Prenatal Alcohol Exposure: The Role of Chemosensory Fetal Programming in Adolescent Alcohol and Nicotine Acceptance

Steven L. Youngentob, PhD
Department of Anatomy and Neurobiology
Department of Psychiatry
University of Tennessee Health Science Center
SUNY Developmental Alcohol Research Center

*The presenter has **no** affiliation (financial or otherwise) with any pharmaceutical, medical device or communications organization.*

Alcoholism Generator

Adapted from Miller & Spear (ACER, 2006)

Flavor Perception

odor

taste

oral irritation

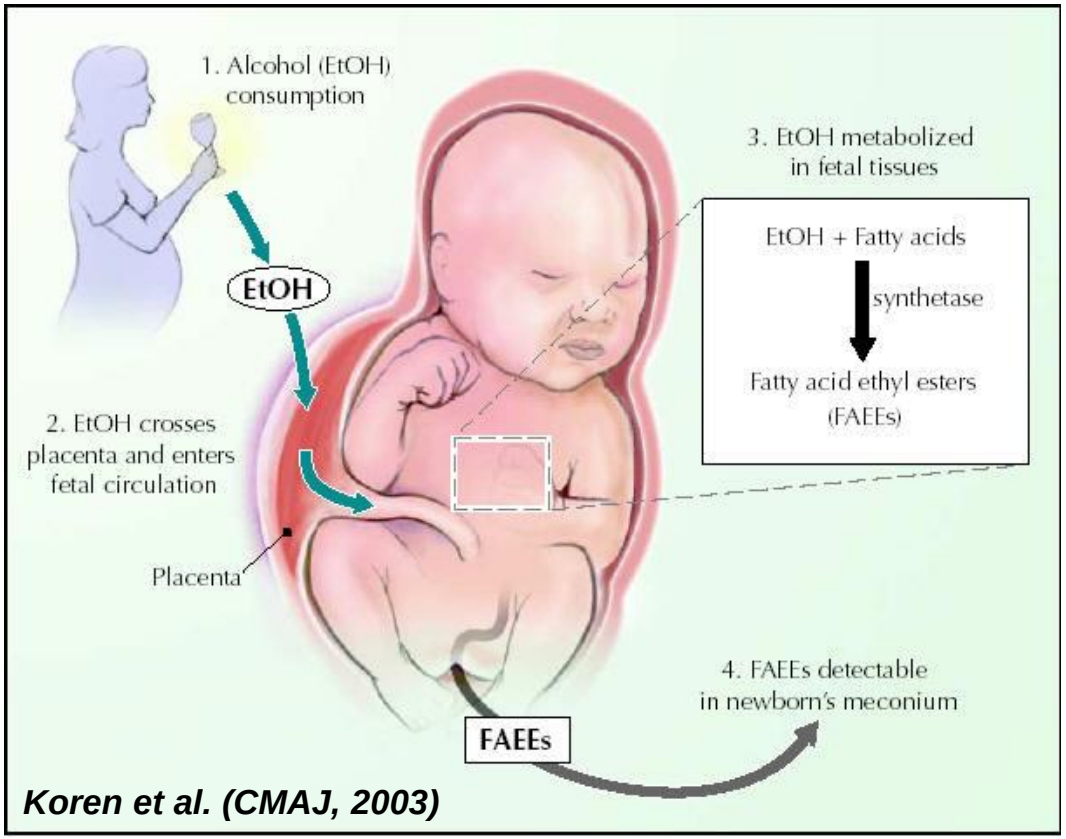
Fetal Programming

Mennella et al. (Pediatrics, 2004)

Fetal Programming

Dominguez et al. (Alcohol, 1998)

Fetal Alcohol Exposure



Koren et al. (CMAJ, 2003)

Overarching Hypotheses

* Fetal alcohol experience alters the developmental trajectory of one or more of the neural systems involved in the preference for alcohol odor and the perception and acceptability of alcohol's flavor.

* These changes are important contributors to the initial risk of intake and continued abuse in adolescence because "alcohol smells and tastes better".

Fetal Programming

Maternal Treatment

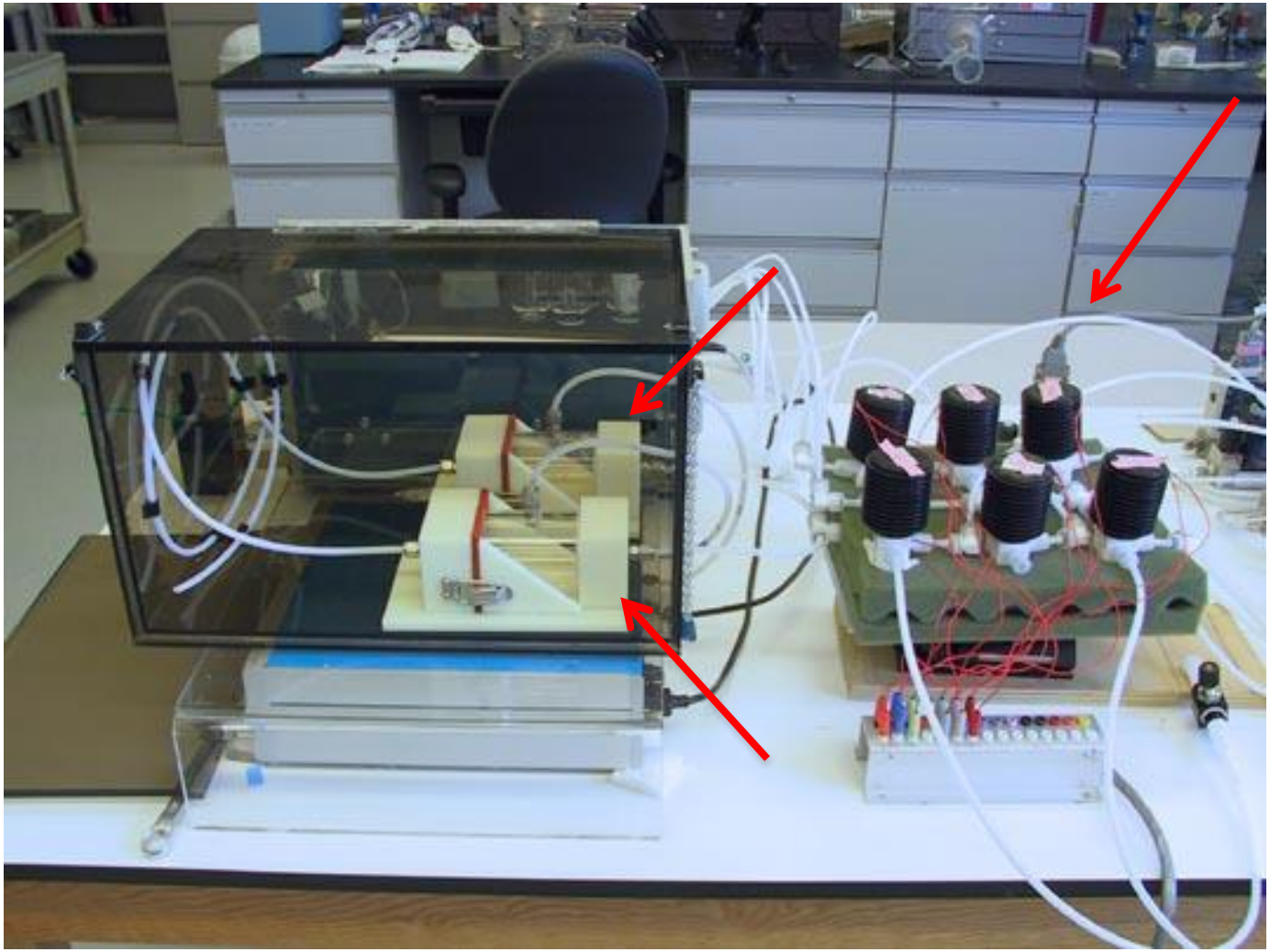
Ethanol ←

Pair-Fed ←

Free Choice ←

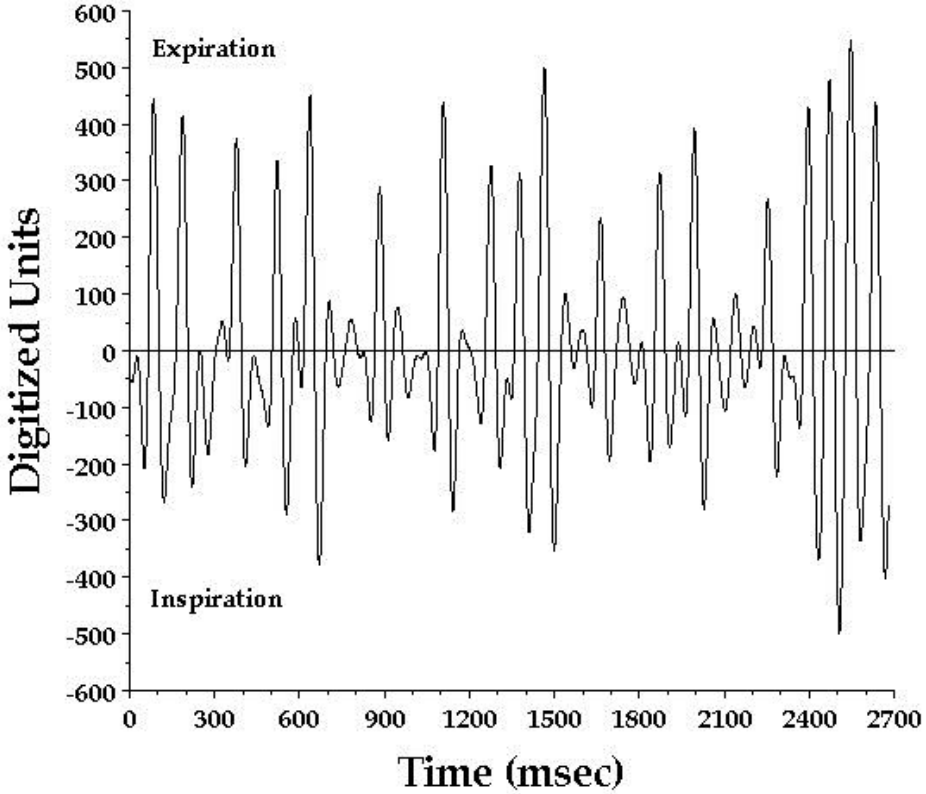
Youngentob et al. (Behav Neurosci, 2007a,b)

Innate Odor-Mediated Response



Youngentob (Chem Senses 2005)

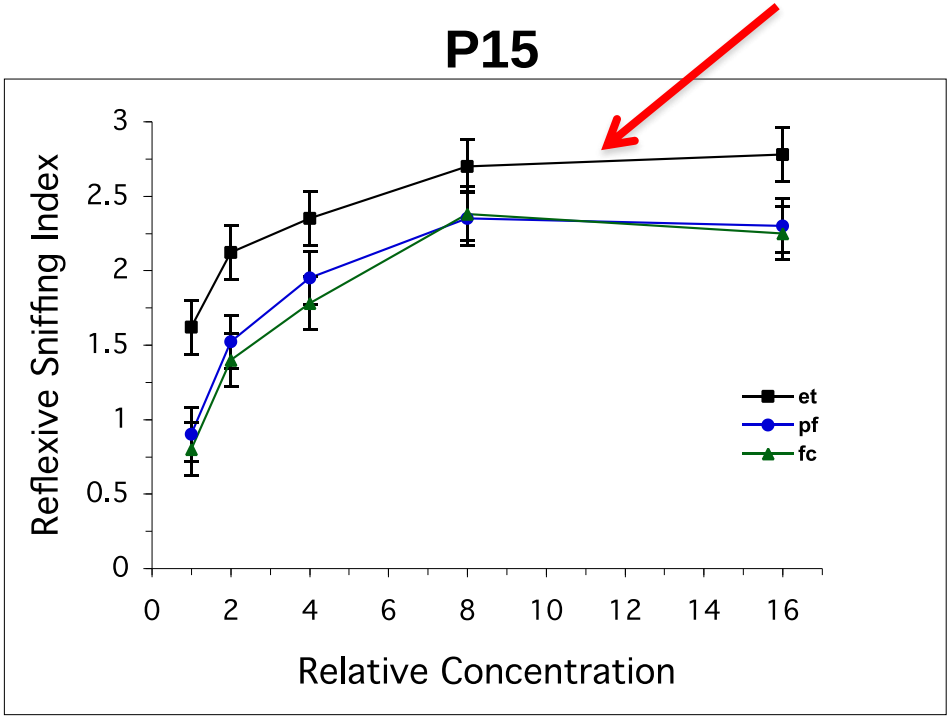
Raw Data

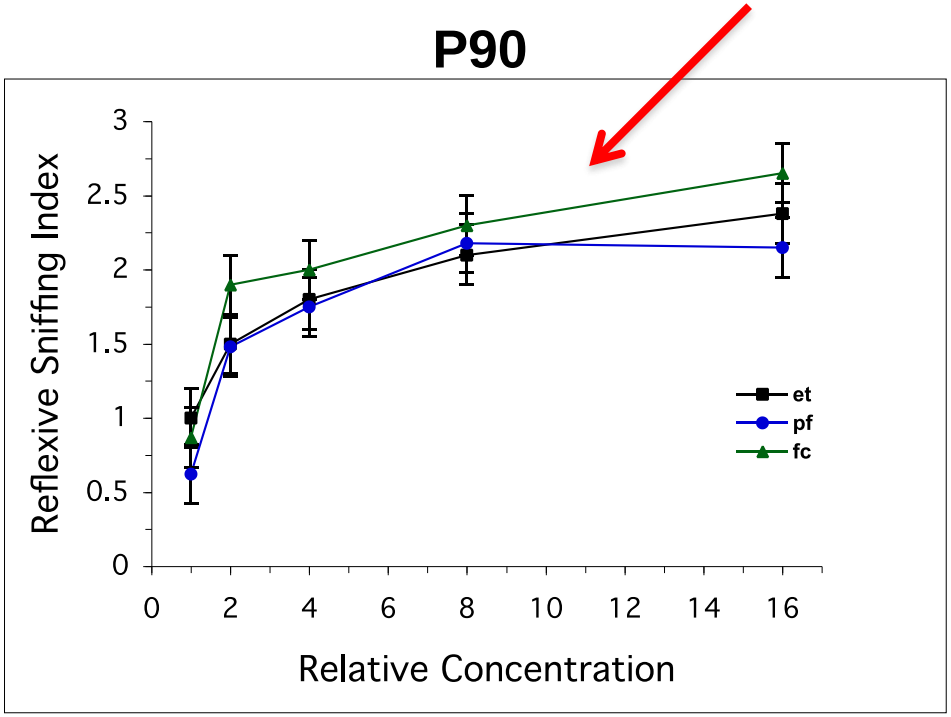


1: Respiratory Frequency
2: Average Expiratory Volume
3: Average Inspiratory Volume
4: Number of Expiratory Sniffs
5: Number of Inspiratory Sniffs
6: Average Expiratory Sniff Duration
7: Average Inspiratory Sniff Duration
8: Average Expiratory Flow Rate
9: Average Inspiratory Flow Rate
10: Total Expiratory Volume
11: Total Inspiratory Volume
12: Aver. Peak Expiratory Flow Rate
13: Aver. Peak Inspiratory Flow Rate
14: Total Apneic Period (ms)

Youngentob (Chem Senses 2005)

Effects of Fetal Ethanol Exposure on Olfactory Functioning

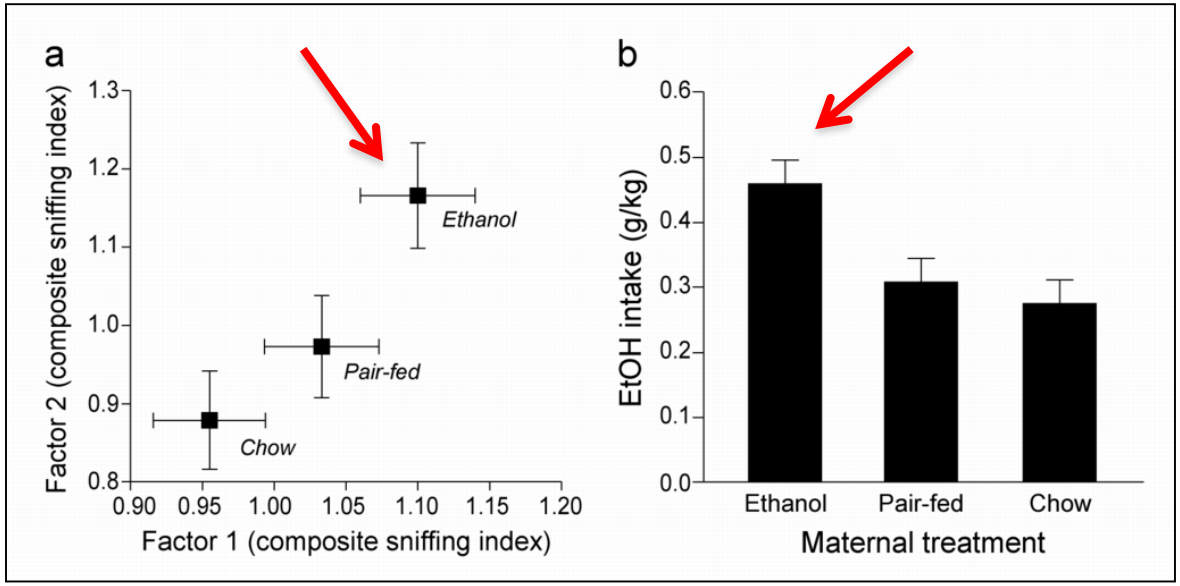


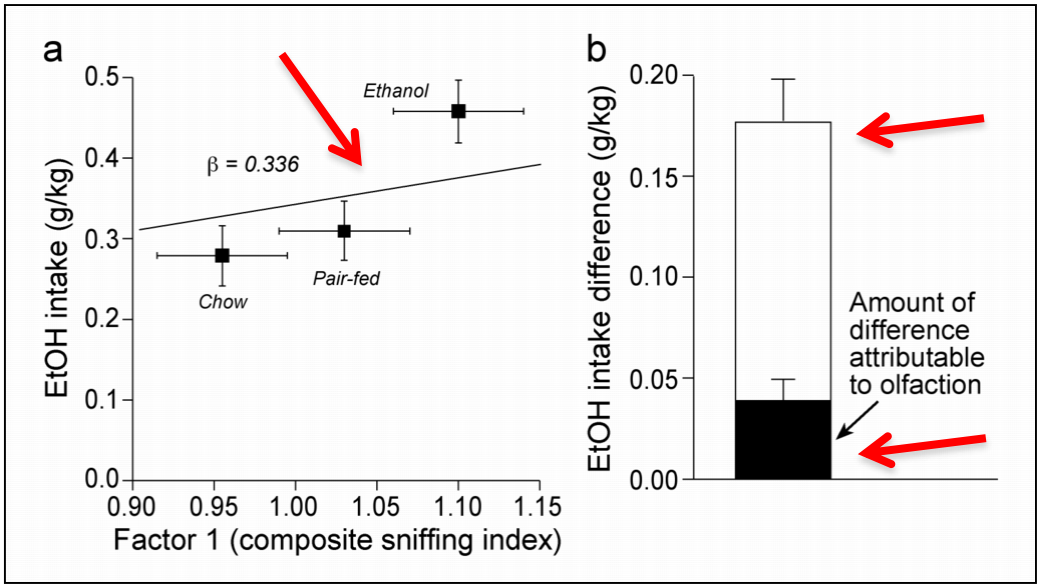


Neural Response

Ethanol Intake

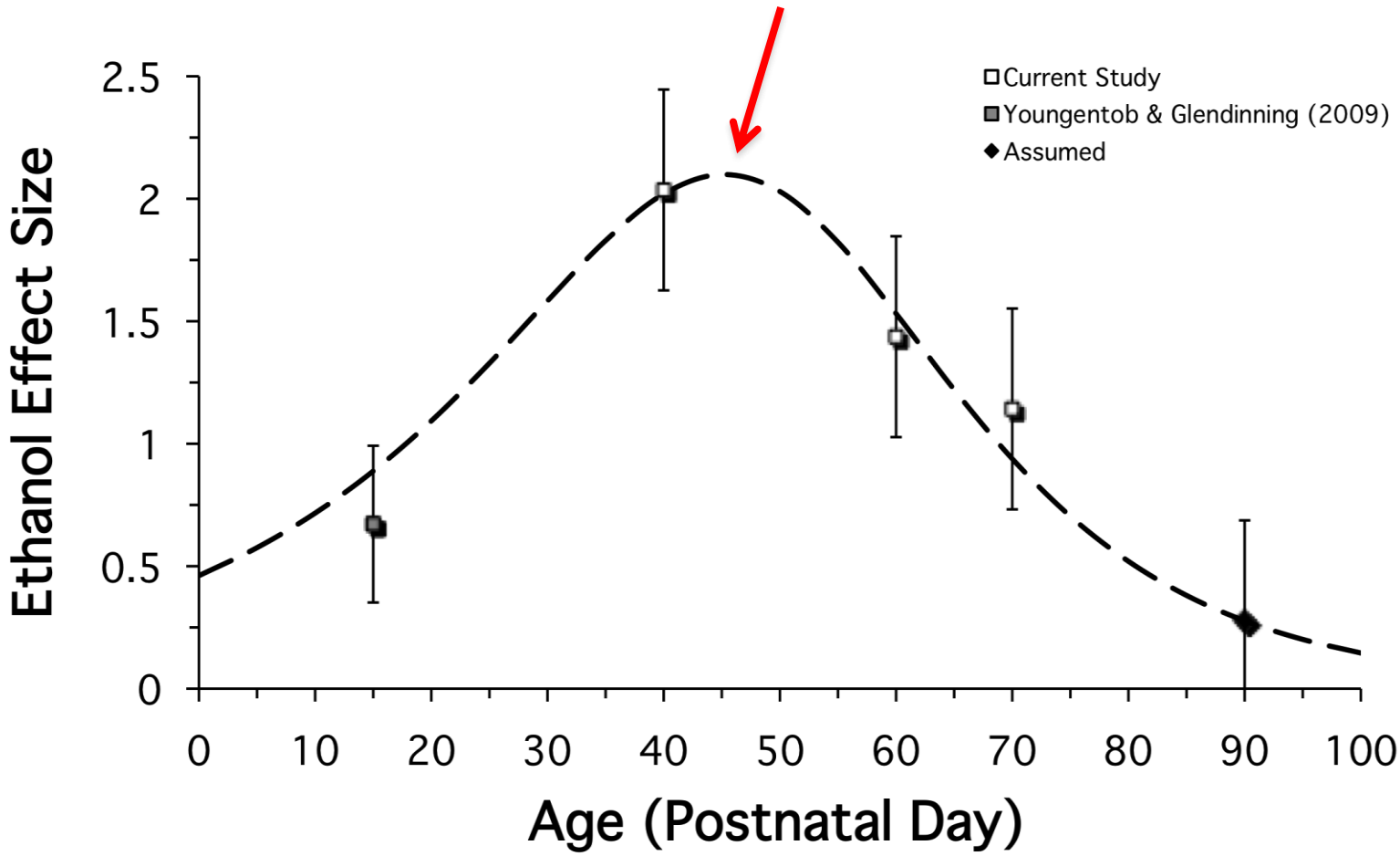
Youngentob et al. (Behav Neurosci, 2007a,b





Youngentob and Glendinning (PNAS, 2009)

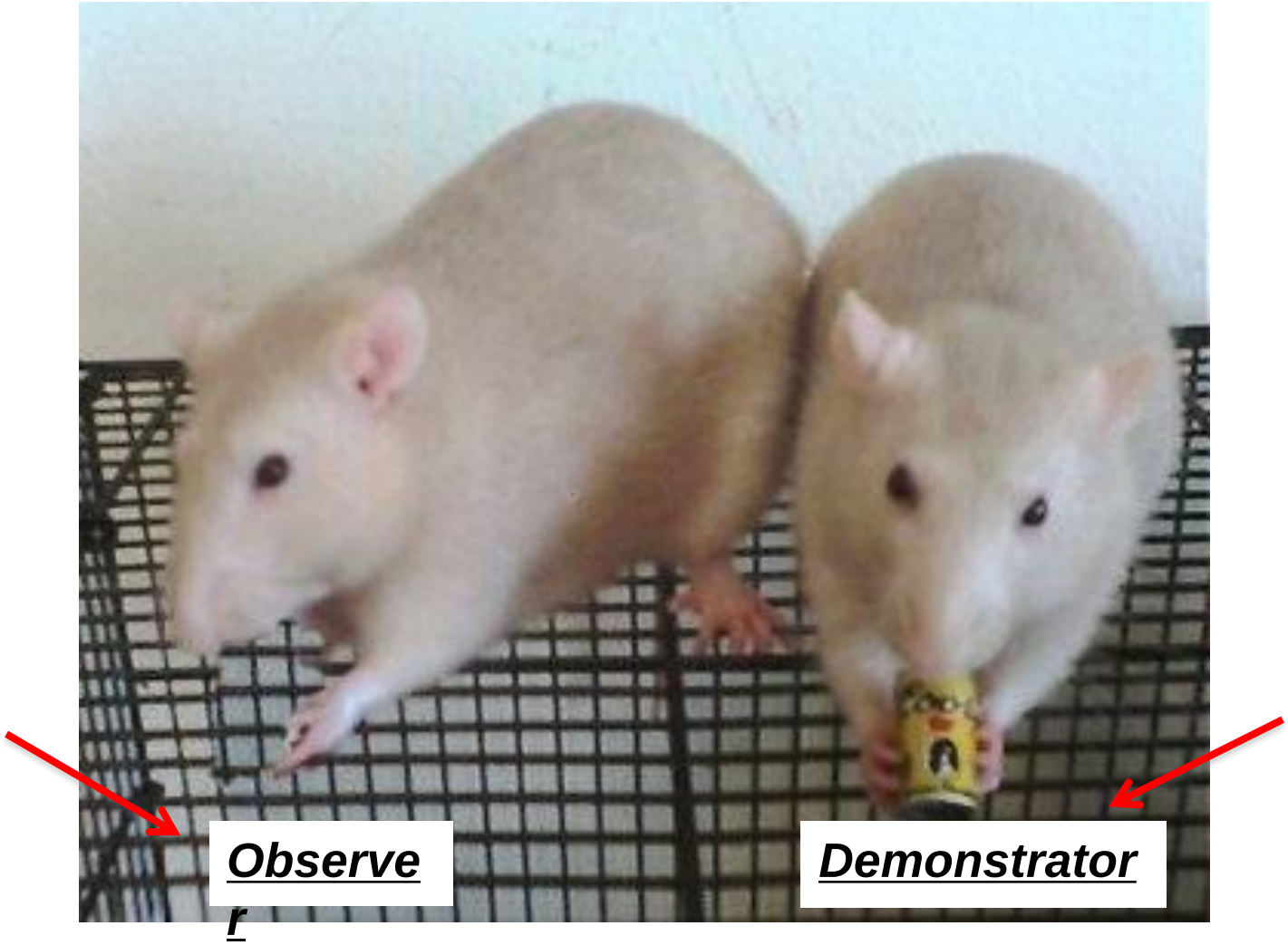
Ontogeny of the Odor-Mediated Effect



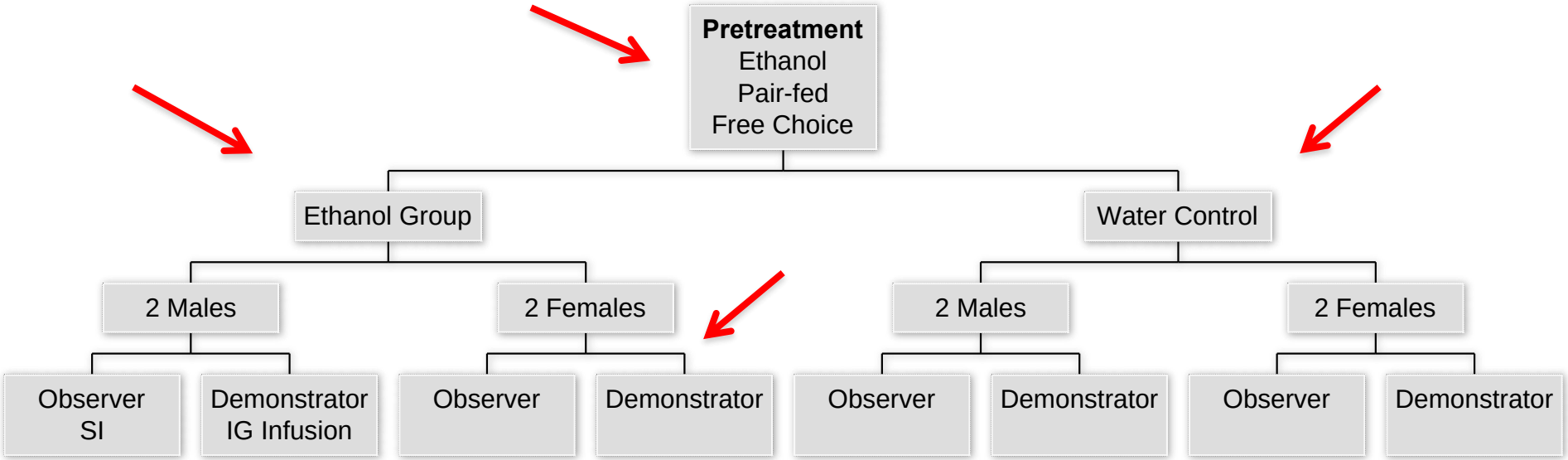
Eade et al.(ACER, 2010)

The “At Risk” Period of Adolescence

The Social Interaction



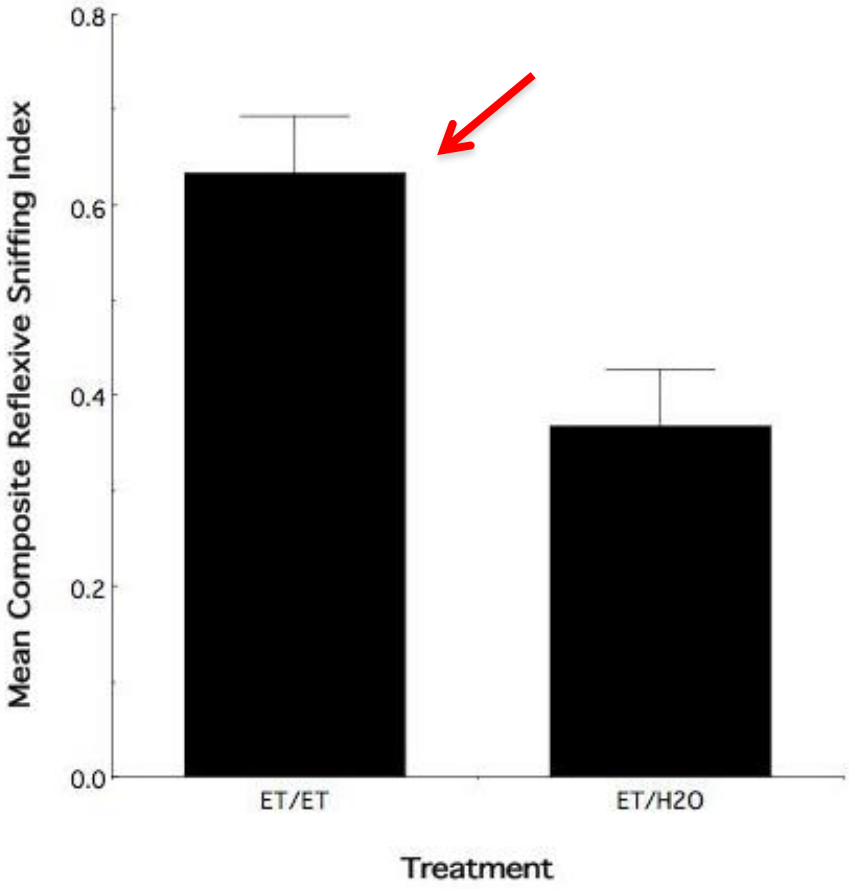
Ethanol Re-exposure Model

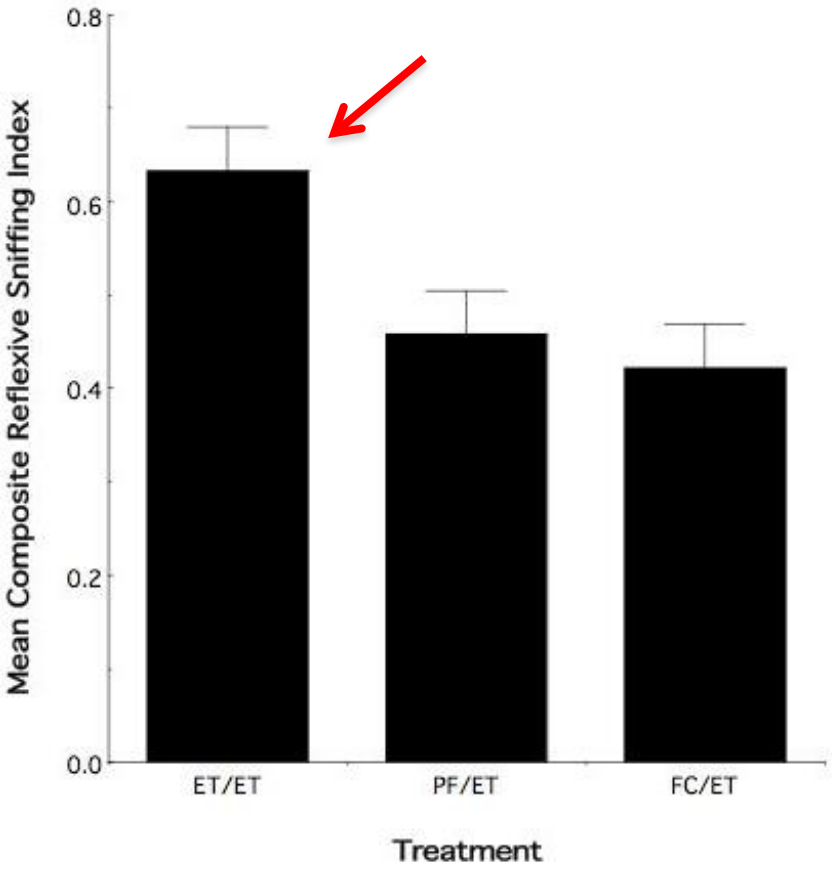


No Ethanol Exposure	**=**	**PF/H2O, FC/H20**
Fetal Exposure Only	**=**	**ET/H20**
Adolescent Exposure Only	**=**	**PF/ET, FC/ET**
Fetal + Adolescent Exposure	**=**	**ET/ET**

Eade et al. (BBF, 2009)

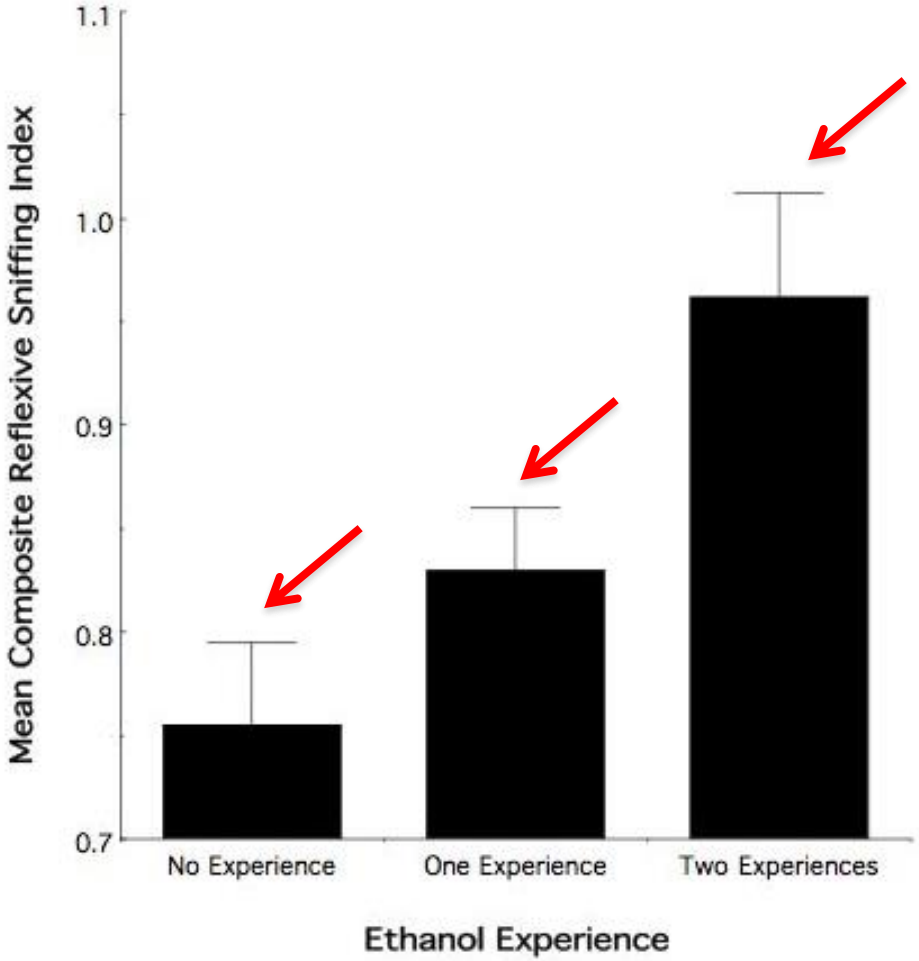
Adolescent Ethanol Exposure Augments the Effect of Prior Fetal Experience





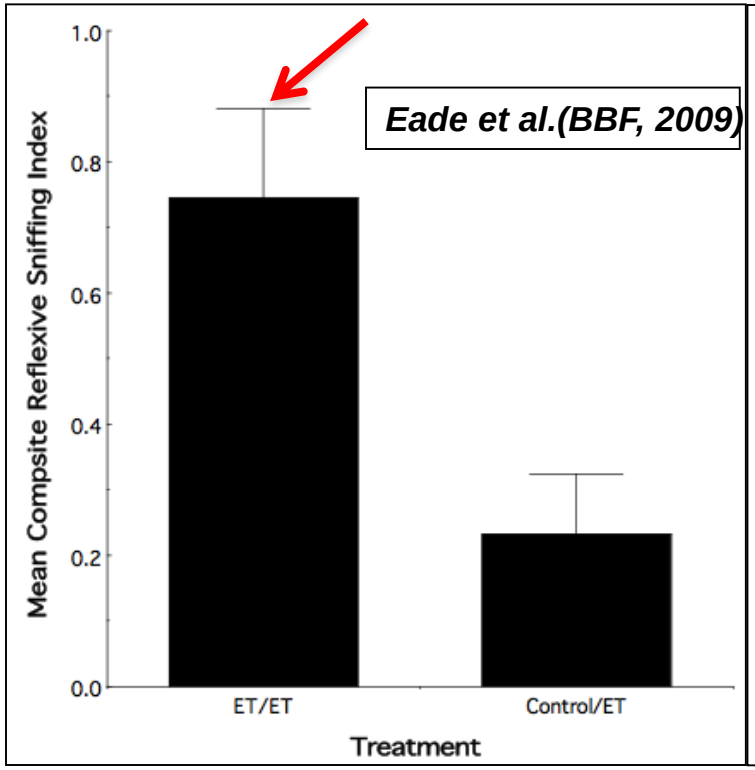
Eade and Youngentob (ACER, 2010)

A Cumulative Effect



Eade et al. (BBF, 2009)

Persistence into Adulthood



Combined fetal ethanol exposure plus adolescent odor re-exposure leads to behavioral alterations in adulthood only in females.

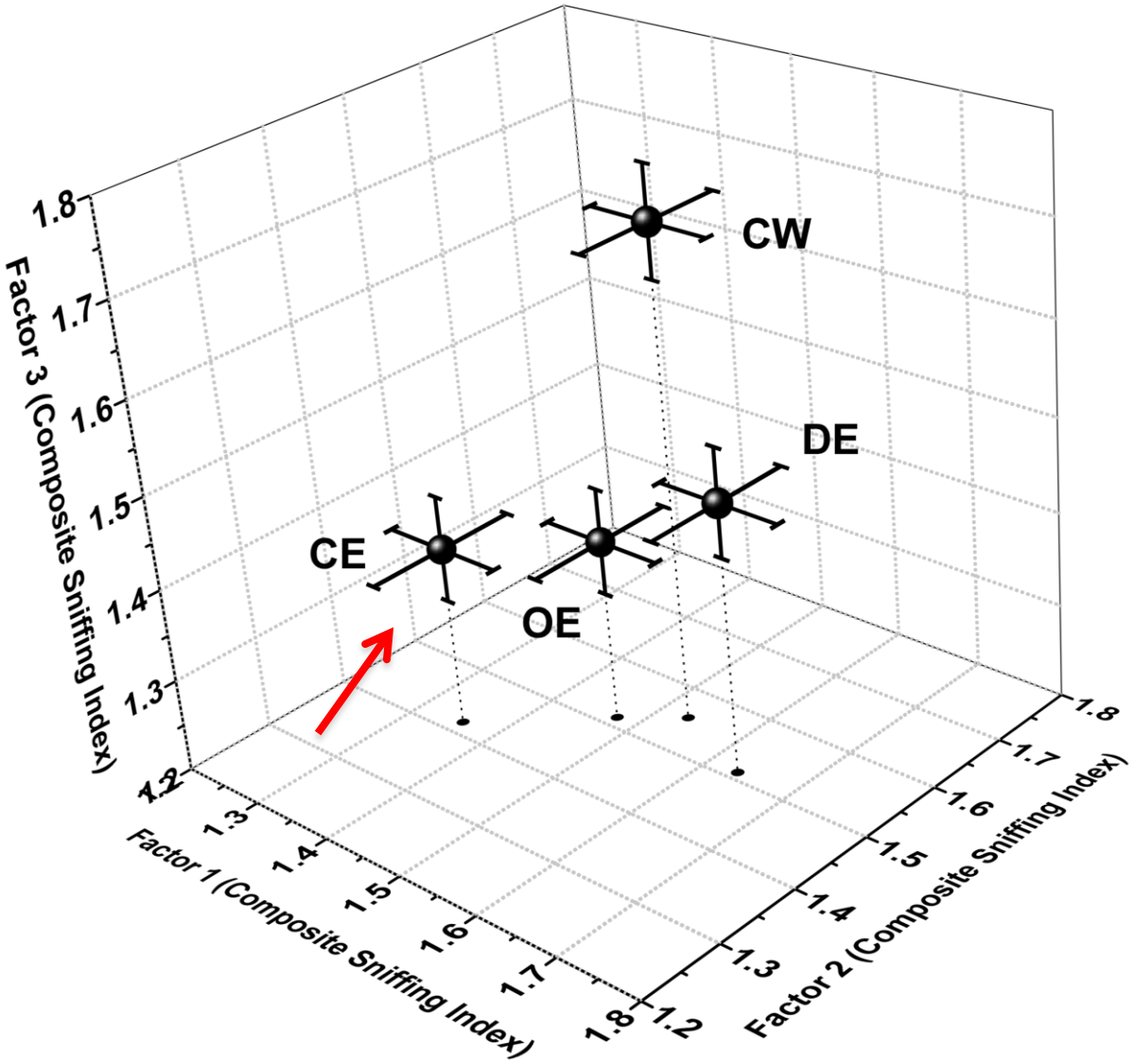
ET/ET = fetal ethanol animals with ethanol odor re-exposure through social transmission in adolescence.
Control/ET = pair-fed and free choice animals with ethanol odor exposure through social transmission in adolescence.

While ethanol odor-specific exposure through social interaction is important, additional factors such as the pairing of retronasal and hematogenic olfaction with ethanol's intoxicating properties appear necessary to achieve adult persistence in both sexes.

Eade and Youngentob (ACER, 2010)

Prenatal Ethanol Exposed Animals are Attracted to an Intoxicated Peer

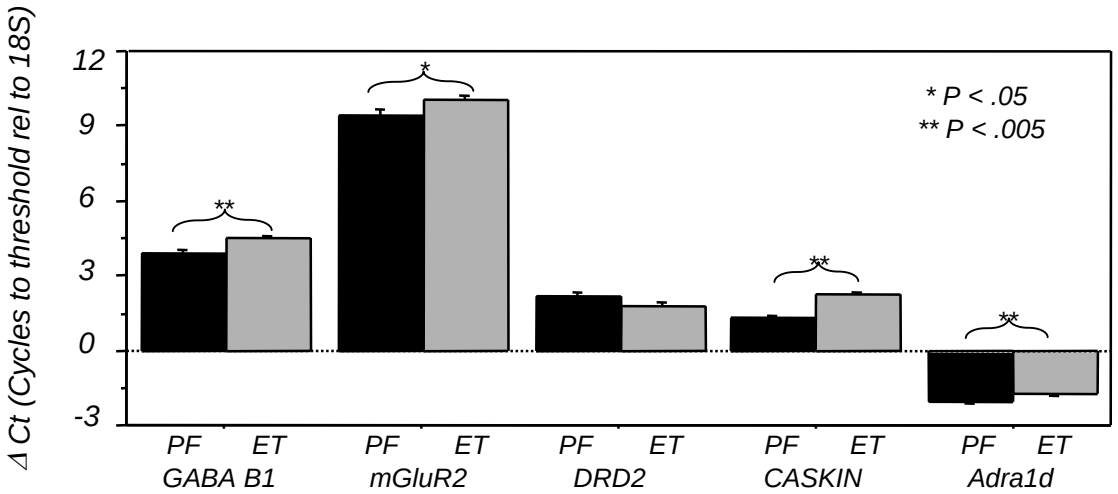
Prenatal Ethanol Exposed Animals are Attracted to an Intoxicated Peer



Eade et al. (ACER, In Press)

Specific Dysregulation Effects on Neurotransmission

A



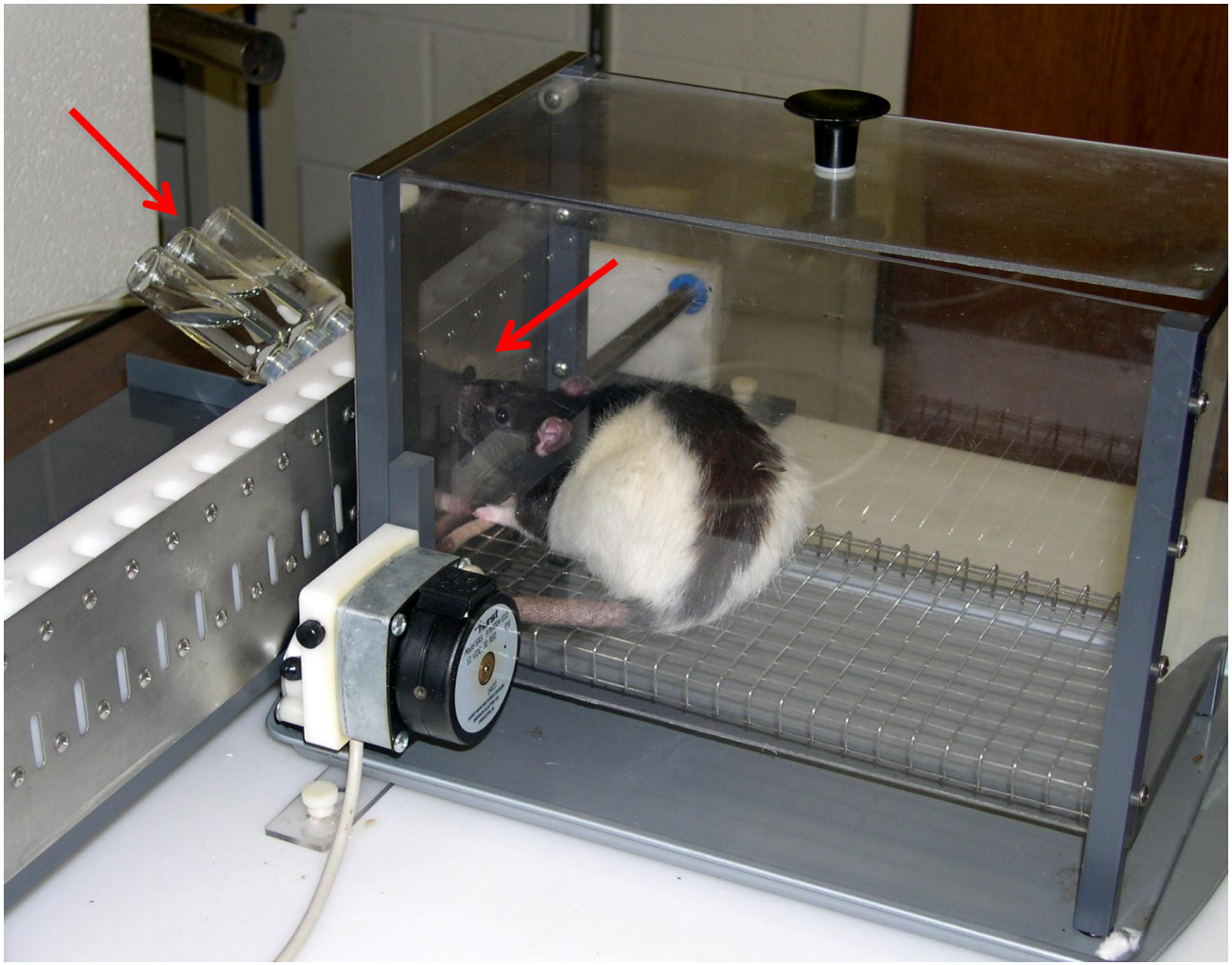
B

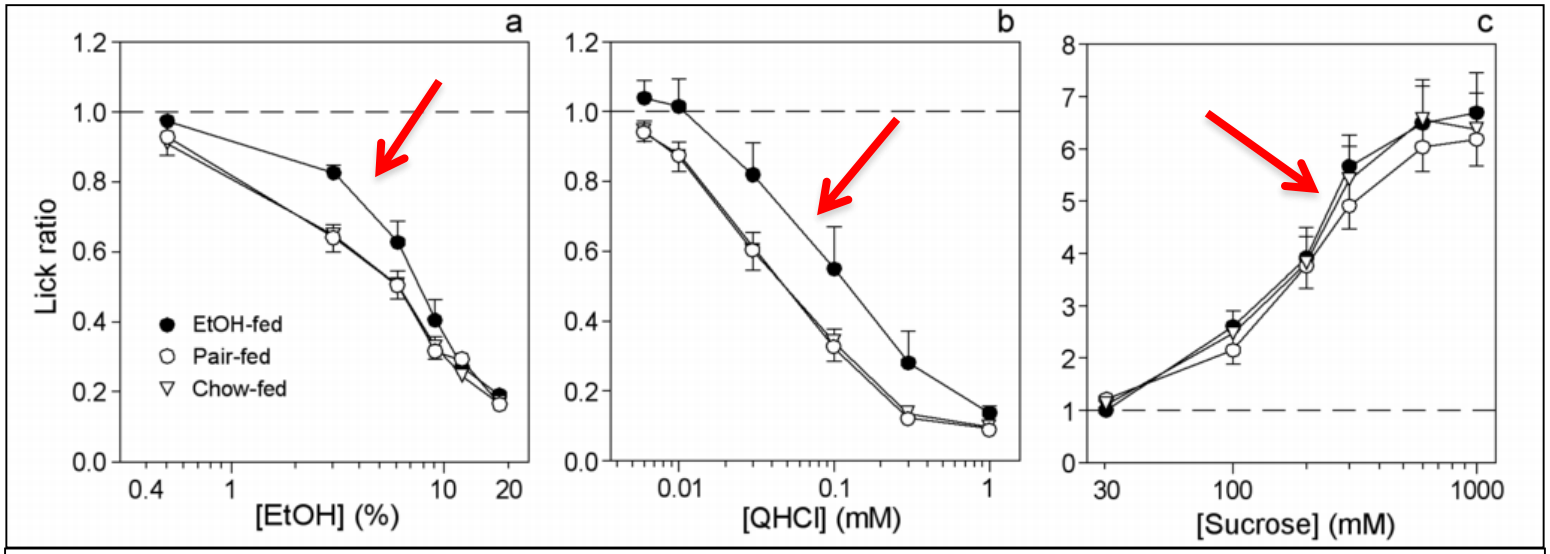
Mean Fold Changes in EtOH Treated vs Ctrl

	Array	PCR	
GABA B1	-1.73	-1.59	**
mGluR2	-2.68	-1.45	*
DRD2	-2.22	1.24	
CASKIN	-1.68	-1.90	**
Adra1d	-2.42	-1.30	**

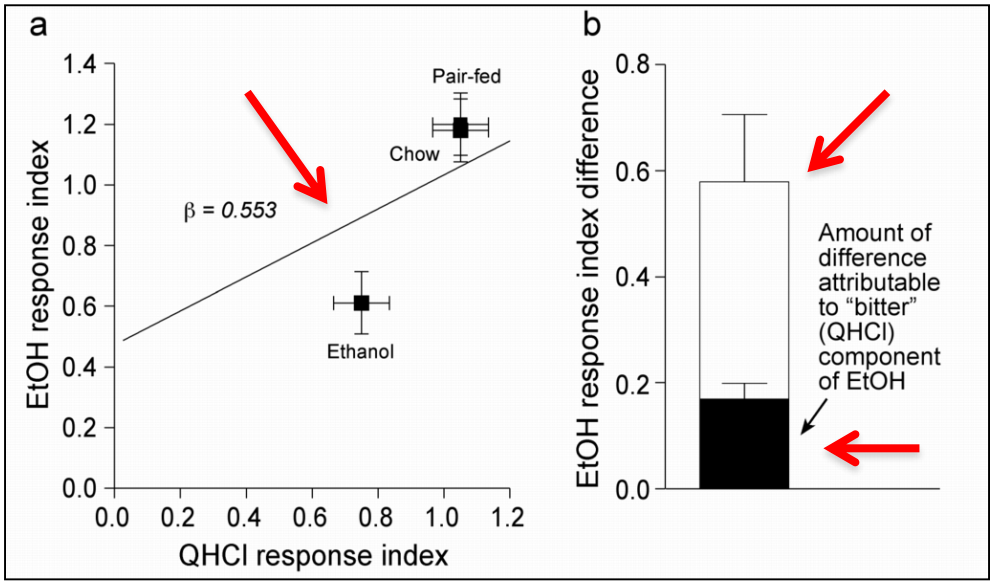
Middleton et al. (Brain Res., 2009)

We Measure Oro-sensory Responses with a Gustometer

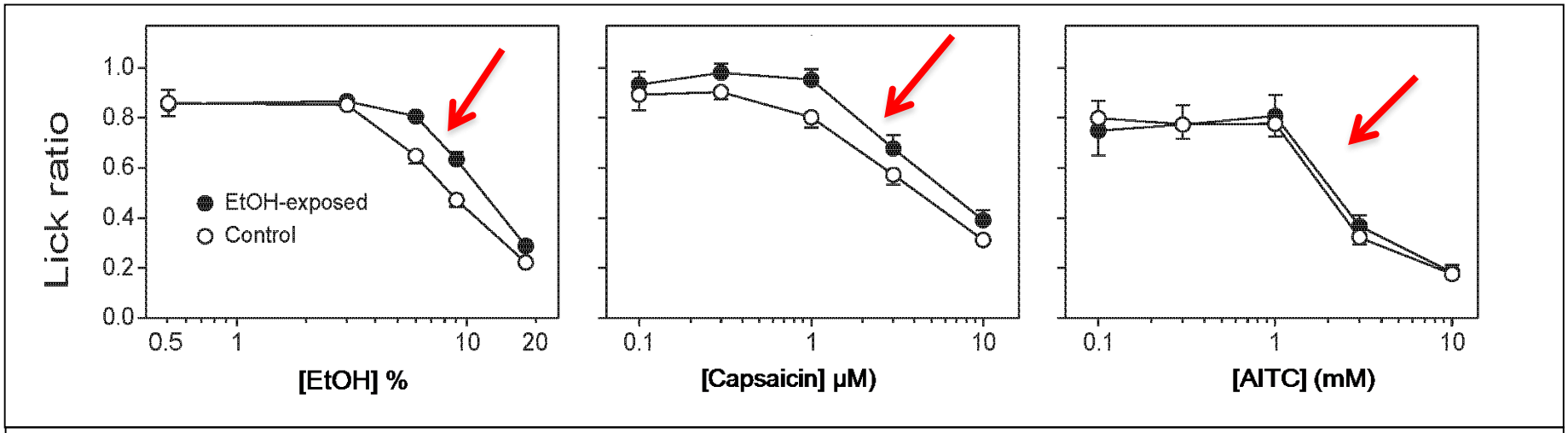




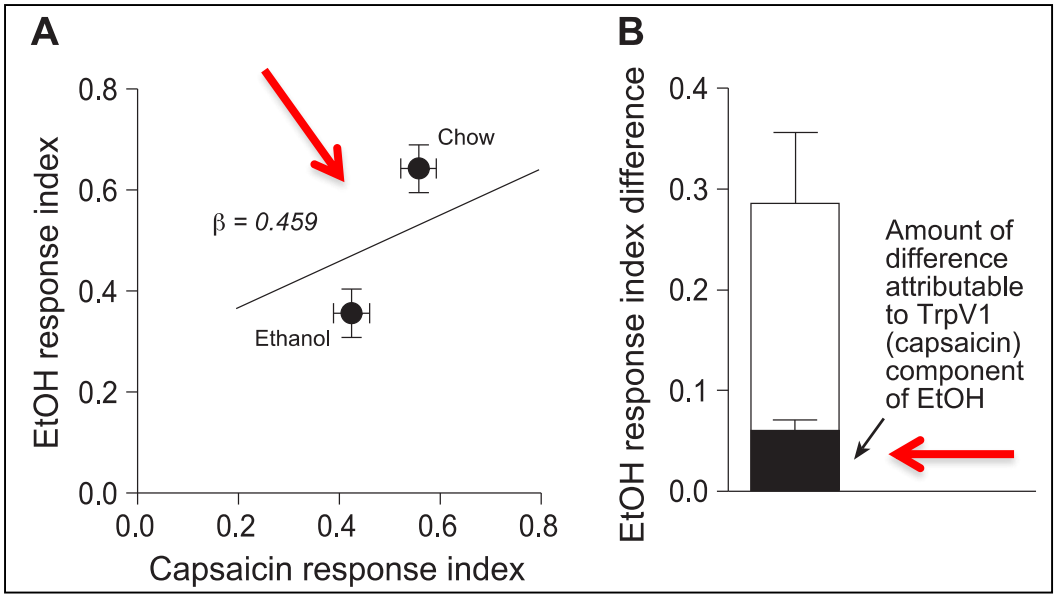
Fetal exposure increases the acceptability of ethanol and QHCl, but not sucrose.



Youngentob and Glendinning (PNAS, 2009)

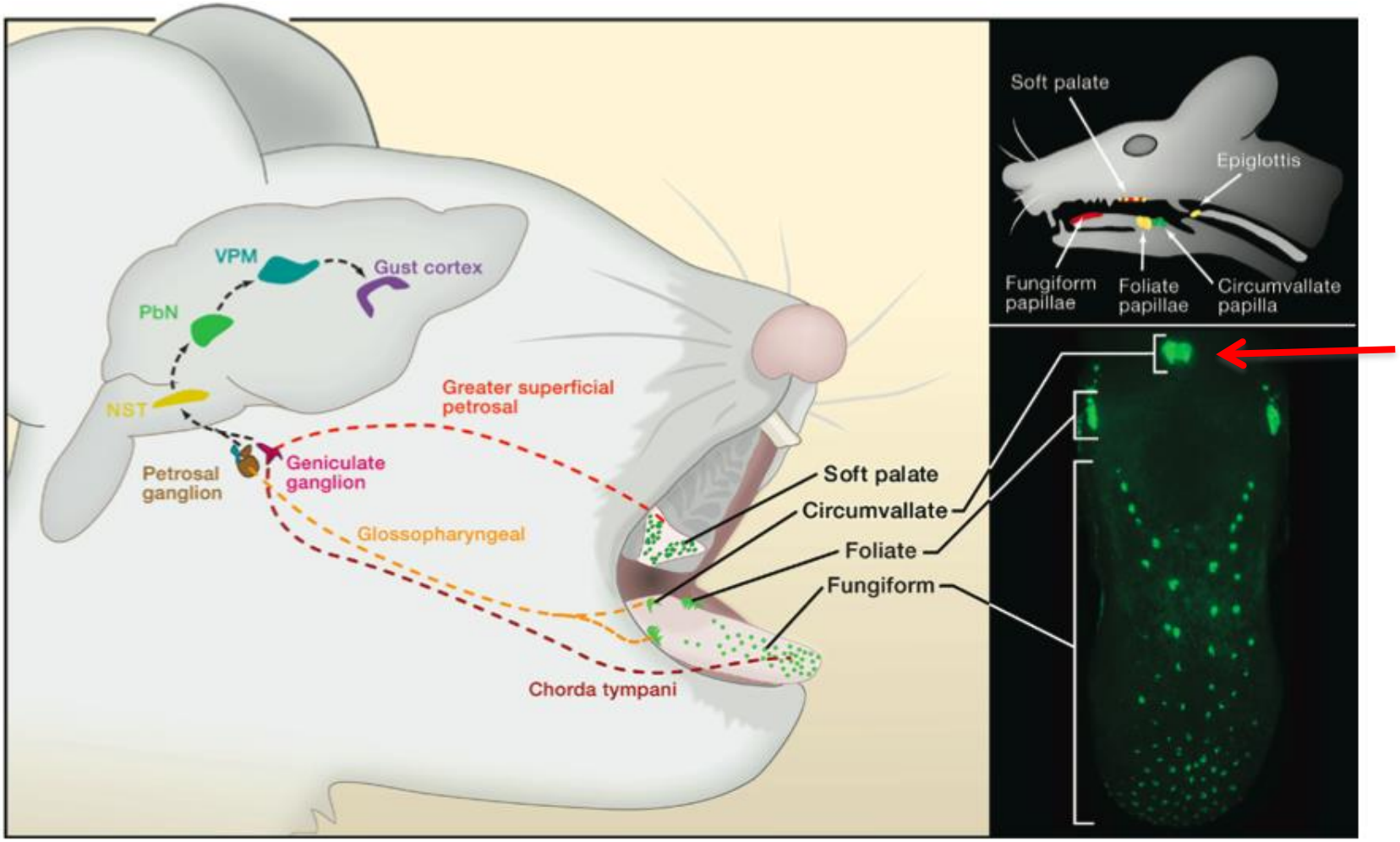


Fetal exposure increases the acceptability of (a) ethanol and (b) Capsaicin, but not (c) AITC.



Glendinning et al.(EBM, 2012)

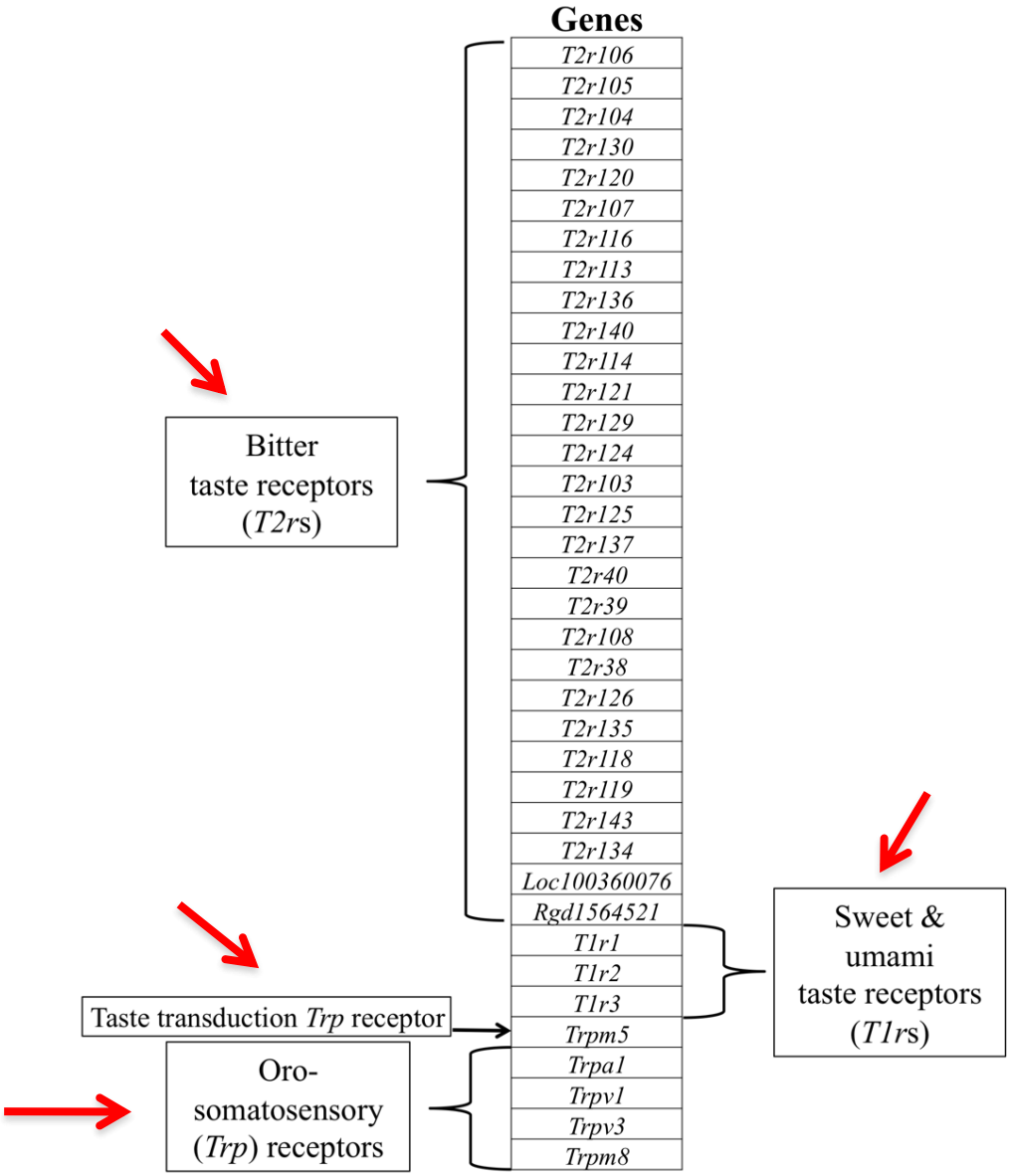
Peripheral Oro-sensation



Yarmolinsky et al.(Cell, 2009)

P35-Adolescence
P90-Adulthood

Oro-sensory Gene Expression



Prestia et al. (In preparation)

qRT-PCR

Adolescent CV

Log_2 Fold Change

BH-FDR

Involved in Quinine sensitivity

* *T2r106*
* *T2r105*
* *T2r104*
* *T2r130*
* *T2r120*
* *T2r107*
* *T2r116*
* *T2r113*
* *T2r136*
* *T2r140*
* *T2r114*
* *T2r121*
* *T2r129*
* *T2r124*

T2r103

T2r125

Located on a quantitative trait locus for increased ethanol consumption *(mice)*

Transient Receptor Channels (*Trps*) of the Adolescent CV

Examples of Ligand

Trpa1- AITC

* ***Trpv1-*** Capsaicin

* ***Trpv3-*** Camphor

* ***Trpm8-*** Menthol

Taste Transduction

* ***Trpm5*** Calcium signaling for bitter, sweet and umami

Additional Taste Receptors of the Adolescent CV

Sweet and Umami

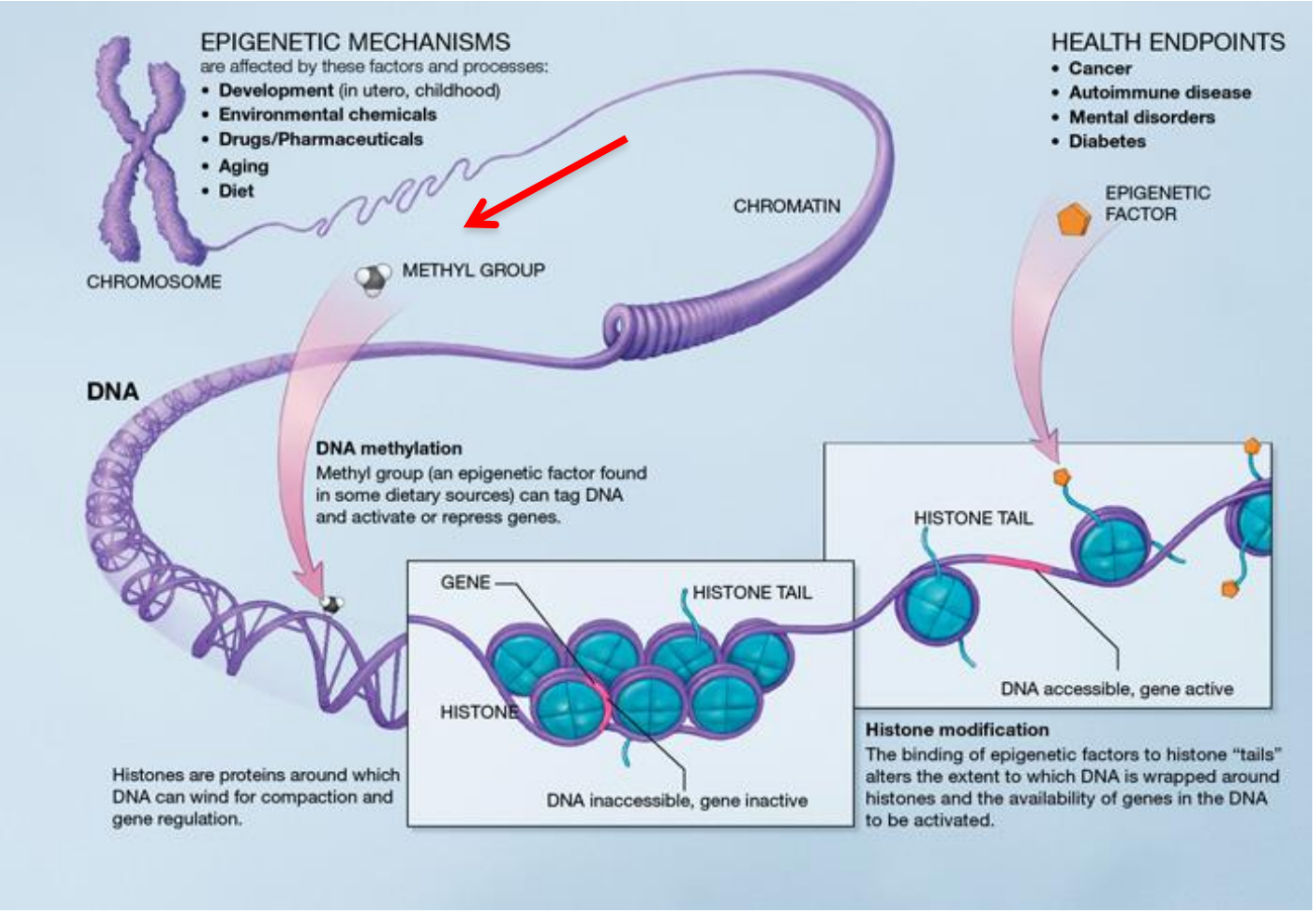
* *T1r1*
* *T1r2*
* *T1r3*

Additional Taste Receptors of the Adolescent CV

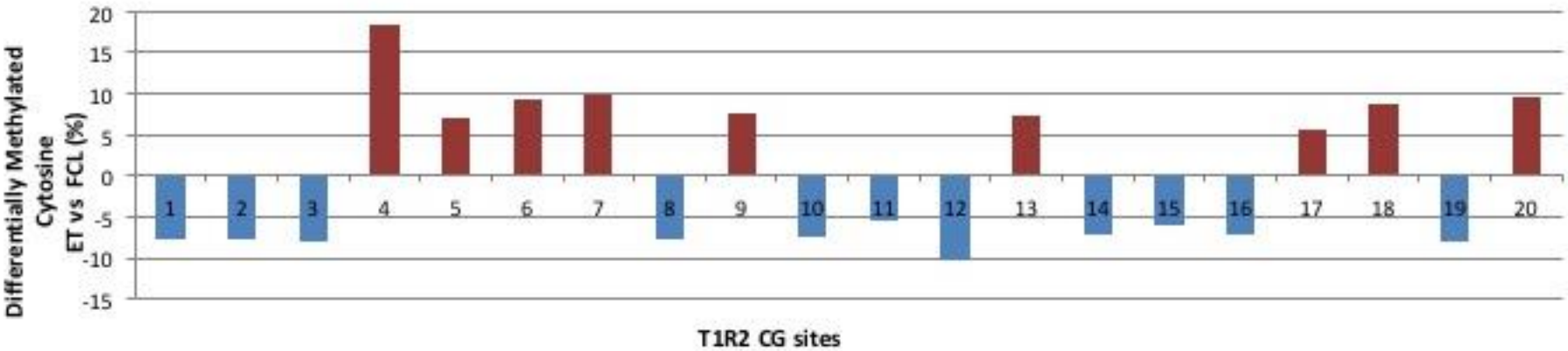
Sweet and Umami

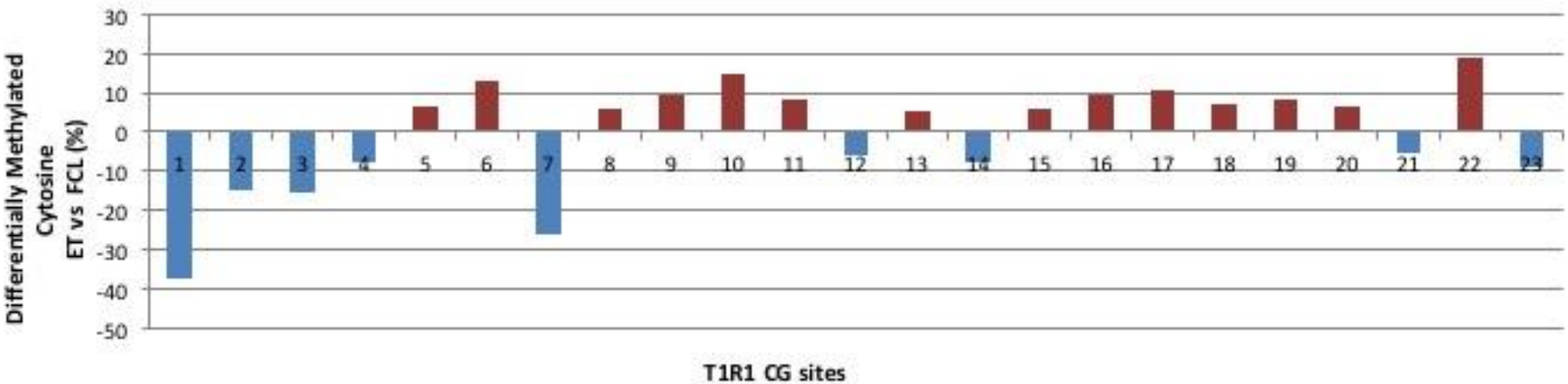
* *T1r1*
* *T1r2*
* *T1r3*

Epigenetic Basics



A Mechanism Underlying Alterations in Gene Expression ?



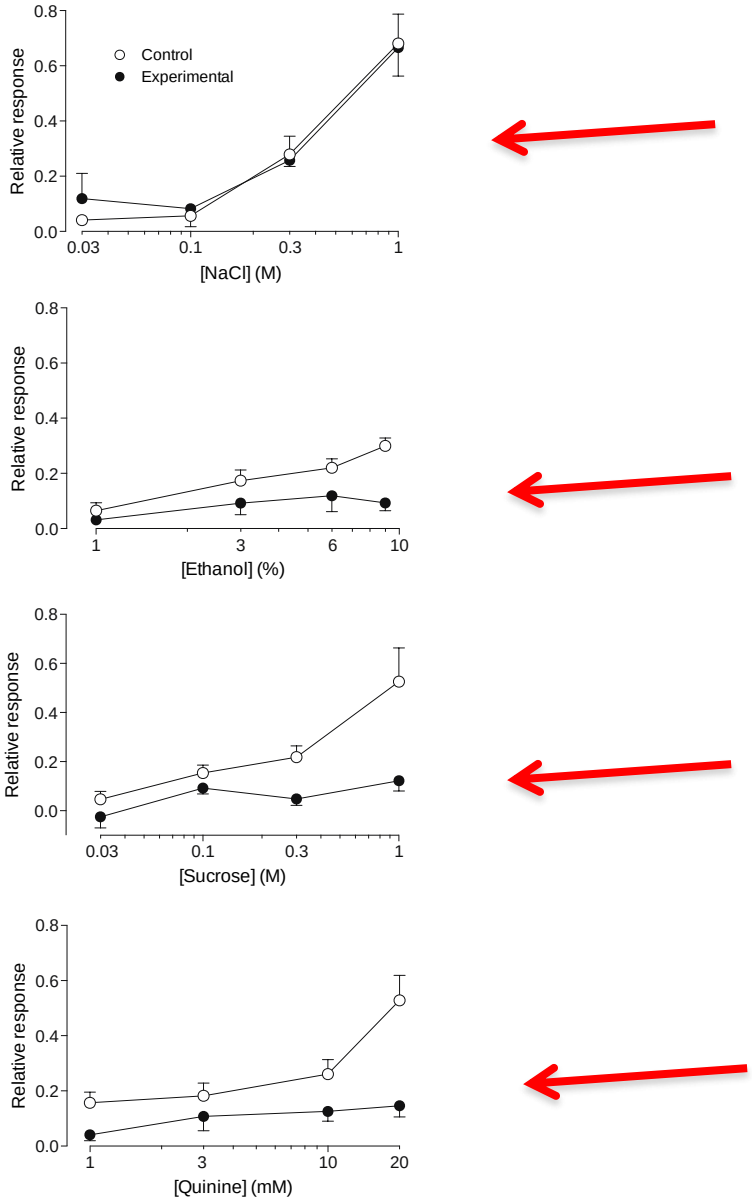


Oro-Sensory Gene Expression Summary

* CV - Bitter, sweet and oral irritation transduction genes
    - Decreased during adolescence
    - Normalized by adulthood
    - Results consistent with previous behavior

* The fetal exposure effect was specific to the CV

* DNA Methylation is one mechanism for changes in expression


Control
Experimental
Relative response
0.0
0.2
0.4
0.6
0.8
0.03
0.1
0.3
1
[NaCl] (M)
Relative response
0.0
0.2
0.4
0.6
0.8
1
3
6
10
[Ethanol] (%)
Relative response
0.0
0.2
0.4
0.6
0.8
0.03
0.1
0.3
1
[Sucrose] (M)
Relative response
0.0
0.2
0.4
0.6
0.8
1
3
10
20
[Quinine] (mM)

General Summary

* Our behavioral, genomic and neurophysiologic data provide evidence for the hypothesis there are epigenetic chemosensory mechanisms by which maternal patterns of alcohol use can be transferred to offspring, and via which, the adolescent system is primed to have the effects of fetal exposure augmented and/or preserved into adulthood

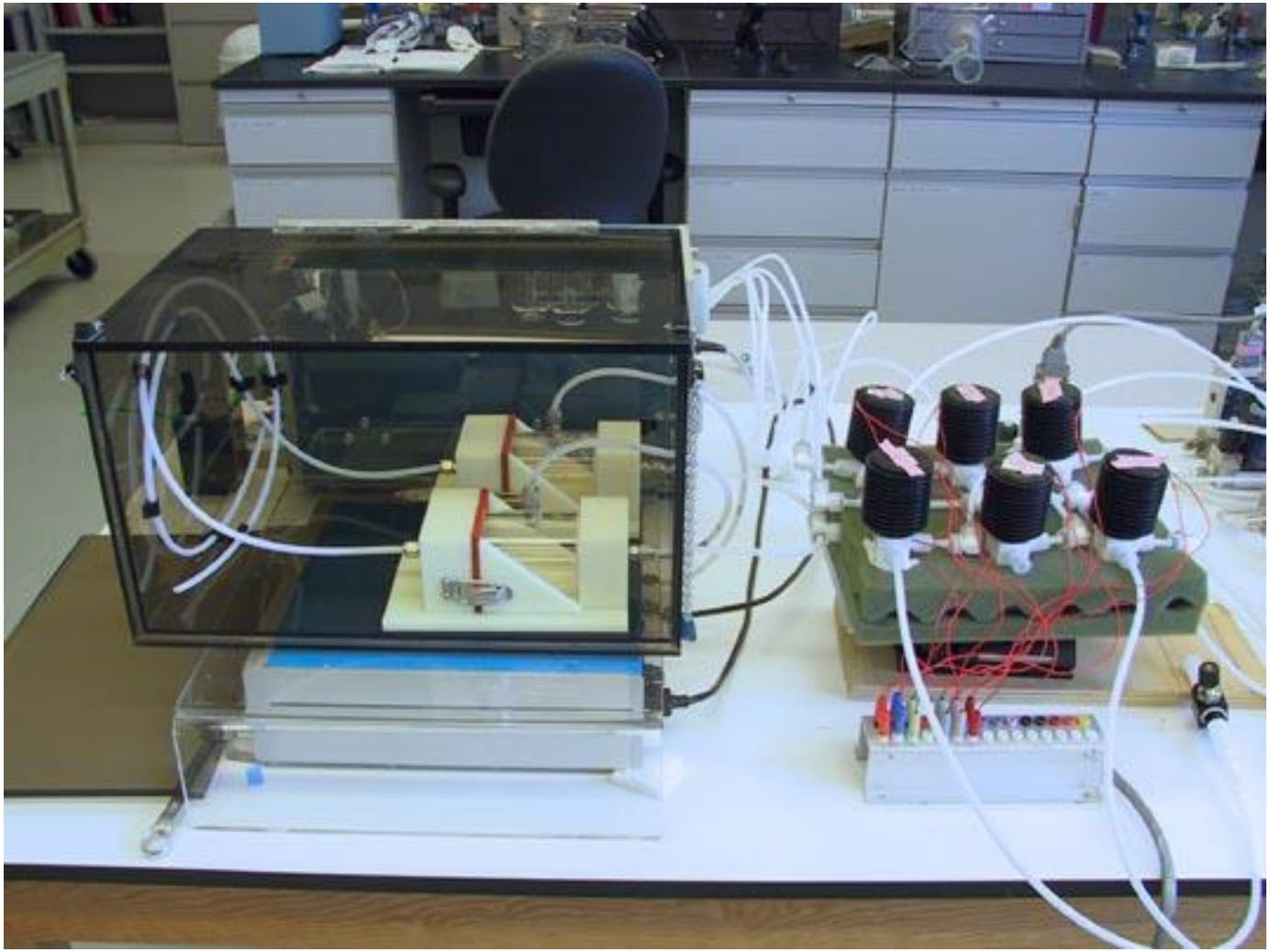
Lessons Learned from Animal Studies of Fetal Alcohol Exposure

?

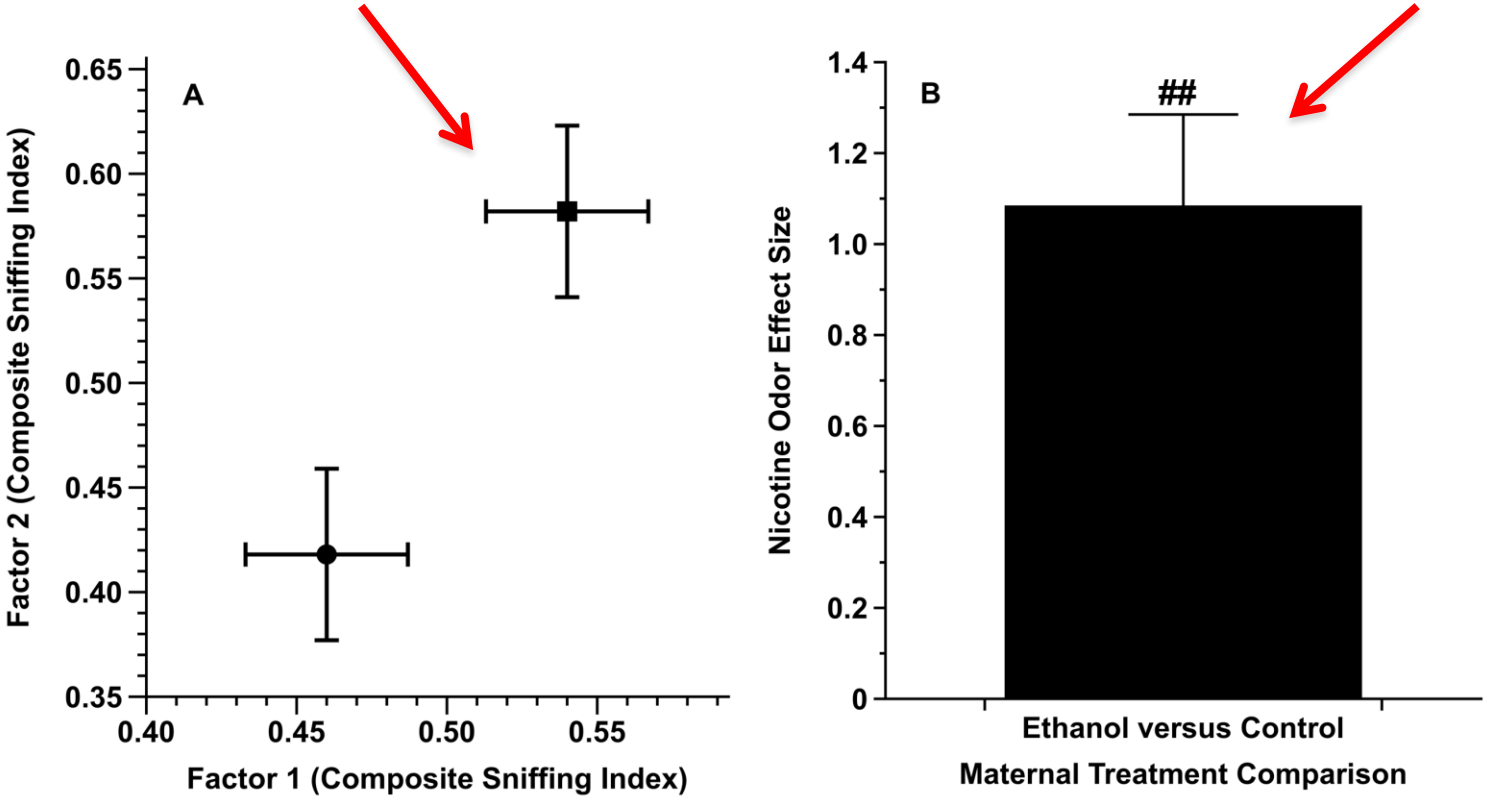
Nicotine and Alcohol have Common Component Chemosensory Qualities

- Both are described as having an irritating and aversive odor
- Their orosensory qualities are described as irritating and having a bitter taste

Innate Odor-Mediated Response

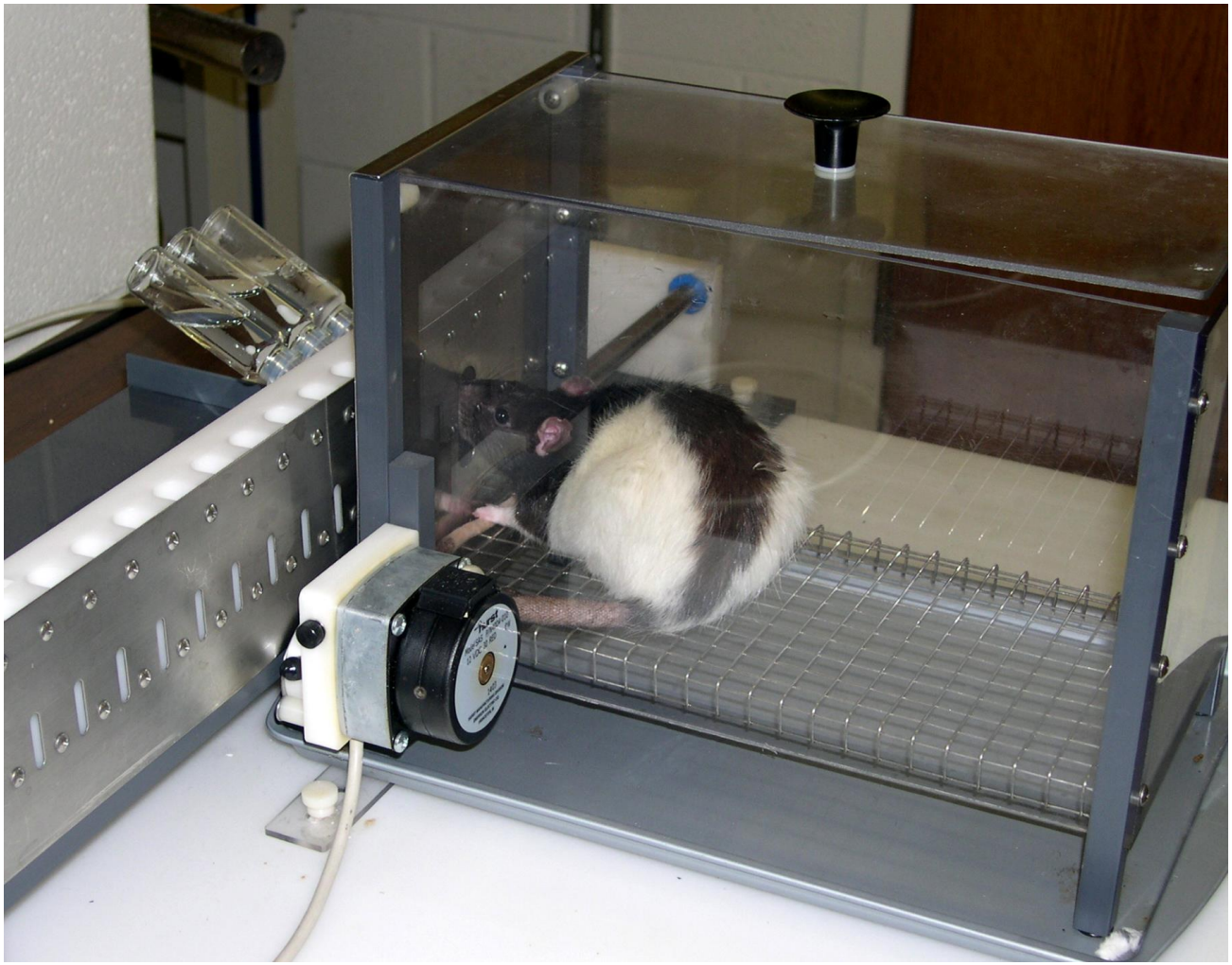


Prenatal Alcohol Exposure Alters the Odor-Mediated Response to Nicotine

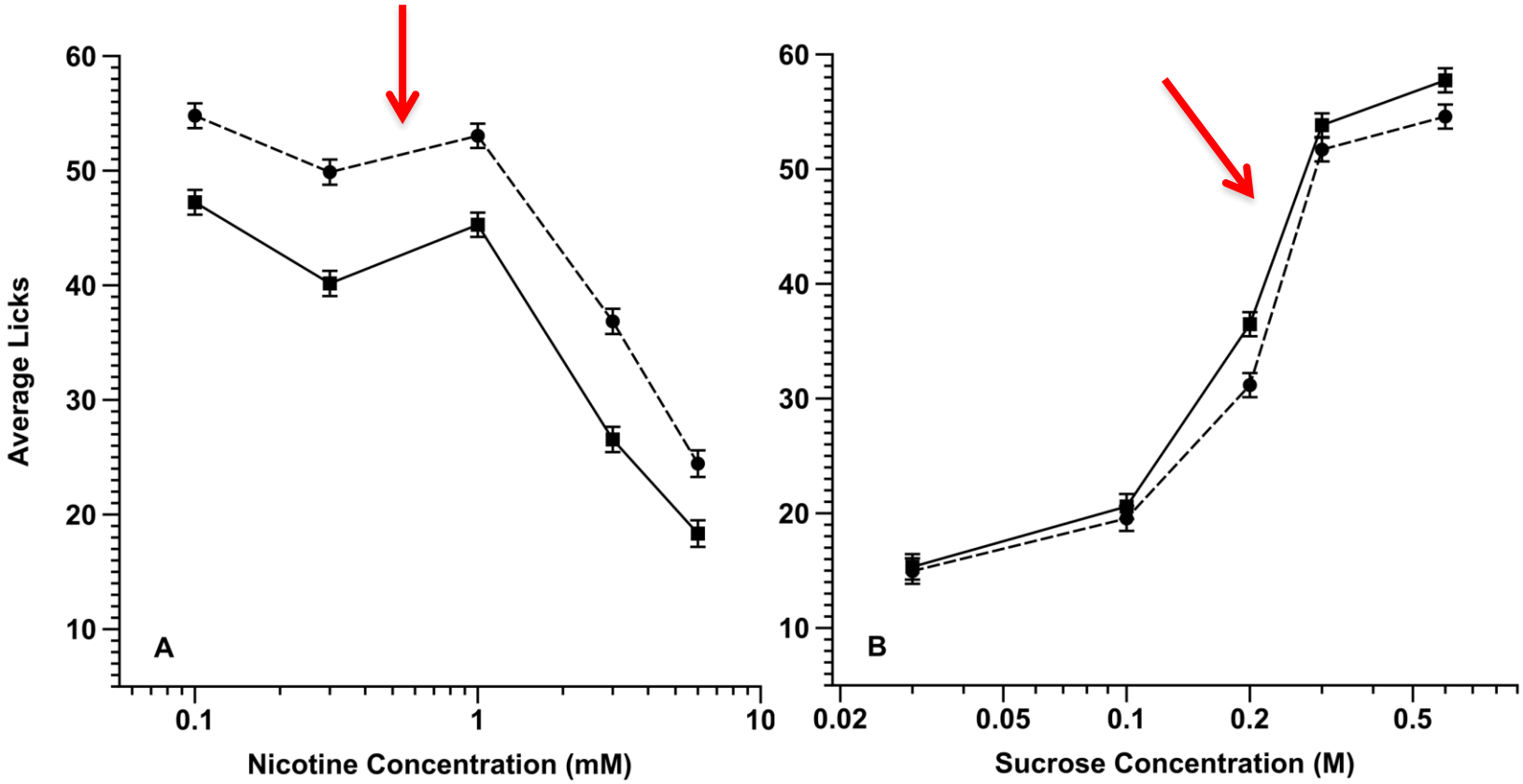


Mantella and Youngentob (PLoS one, 2014)

We Measure Oro-sensory Responses with a Gustometer



Oral Acceptability of Nicotine and Sucrose Solutions to Prenatal Alcohol- and Control-Exposed Adolescent Rats



Mantella and Youngentob (PLoS one, 2014)

Additional Conclusions

Fetal exposure to alcohol also influences initial nicotine postnatal acceptability, at a minimum, by decreasing the aversive properties of both its smell and taste

The present findings point to a broader mechanistic concern regarding the consequence of fetal exposure with one substance of abuse and its impact on the potential initial acceptability of others

Acknowledgements

Lab

Amber Eade
Lisa Youngentob
Laura Prestia
Leana Doherty
Kellyn Carrierfenster
Nicole Mantella
Dan Garman
Jenna Padenna

SUNY Collaborators

Dr. Paul Sheehe
Dr. Paul Kent
Dr. Frank Middleton
Dr. Sandra Mooney

Barnard

Dr. John Glendinning

Binghamton University

Dr. Norman Spear
Dr. Juan Carlos Molina

Funding

NIAAA: AA014871 & AA017823
NIDA: DA027740