UNIVERSITY of MARYLAND
SCHOOL OF MEDICINE

Prenatal Ethanol Exposure Induces Deficits in Cognitive Function in Adulthood; Improvement with Choline and Behavior Training

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No conflicts of interest to disclose

NIAAA NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM
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DEARC
Developmental Exposure Alcohol Research Center

Acknowledgements

Jaylyn Waddell, Ph.D.
Eric Ho
Devon Atkinson

Learning objectives:

- Understand one animal model of fetal alcohol syndrome
- Learn tests of executive function that can be used with rodents
- Recognize the potential for a combination of interventions to be more effective than either intervention alone

Cognitive Function

"Cognitive functions encompass reasoning, memory, attention, and language and lead directly to the attainment of information and, thus, knowledge."

http://www.cereboost.com/cognitive-function/

Executive function

"Cognitive processes… that are necessary for the cognitive control of behavior"
Wikipedia

Organization and Planning Skills - Tower of Hanoi
Attention - Test of Variables of Attention (TOVA)
Inhibitory Control - Stroop Color and Word Test
Word and Idea Generation - Controlled Oral Word Association Test
Concept Formation - Matrix Analogies Test

Working Memory - Digit Span and Spatial Span subtests of the Wechsler Intelligence Test for Children (WISC)
Set Shifting - Wisconsin Card Sorting Test
Cognitive Flexibility - Wisconsin Card Sorting Test, Stroop

https://www.understood.org/en/school-learning/evaluations/types-of-tests/tests-for-executive-functioning-issues

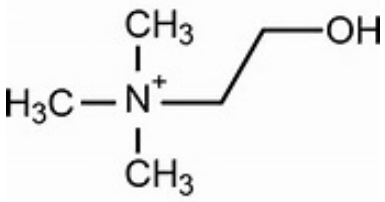
Executive function in rats

Working Memory – Delayed non-matching to place (T-maze)

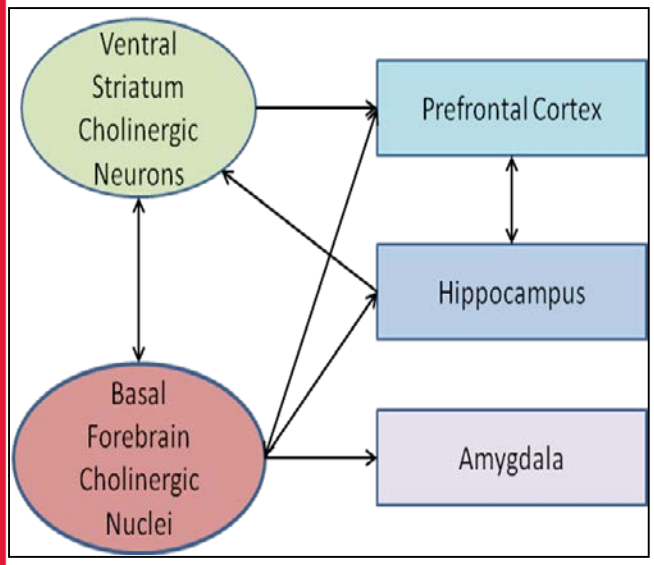
Set Shifting – Attentional Set Shifting task

Cognitive Flexibility – Reversal learning

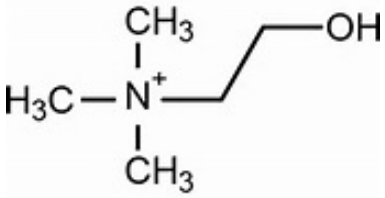
Choline



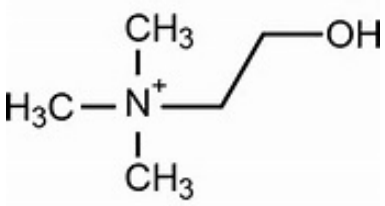
- Precursor for neurotransmitter acetylcholine
- Methyl donor – epigenetic regulation of gene expression
- Incorporated into membranes – phosphatidylcholine and sphingomyelin



Choline



- Rapid accumulation in late prenatal and early postnatal period
- Critical neurotransmitter in circuits underlying cognition
- Also needed during remodeling of prefrontal cortex

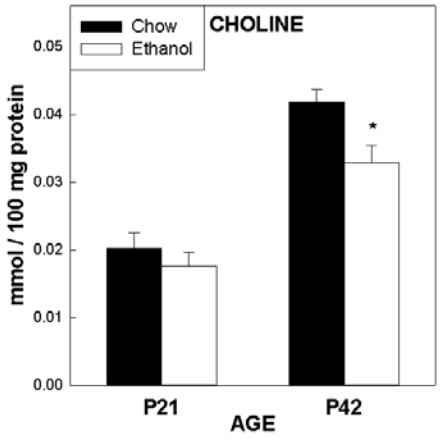


Choline

Choline may be depleted in alcohol-exposed brains

Choline can improve behavior outcomes in rat models of FASD (Thomas)

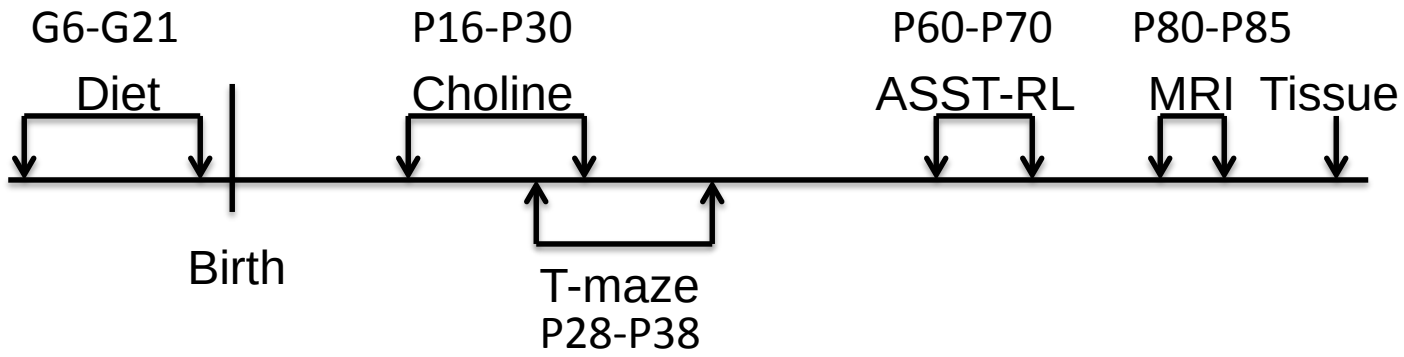
Data from human studies are less compelling



Does prenatal exposure to a relatively low dose of alcohol alter cognitive function?

Does choline improve cognitive function in adolescence?

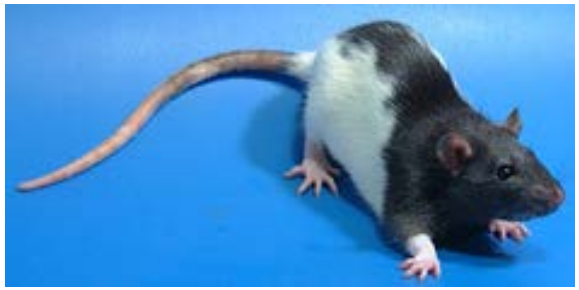
Does choline, behavior training, and/or the combination improve cognitive function in adulthood?

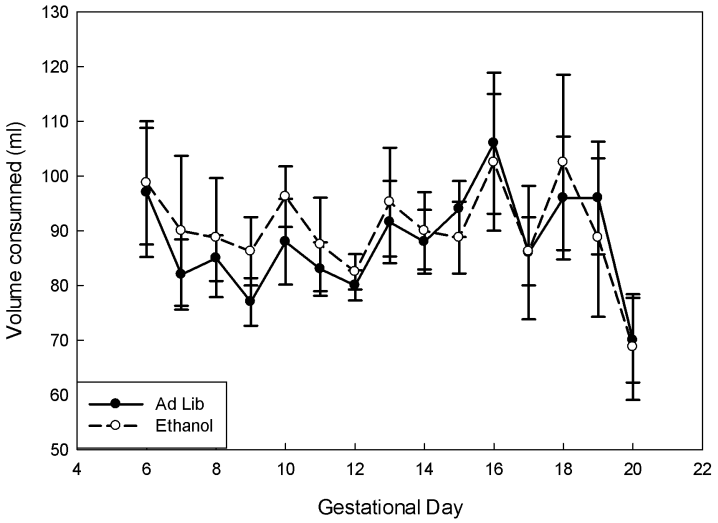


Long Evans rats

Diet – 3% ethanol or non-ethanol liquid diet (others show BECs ~30 mg/dl)

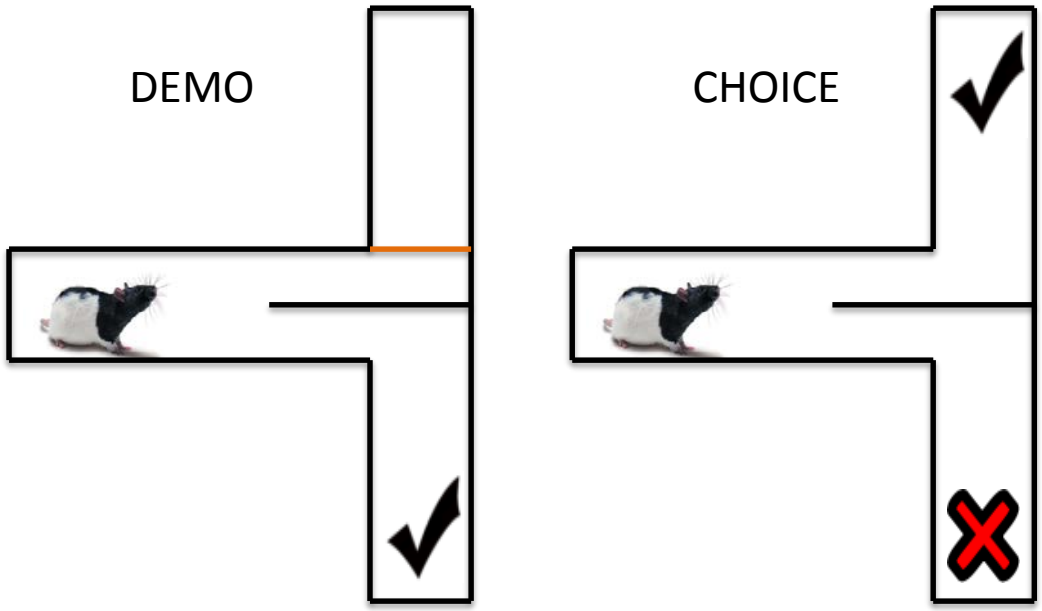
Choline - 100 mg/kg subcutaneously (or saline)

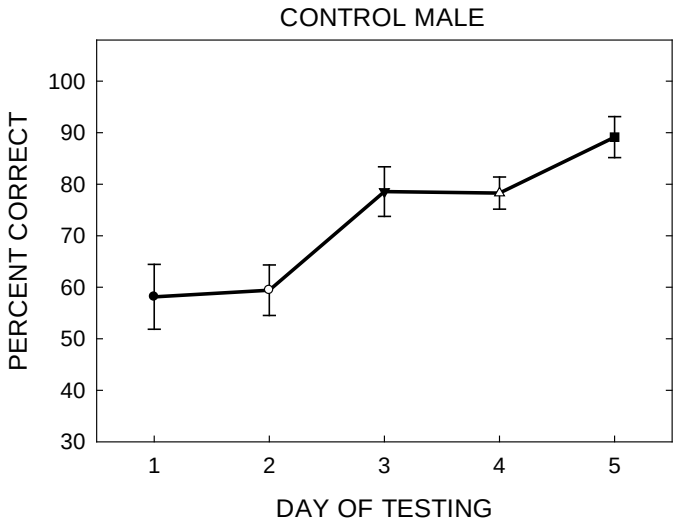




Working Memory

Delayed Non-matching to Place




CONTROL MALE
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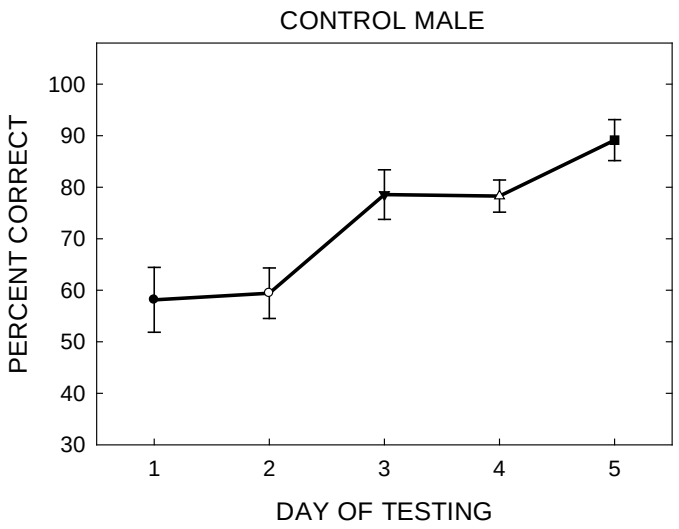
DAY OF TESTING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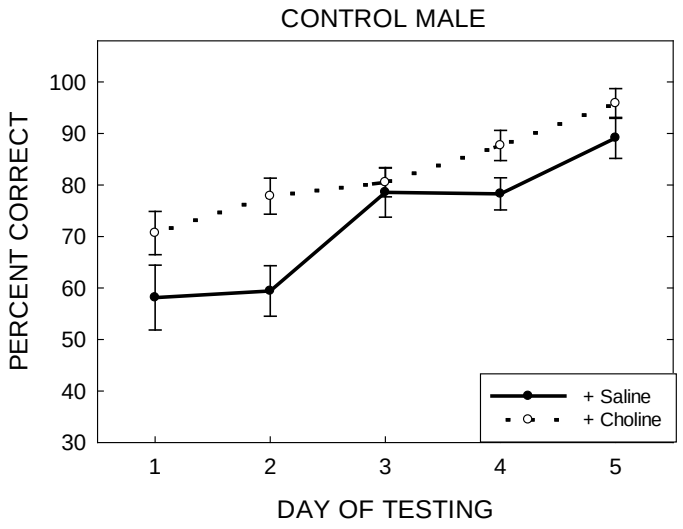
CONTROL MALE
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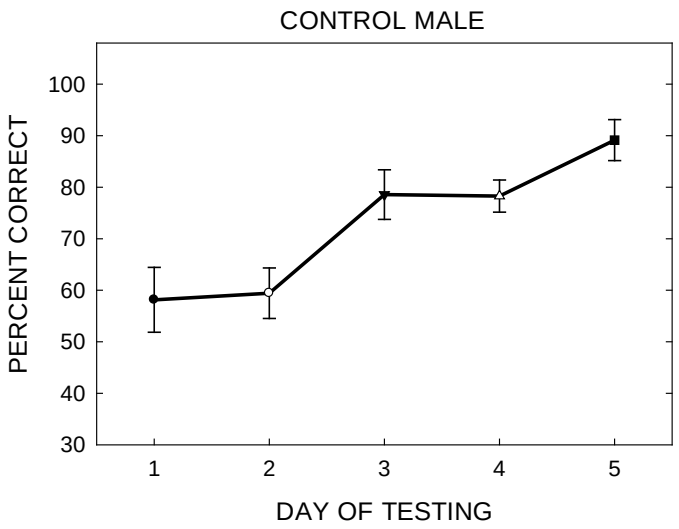
DAY OF TESTING
+ Saline
+ Choline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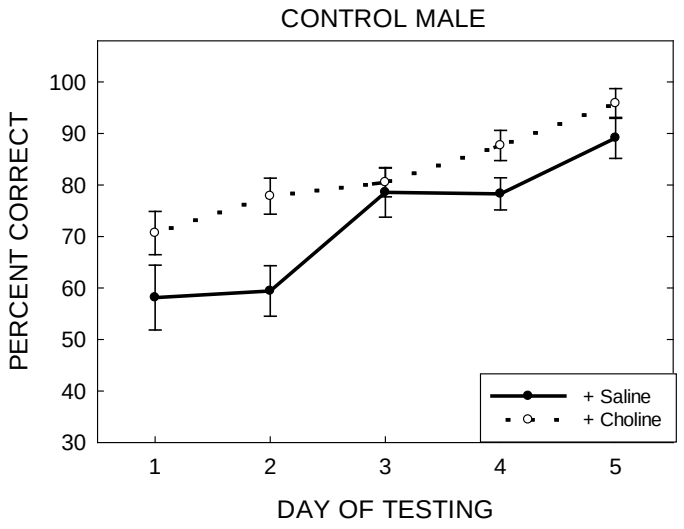
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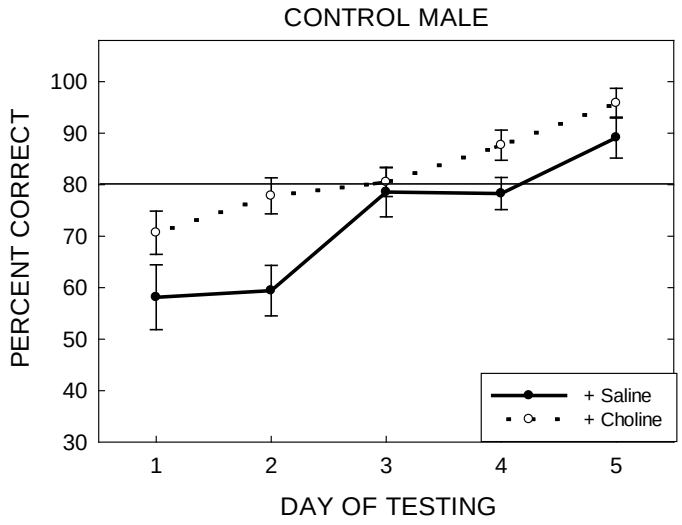
+ Saline
+ Choline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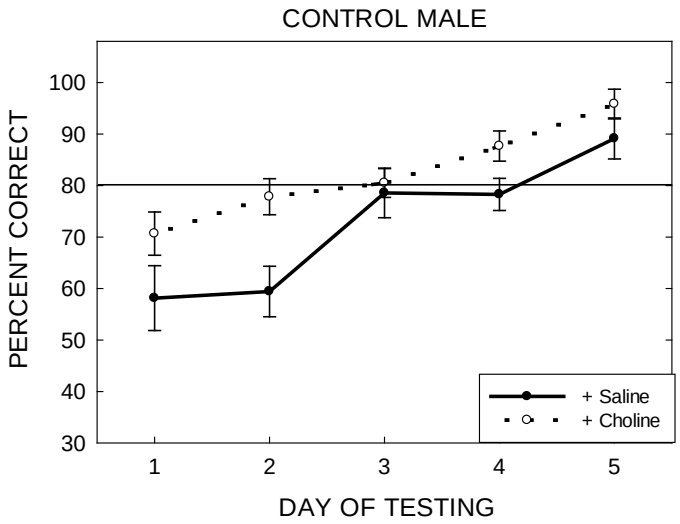
+ Saline
+ Choline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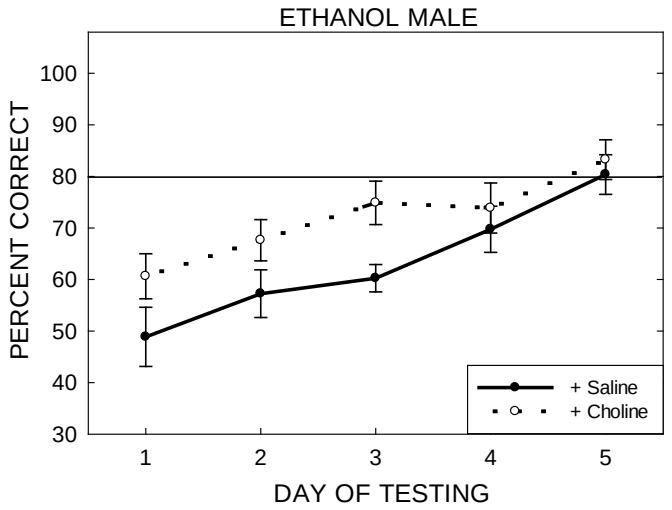
ETHANOL MALE
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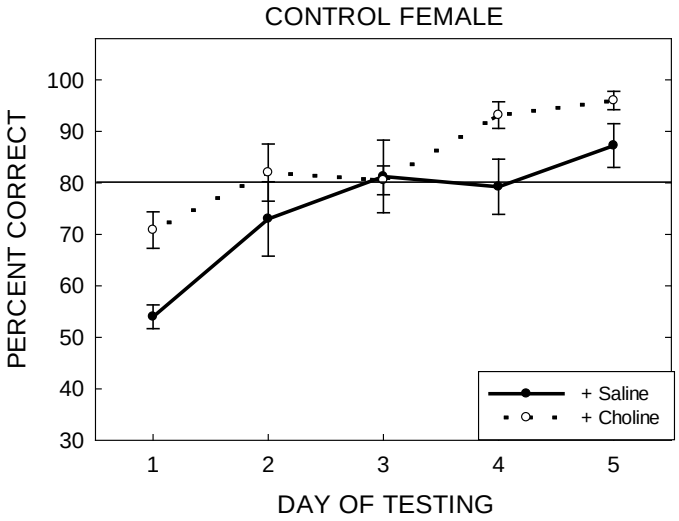
DAY OF TESTING
+ Saline
+ Choline


CONTROL FEMALE
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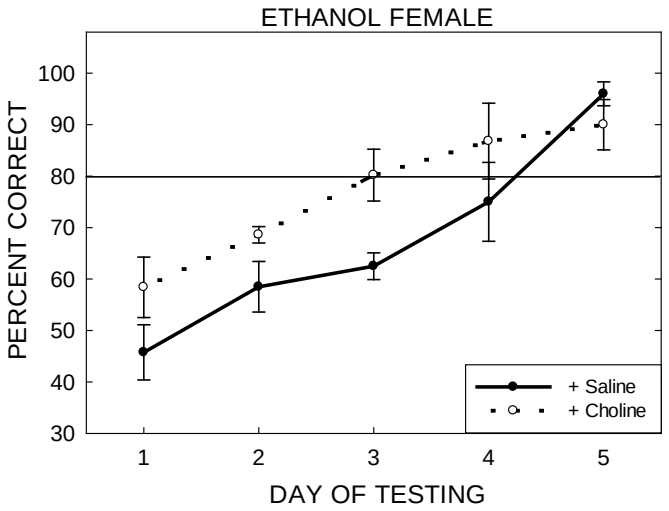
DAY OF TESTING
+ Saline
+ Choline


ETHANOL FEMALE
PERCENT CORRECT
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5
DAY OF TESTING
+ Saline
+ Choline

Cognitive Flexibility

Attentional Set Shifting & Reversal Learning

1 Simple

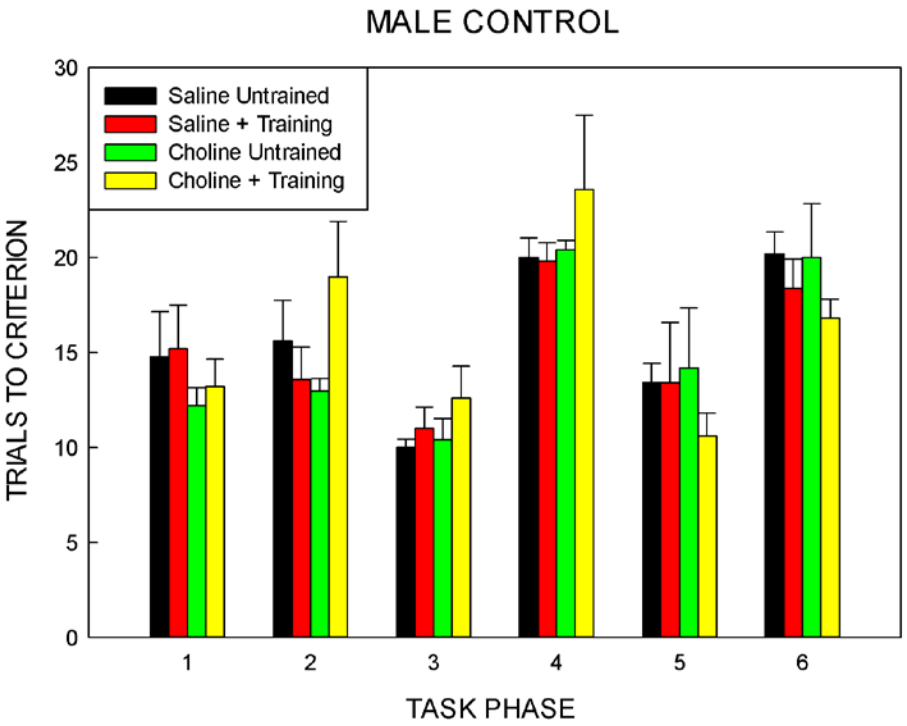
2 Compound

3 Intra-dimension shift

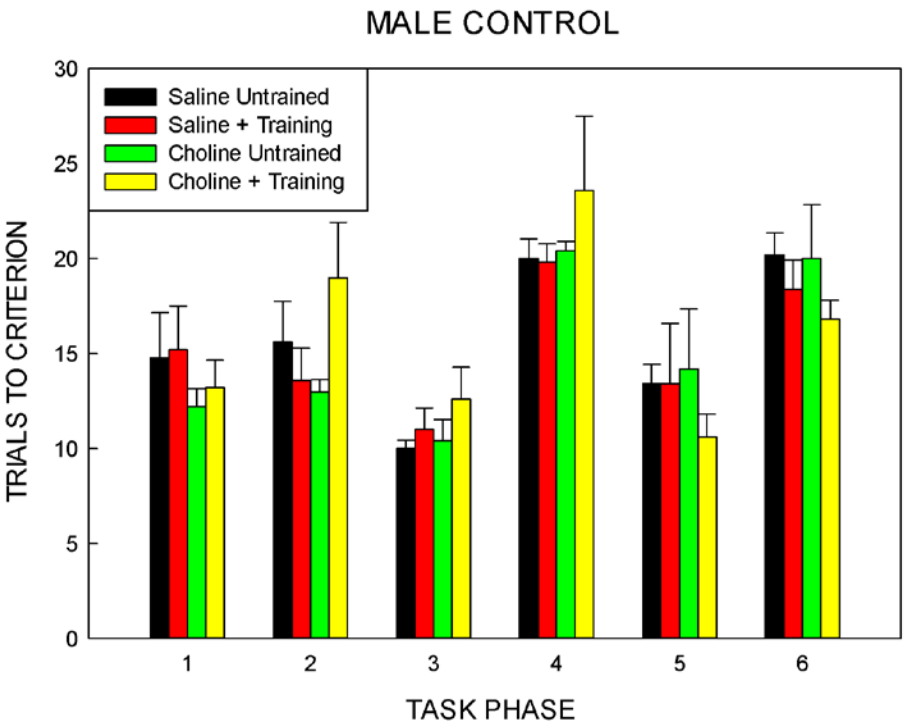
4 Reversal

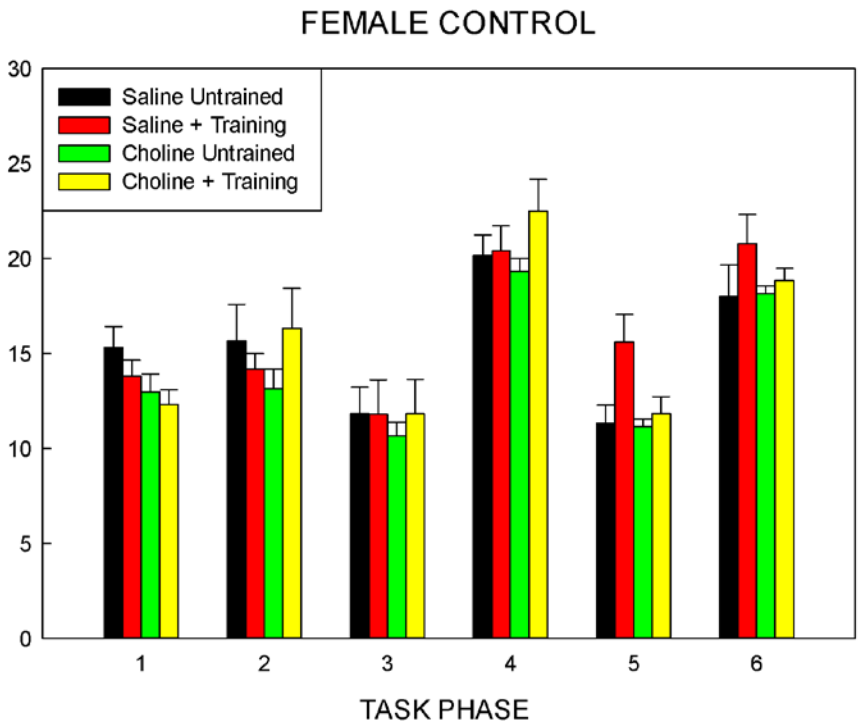
5 Intra-dimension shift

6 Extra-dimension shift



1. Simple
2. Compound
3. Intra-dimension shift
4. Reversal
5. Intra-dimension shift
6. Extra-dimension shift





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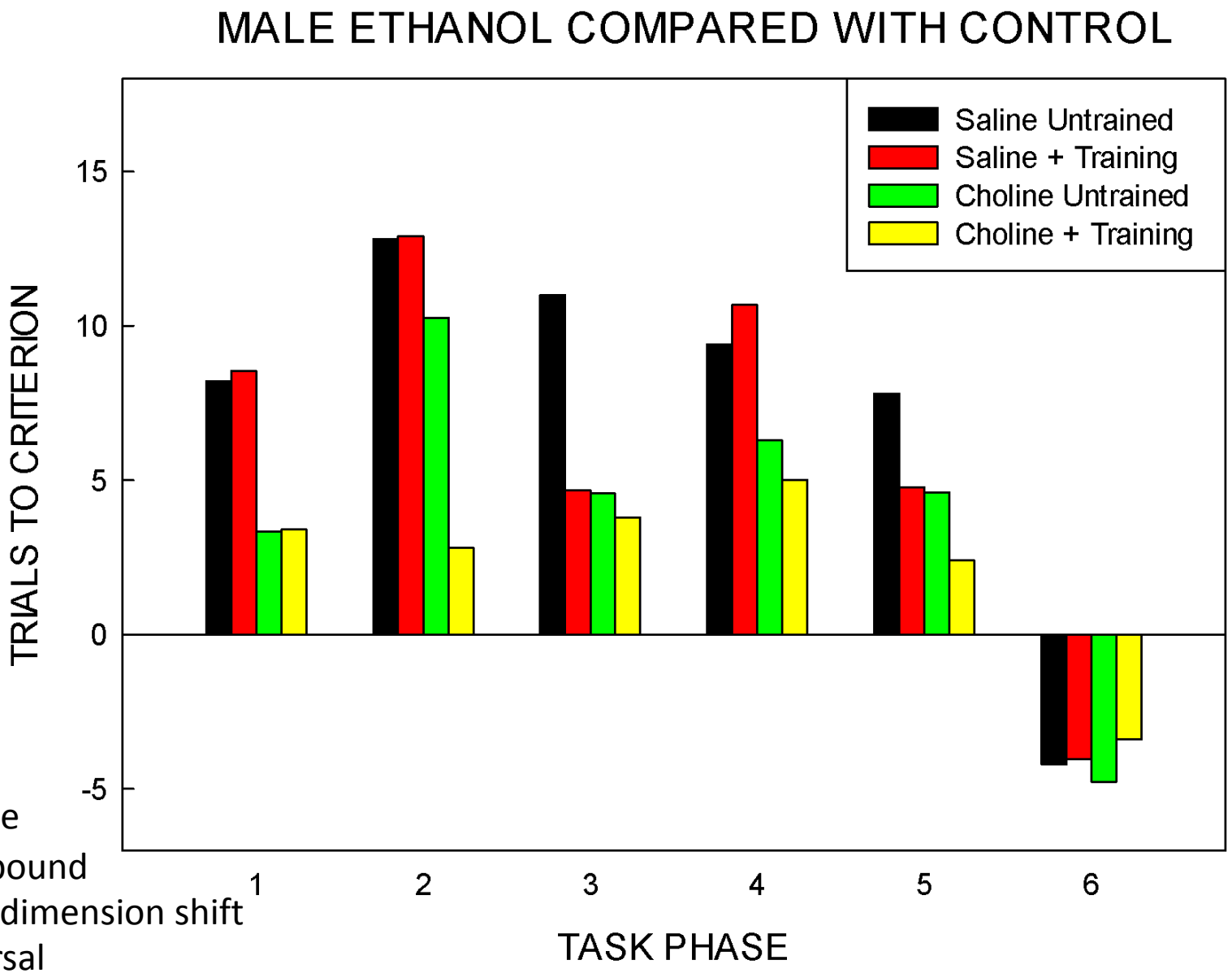
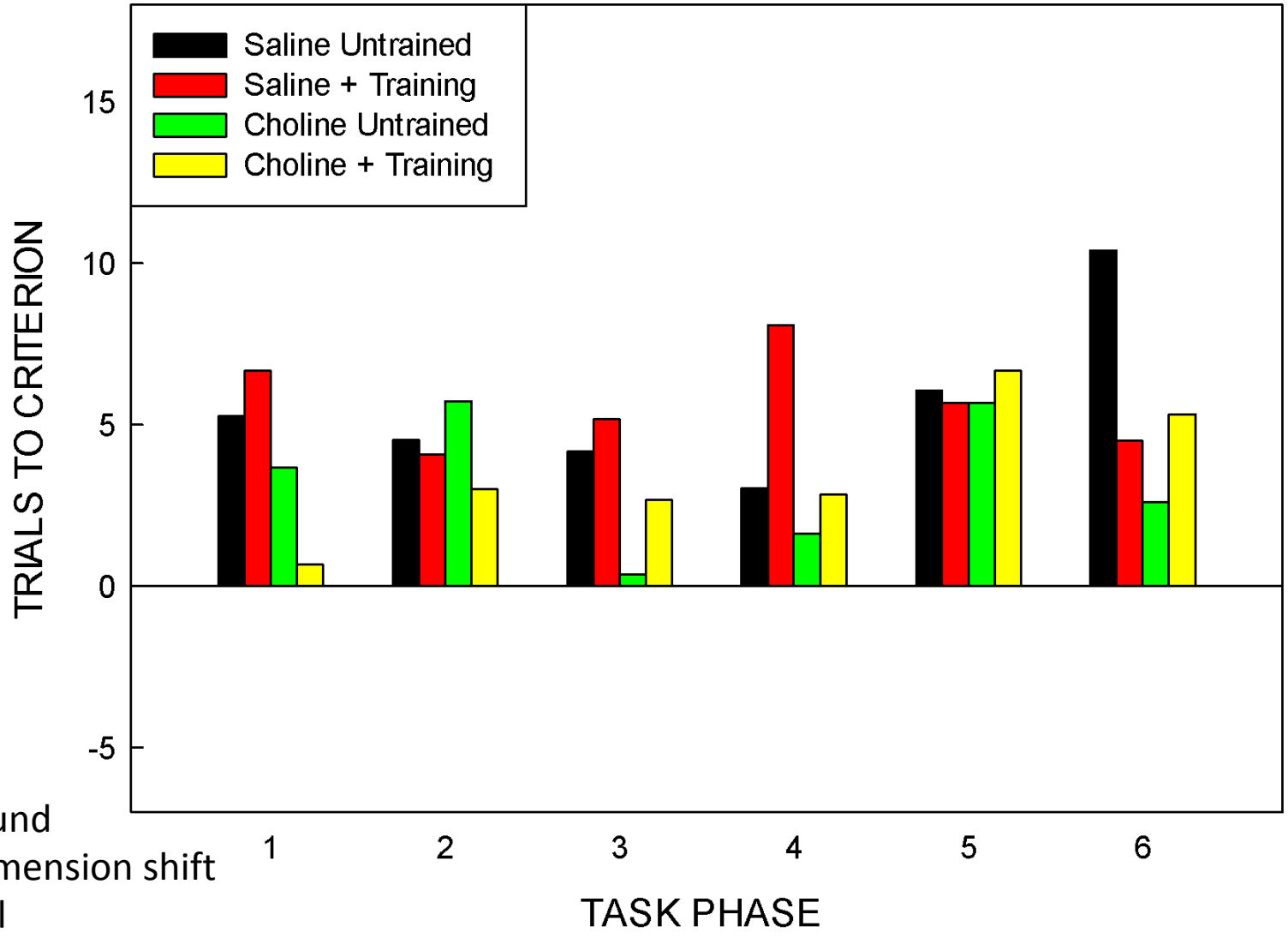


1. Simple
2. Compound
3. Intra-dimension shift
4. Reversal
5. Intra-dimension shift
6. Extra-dimension shift

FEMALE ETHANOL COMPARED WITH CONTROL



1. Simple
2. Compound
3. Intra-dimension shift
4. Reversal
5. Intra-dimension shift
6. Extra-dimension shift

Does prenatal exposure to a relatively low dose of alcohol alter cognitive function?

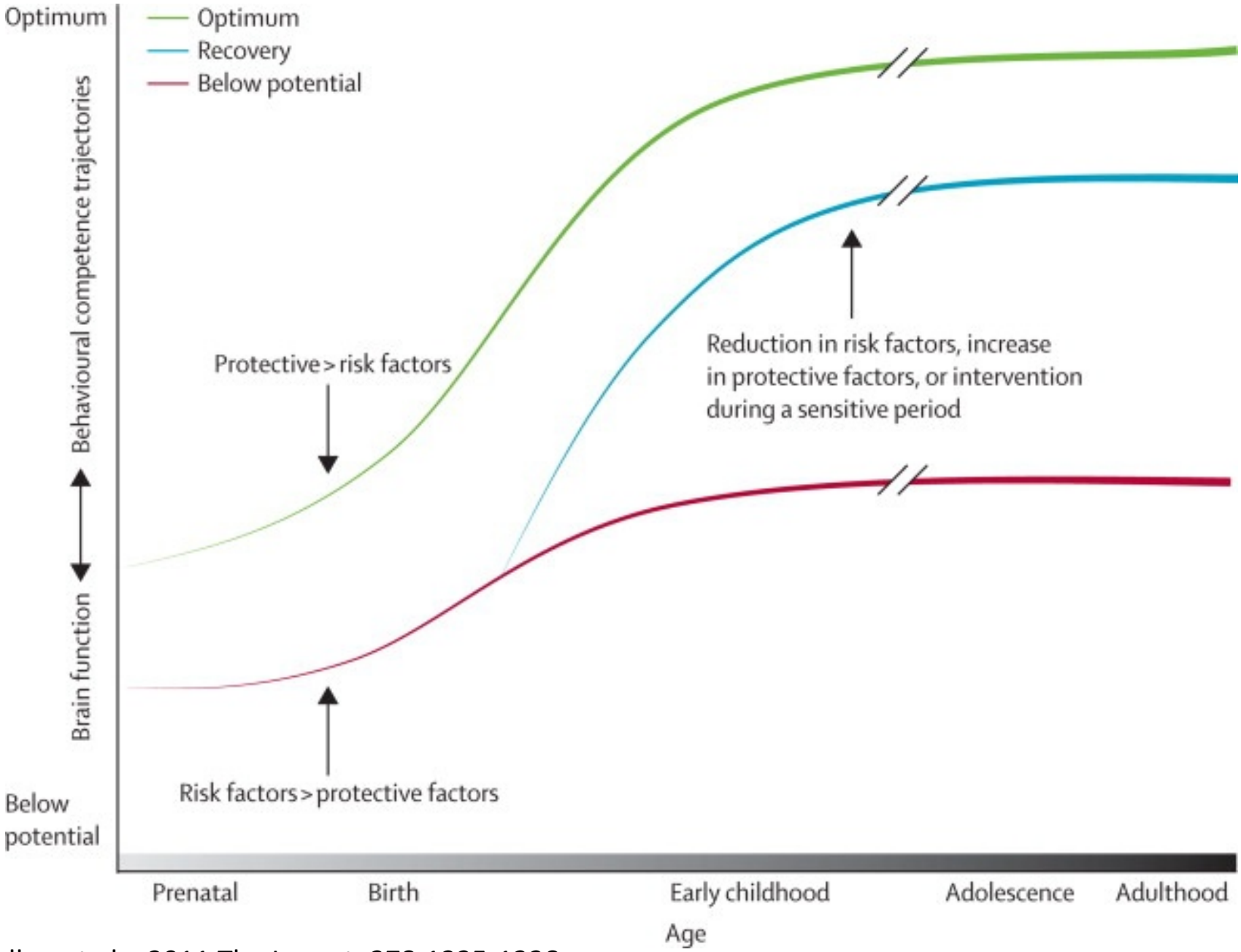
Yes. In adolescents and young adults.

Does choline improve cognitive function in adolescence?

Yes.

Does choline, behavior training, and/or the combination improve cognitive function in adulthood?

Yes – the combination is best (although not perfect).

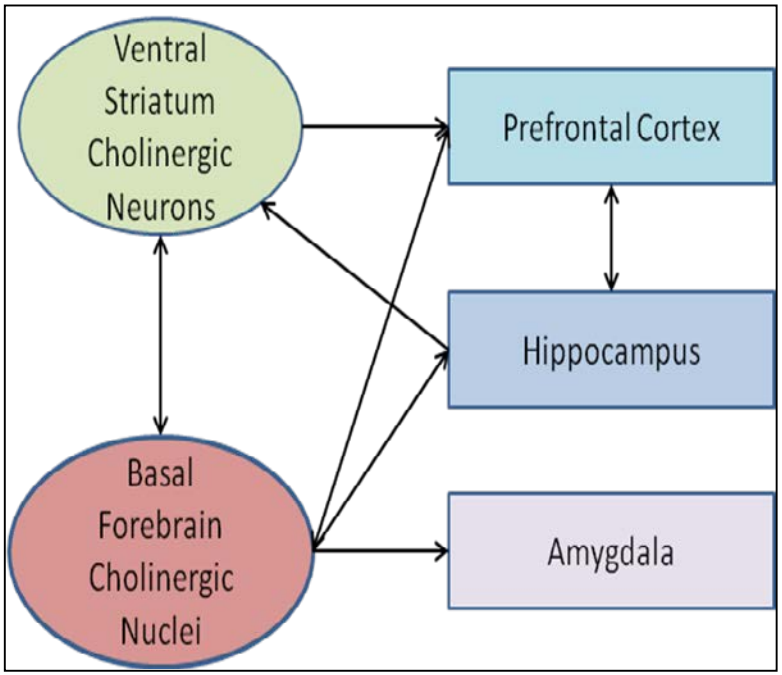


Walker et al., 2011 The Lancet. 378:1325-1338

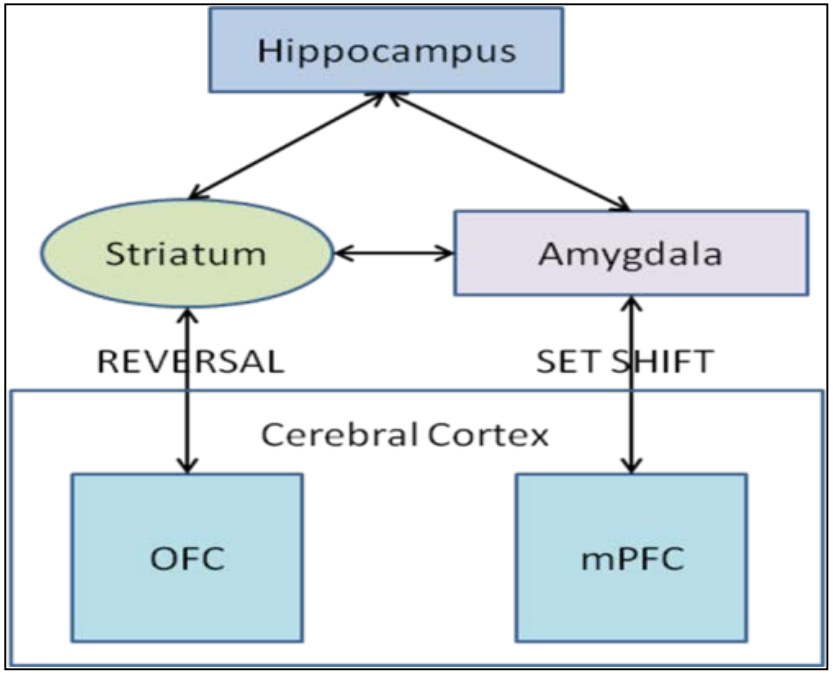
THANK YOU

Brain Regions of Interest

Cholinergic pathways in cognition

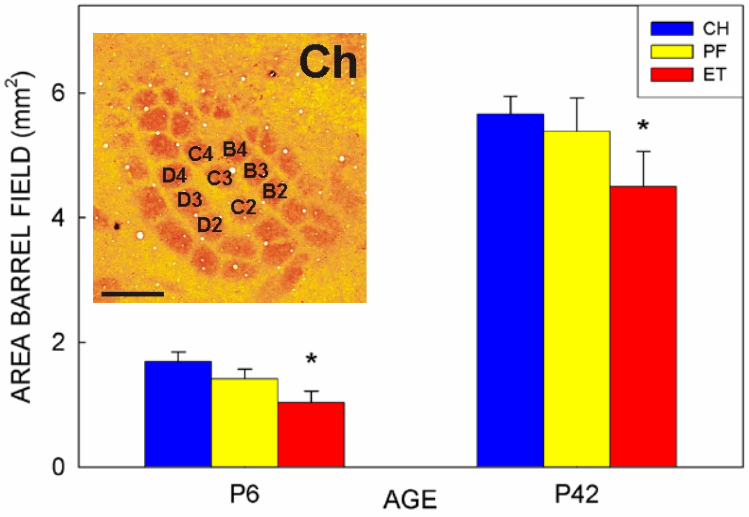


Simplified schematic of pathways involved in attentional set shifting and reversal learning.



OFC, orbitofrontal cortex. mPFC, medial prefrontal cortex.
Based on Bissonette and Powell, 2012.

Anatomy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P6
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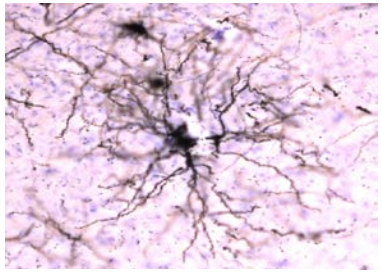
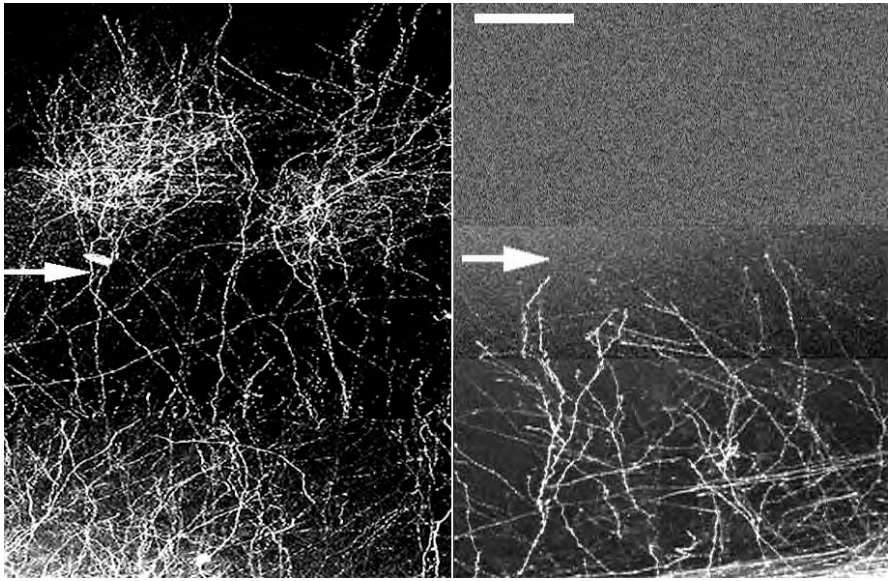
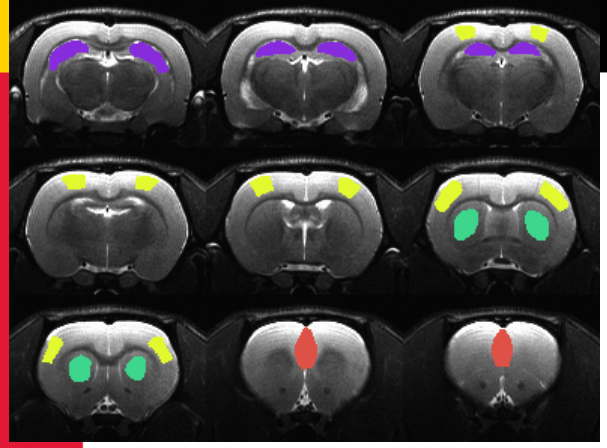
P42



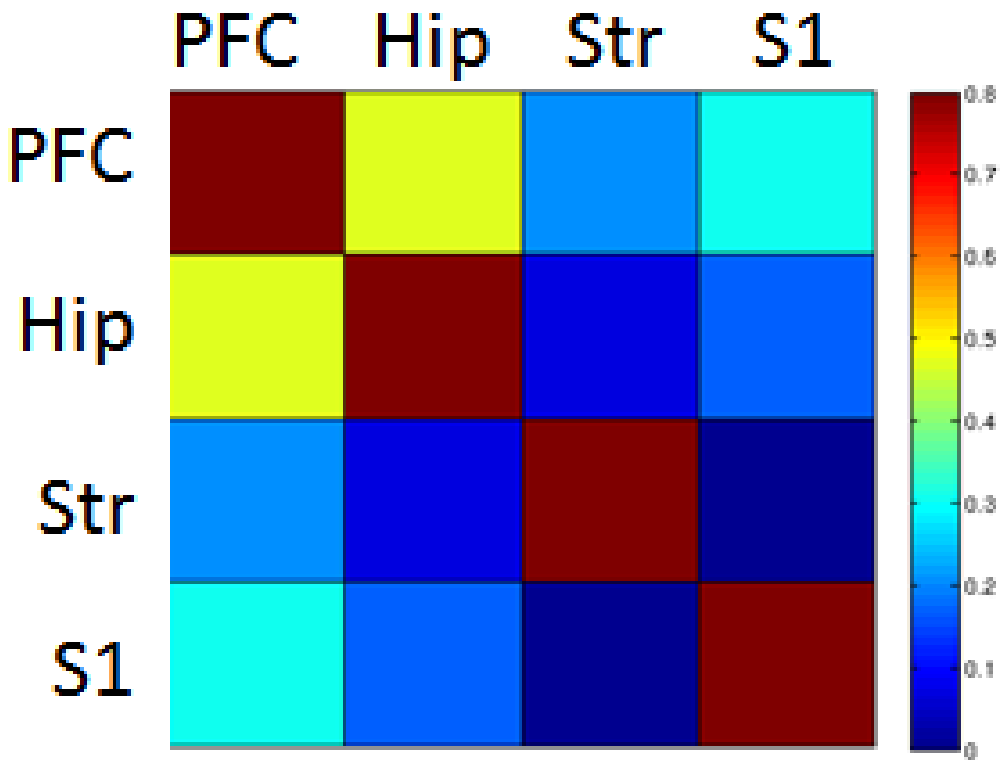




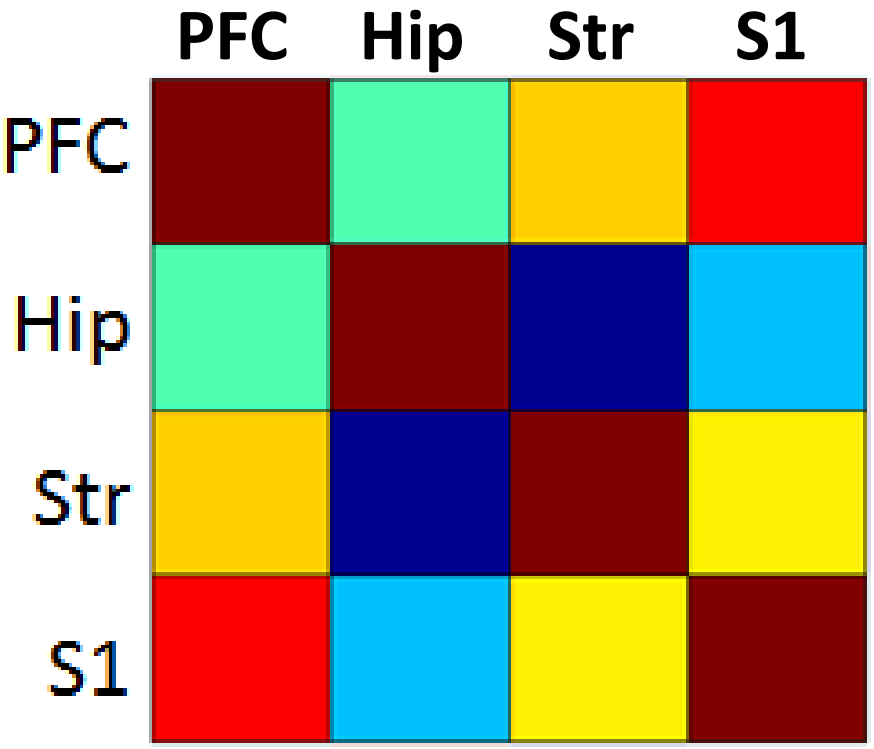
rsfMRI

[with Department of Diagnostic Radiology and Nuclear Medicine]

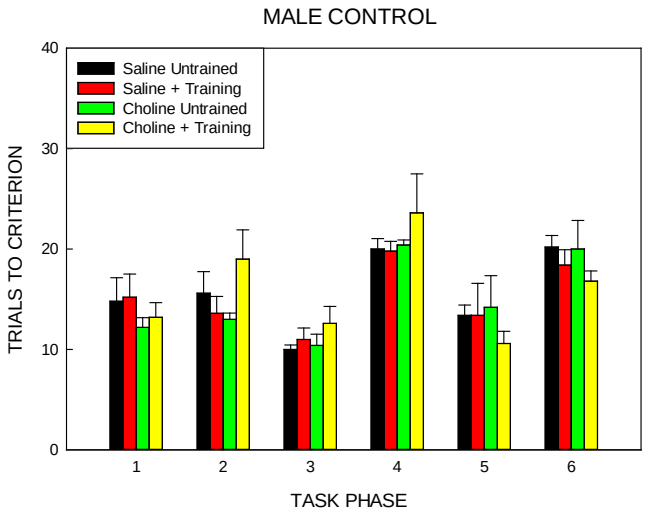
CONTROL

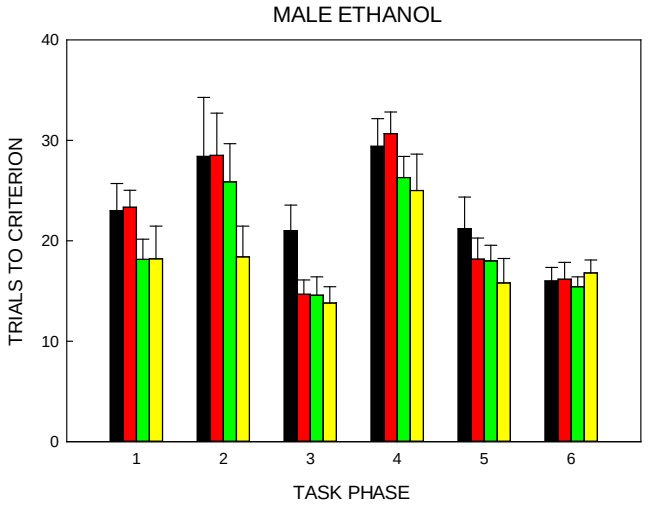


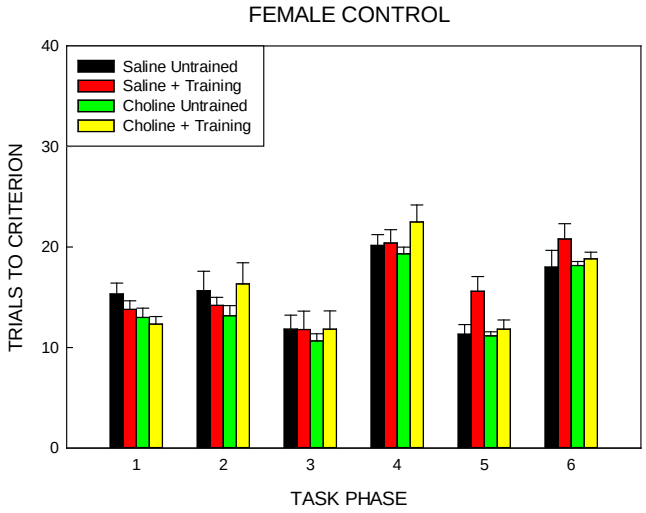
ETHANOL

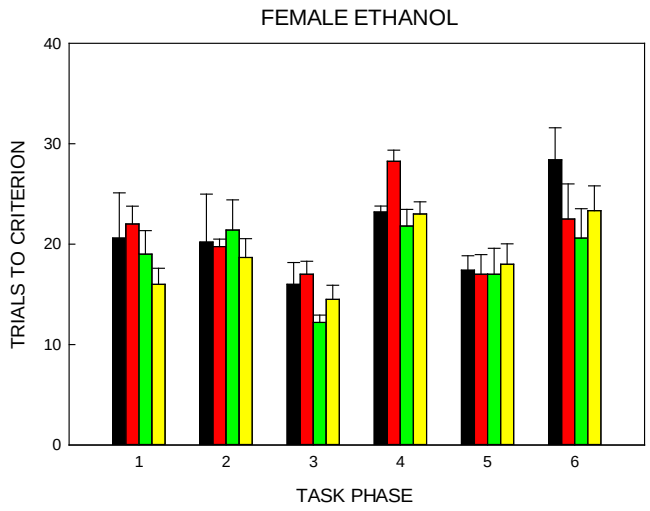


With Su Xu, Shiyu Tang, Marie Hanscom & Jaylyn Waddell









1. Simple
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4. Reversal
5. Intra-dimension shift
6. Extra-dimension shift