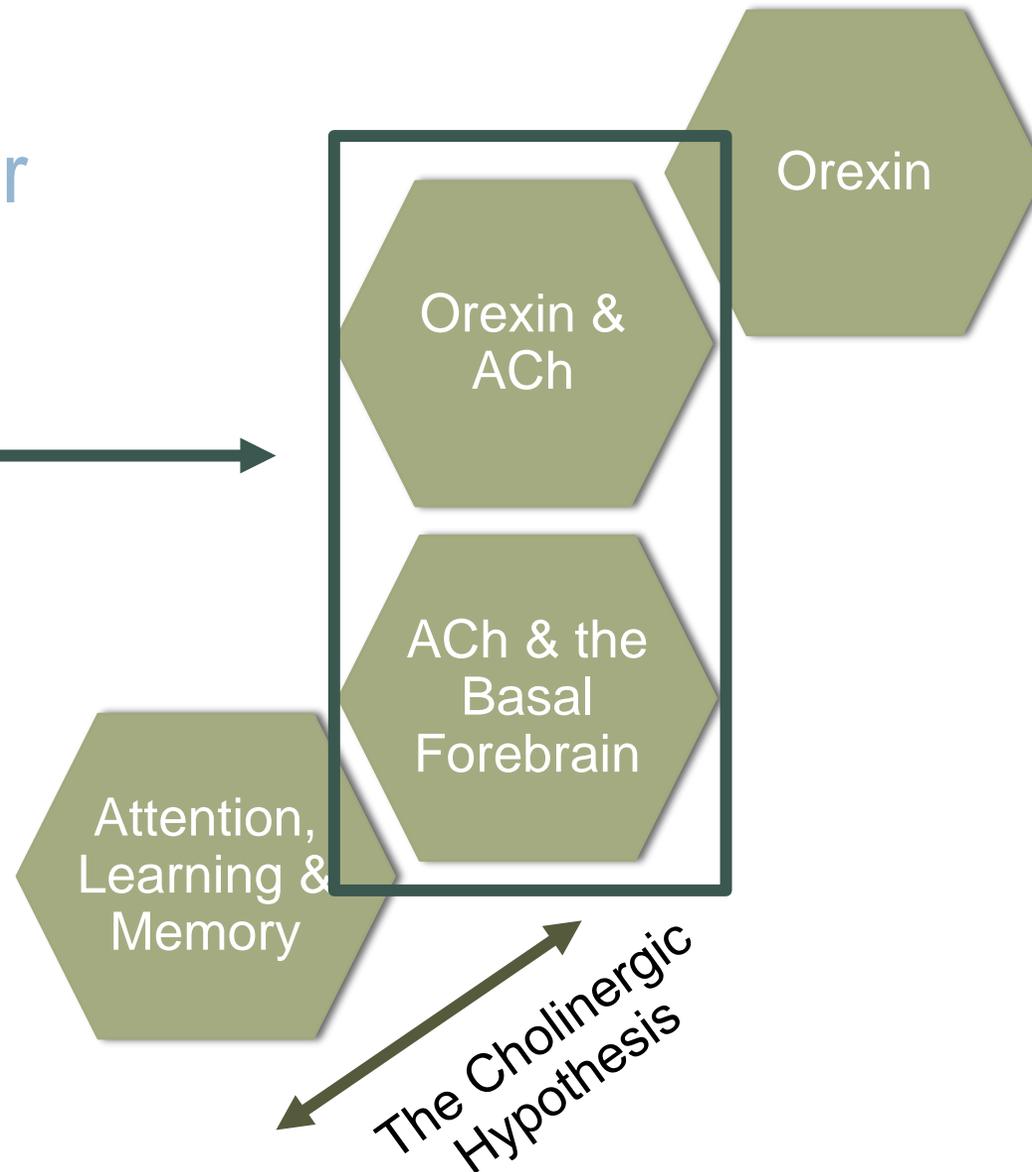
The Orexins

- **Class of neuropeptide** (Sakurai et al., 1998)
- **Involved in feeding and sleep**
(Sakurai et al., 1998; Smart & Jerman, 2002)
- **Receptors located in the Basal Forebrain** (Liu et al., 2015; Marcus et al., 2001)
- **Modulator of ACh** (Fadel et al., 2005)

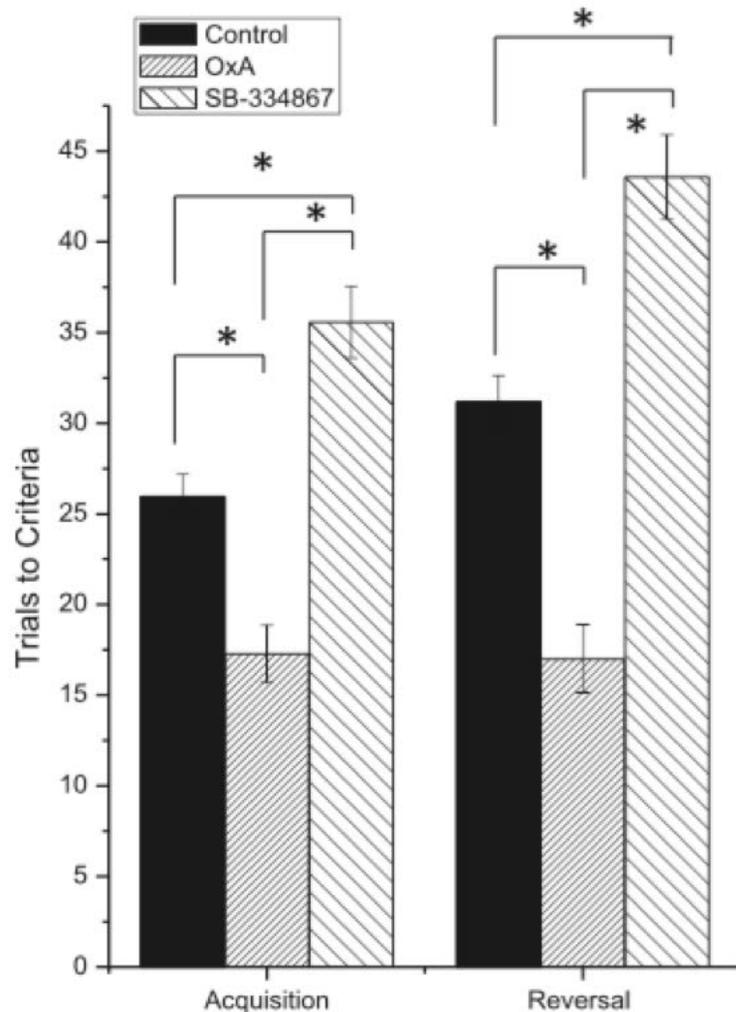


Putting it all together

Next Steps



Piantadosi, P. T., Holmes, A., Roberts, B. M., & Bailey, A. M. (2015)



- Olfactory reversal discrimination task
- Reversal of rule
 - Trials to criteria
 - Antagonist > control

Hypotheses

	Rule	Prediction
h_1	Trials to Set	Control = Antagonist
	Trials to Shift	Control < Antagonist
h_2	Errors to Set	Control = Antagonist
	Errors to Shift	Control < Antagonist

Methods: Subjects

- 9 male Sprague-Dawley rats
- 56 PND upon arrival

Control	Antagonist
n = 3	n = 6



Methods: Pretraining



Phase 1

- FR-1 schedule of reinforcement
- Both levers extended
- House light + cue lights illuminated
- *Criteria: 50 consecutive presses 2 days in a row*

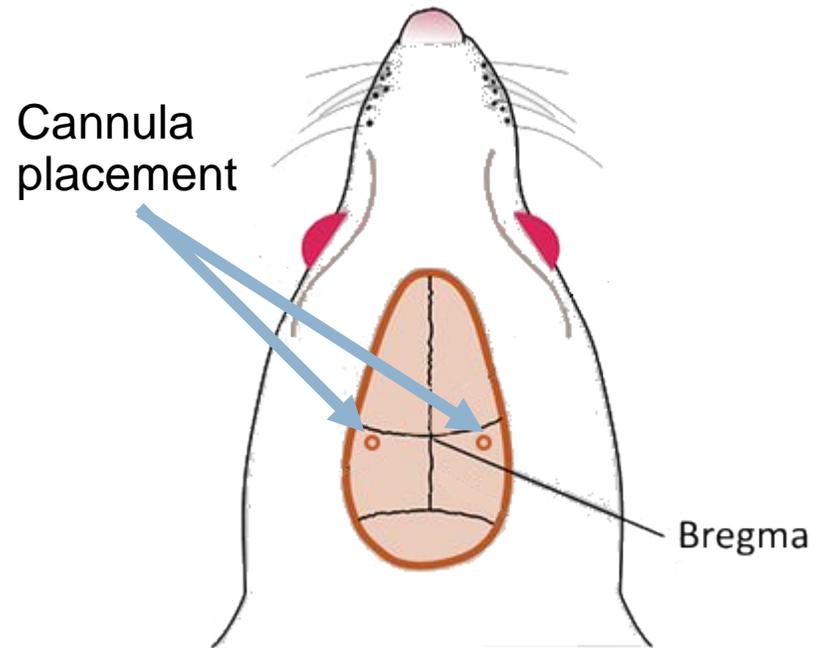
Phase 2

- FR-1 schedule of reinforcement
- Light cue + lever extension paired, alternating sides
- *Criteria: ≥ 5 omissions 2 days in a row*

Side Bias

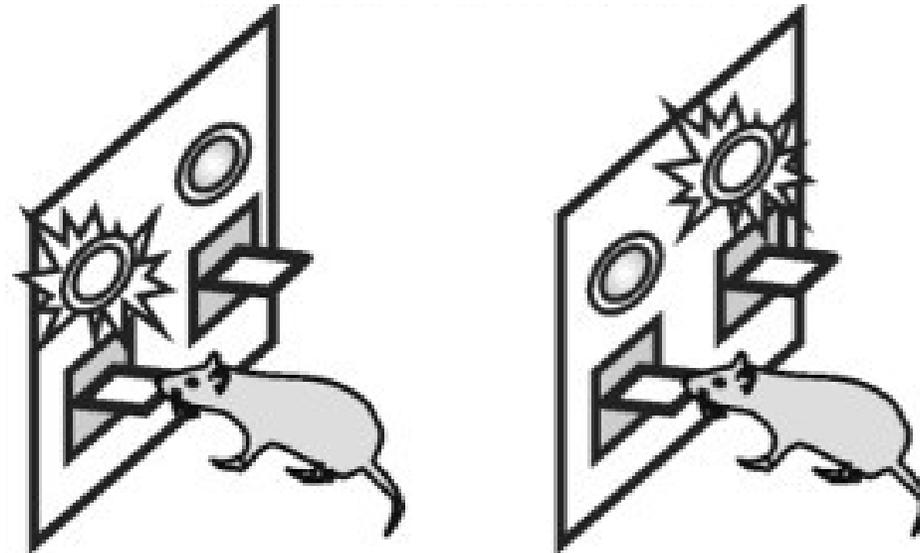
- Both levers extended
- Side preference by left or right lever pressed first most often

Methods: Cannulation



- Stereotaxic surgery
 - nbM bilateral guide cannula
 - Coordinates
 - AP = -0.92 mm
 - M/L = ± 3.8 mm
 - DV = -0.92 mm

Methods: Set



Rule: Always press **LEFT** lever
Ignore visual cue

Figure reproduced with permission
(Brady & Floresco, 2015)

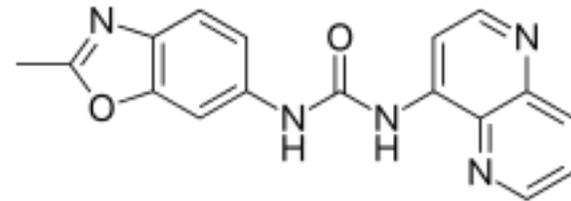
Methods: Infusion

control

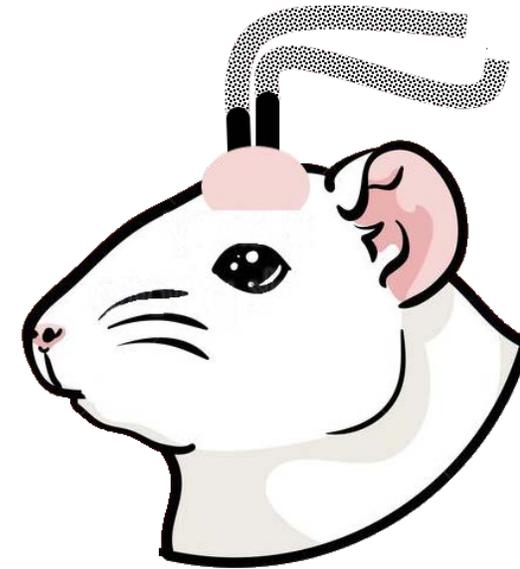
aCSF



n = 3

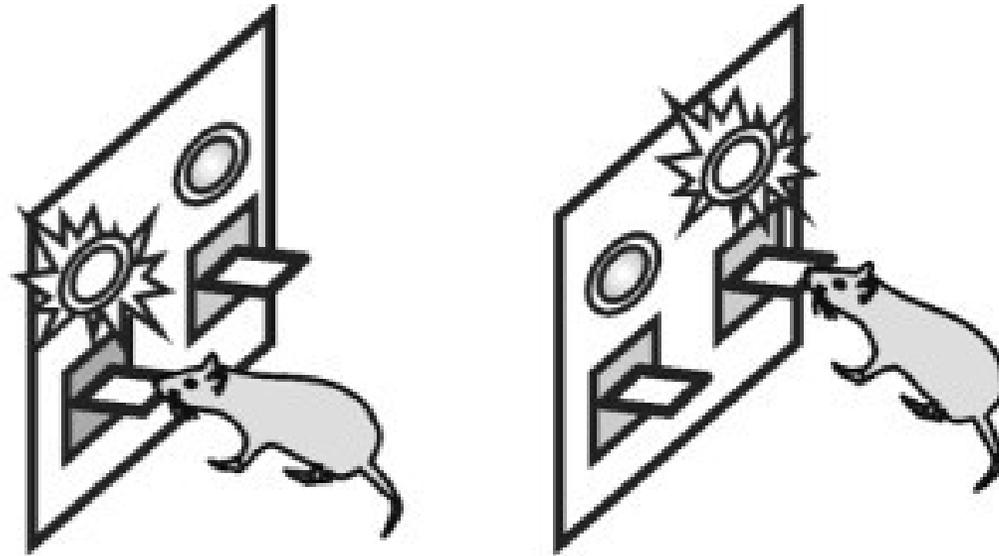


Orexin antagonist: SB-334867



n = 6

Methods: Shift



Rule: Always press lever with CUE light above it

Results: Trials to Criteria

- No significant main effects
 - time
 $F(1,7) = .480, p = .511, \eta^2 = .084$
 - drug
 $F(1,7) = .300, p = .601, \eta^2 = .041$
- No group x time interaction
 $F(1,7) = .148, p = .712, \eta^2 = .021$
- Between-group difference during shift not significant, $t(7) = .640, p > .05, \eta^2 = .055$

■ Control

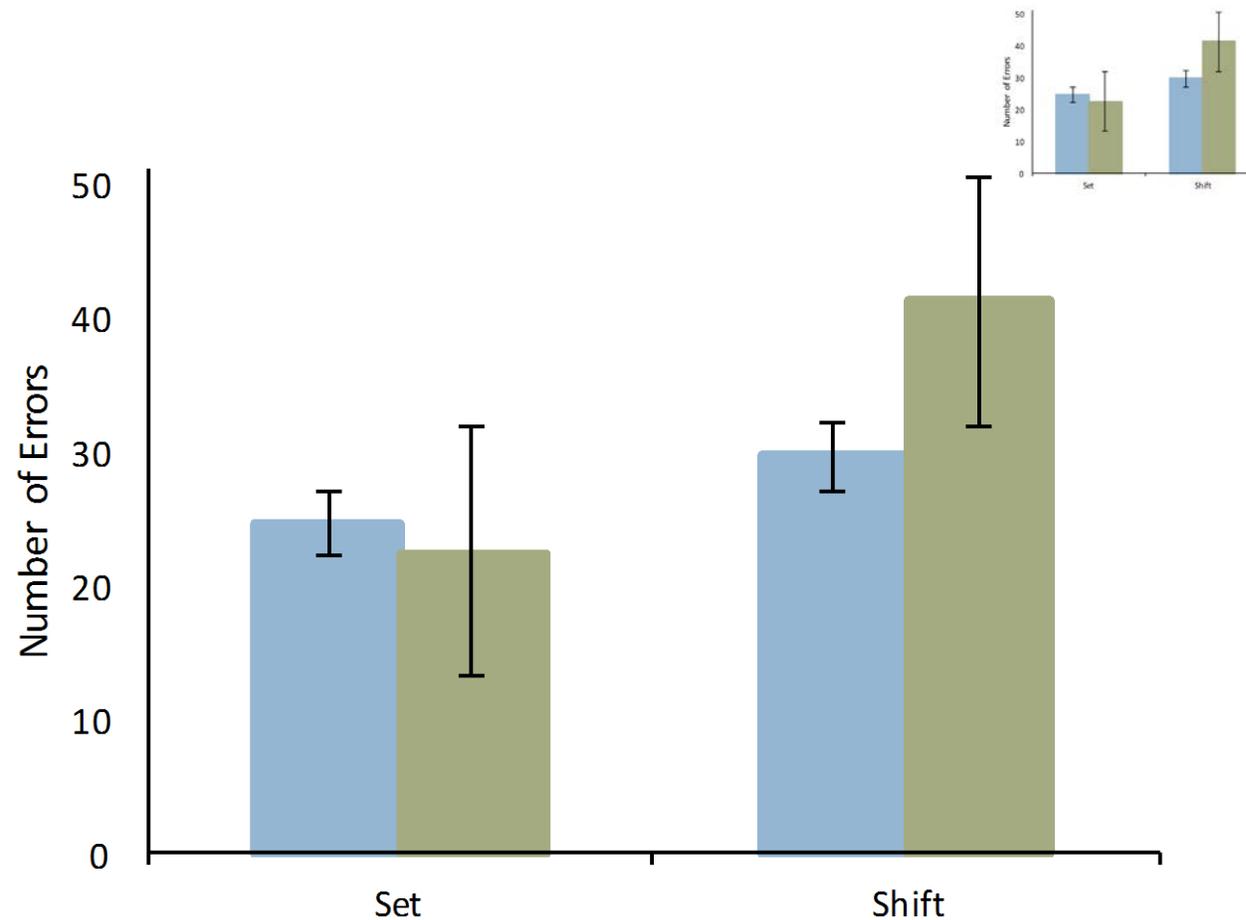
■ Antagonist

■ Control

■ Antagonist

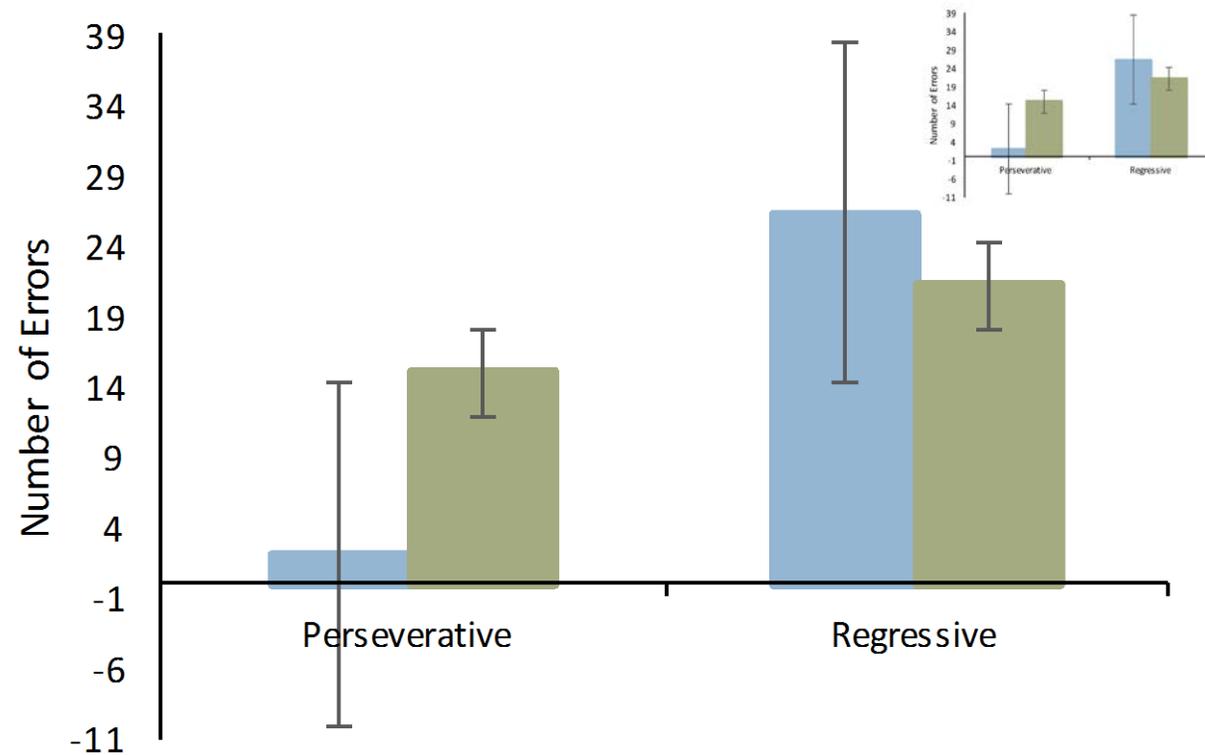
Results: Errors to Criteria

- No significant main effects
 - time
 $F(1,7) = .660, p = .443, \eta^2 = .086$
 - drug
 $F(1,7) = .216, p = .656, \eta^2 = .030$
- No group x time interaction
 $F(1,7) = .220, p = .653, \eta^2 = .030$



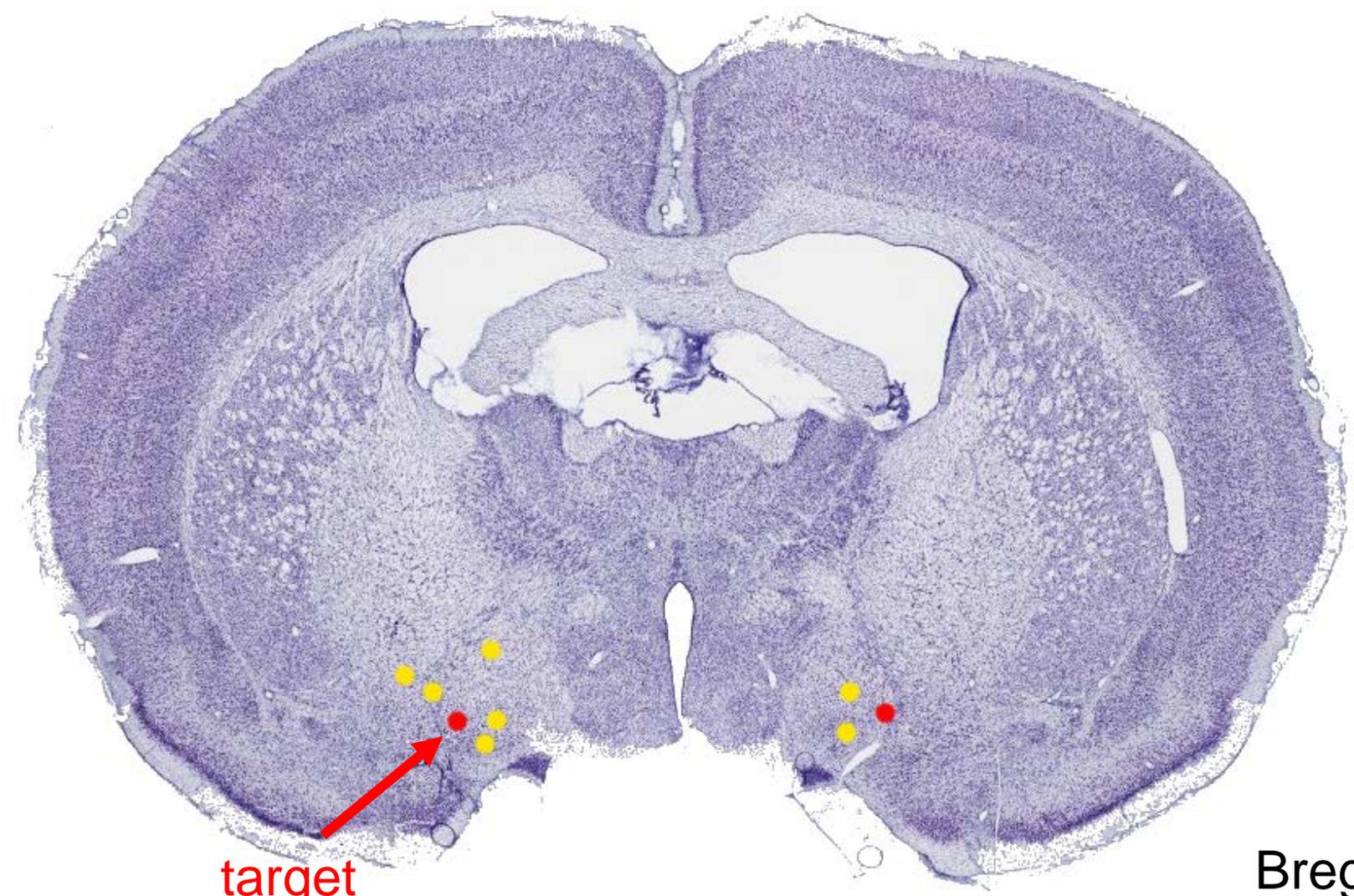
Results: Types of Errors

- No significant main effect
 - error type
 $F(1,7) = 1.401, p = .275, \eta^2 = .167$
 - drug
 $F(1,7) = .116, p = .744, \eta^2 = .016$
- No group x error type interaction
 $F(1,7) = .497, p = .504, \eta^2 = .066$
- Control rats made less perseverative errors than antagonist group





Results: Histology



target

Bregma: -0.92 mm

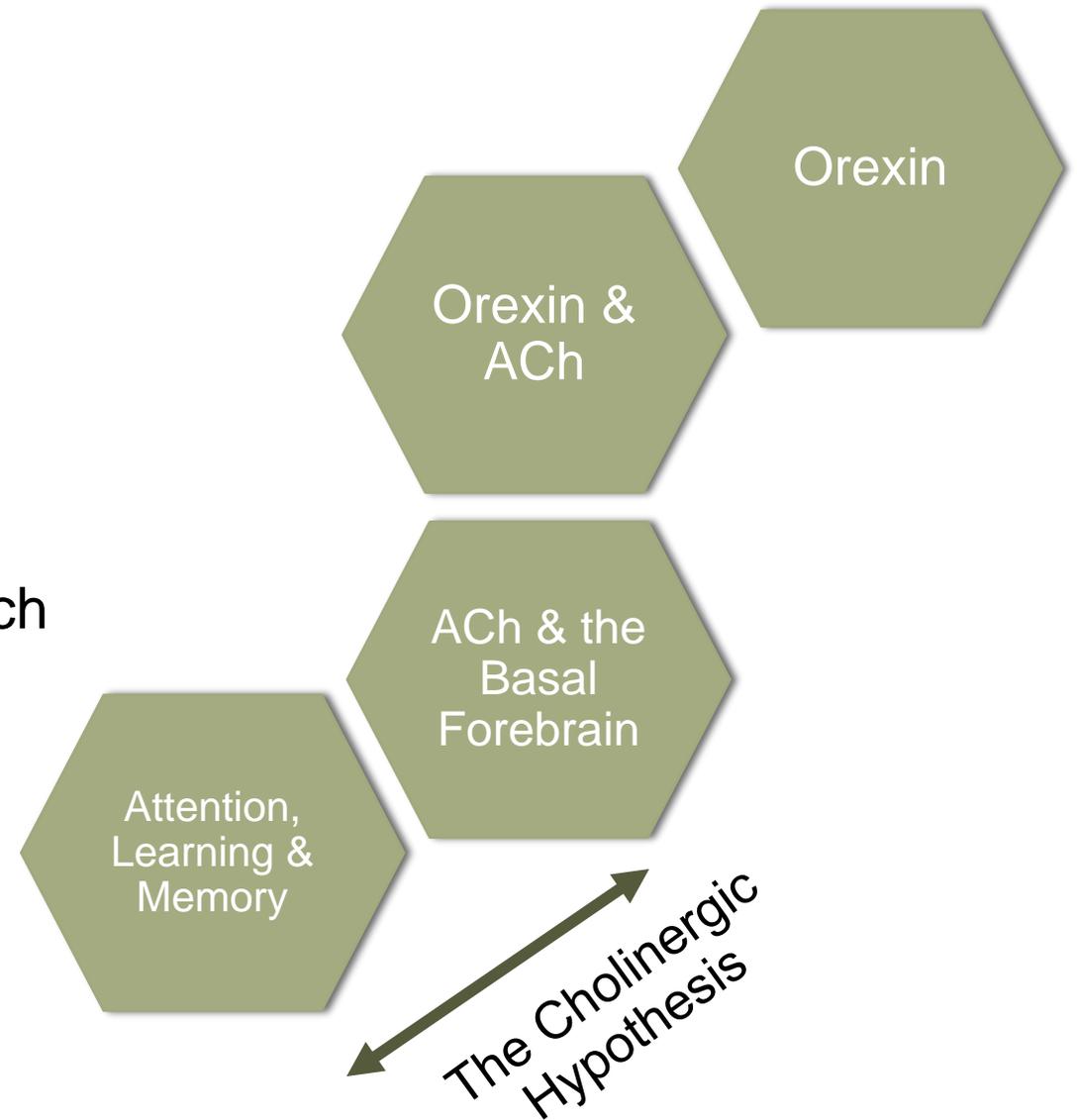
Discussion: SB-334867 and Performance

- No group differences were found
- Trends in performance align with hypotheses
 - Trials to Shift: **Control < Antagonist**
 - Errors to Shift: Control < Antagonist
 - Antagonist group made more perseverative errors

	Rule	Prediction
h₁	Trials to Set	Control = Antagonist
	Trials to Shift	Control < Antagonist
h₂	Errors to Set	Control = Antagonist
	Errors to Shift	Control < Antagonist

Discussion: Implications

- Patterns in performance (and errors) mimics that of previous research
 - Piantadosi et al. (2015)
 - Cabrera et al. (2006)
- Patterns in performance (and errors) mimics the reversal of previous research
 - Fadel et al. (2005)
 - Zajo et al. (2016)
- ACh is implicated in cognitively-demanding tasks (Arnold et al., 2002)
- ACh is likely transmitted through the BFCS during performance of operant control tasks (Arnold et al., 2002)





Discussion: Limitations

- Inadequate sample size
- Histology
- Did not perform microdialysis
- Administration of a limited dose of SB-334867 only



Discussion: Future Directions

- More subjects!
- Comparison to administration of OxA agonist
- Microdialysis
- Different doses of SB-334867

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