Adolescent Stress Reprograms the Medial Amygdala and Sex Differences in Reward

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National Academy of Science, Engineering, and Medicine

September 23, 2020

Sex Differences in Risk for Addiction

Men > Women:
- Rate of Use

Adolescence

Women > Men:
- Initiation of Use (age)
- Progression to Dependence
- Craving & Relapse
- Consumption During Relapse
- Less Likely to Seek Treatment

Reviewed Bobzean, S et al, 2014

Psychopharmacology (Women vs Men):
- Lower amphetamine-induced striatal dopamine
- Report less euphoric effects of amphetamine (Justice and Wit, 1999)
- Greater comorbitity of other mental disorders (Back et al., 2011; Yates et al., 1993)
- More likely to report self-medication as a major reason for use

(Torres, OV and O'Dell, LE 2016)

Why is Adolescence Important?

Feeding

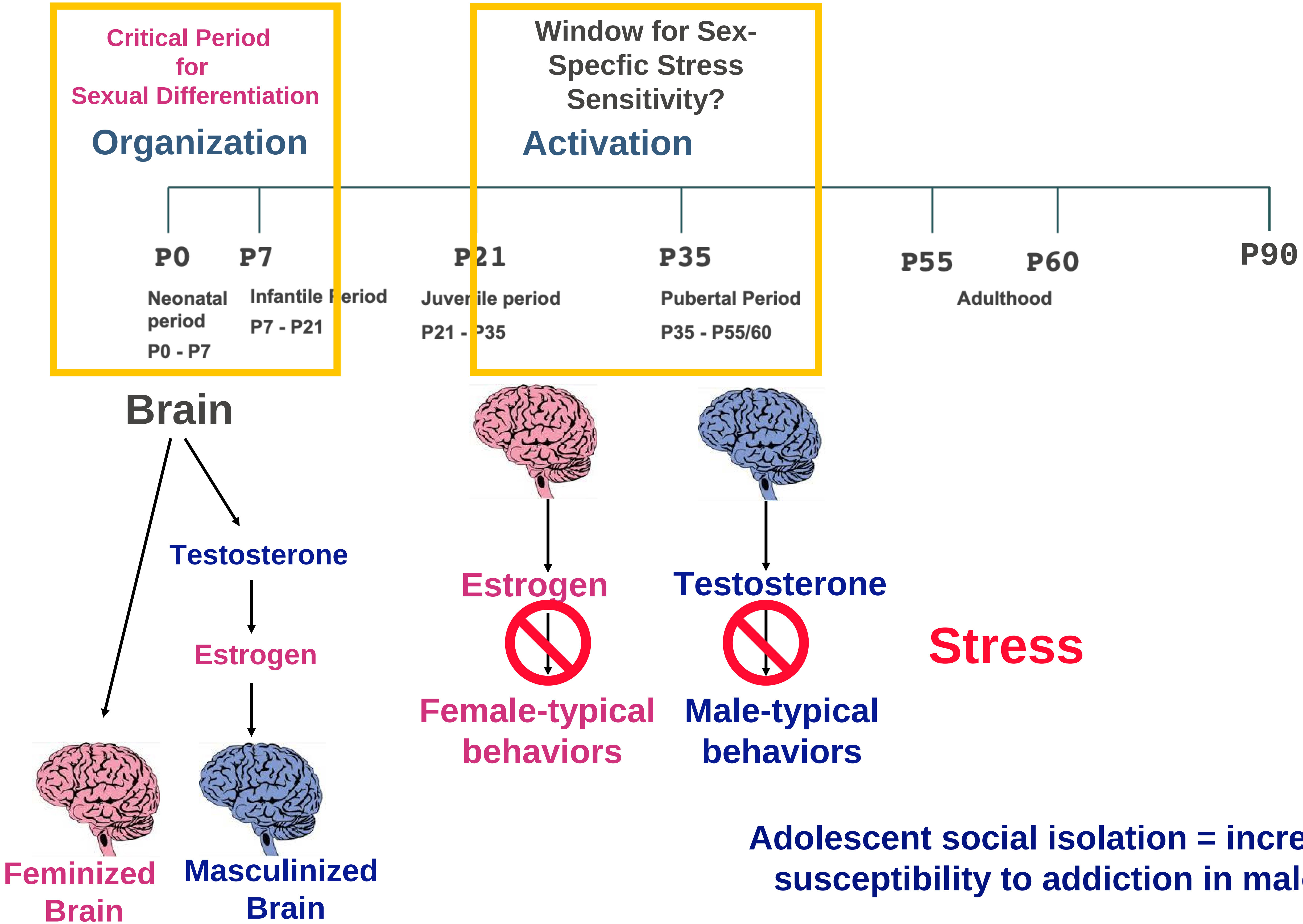
- Period of enhanced vulnerability to psychiatric disorders
- Enhanced response to stress and reward
- Reward circuitry is reorganized
- Change what we perceive as rewarding

Social Bonding

Play Behavior

- Associated with molecular and structural changes
- Behaviors are sexually dimorphic and influenced by hormones

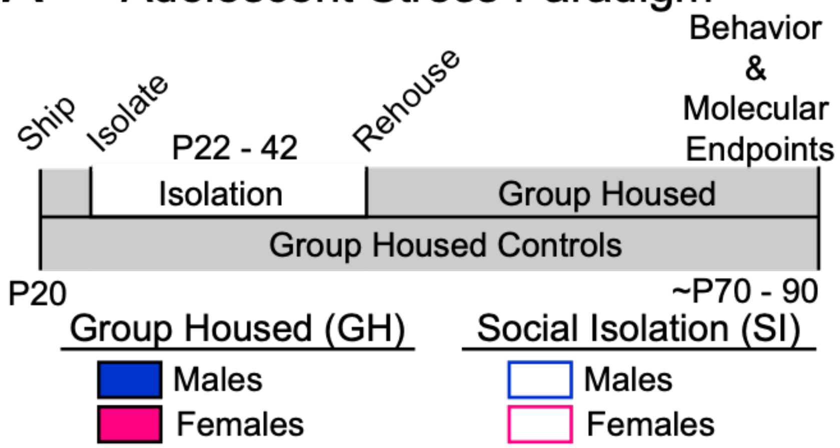
Adolescent Stress Results in Opposite Effects in Males and Females



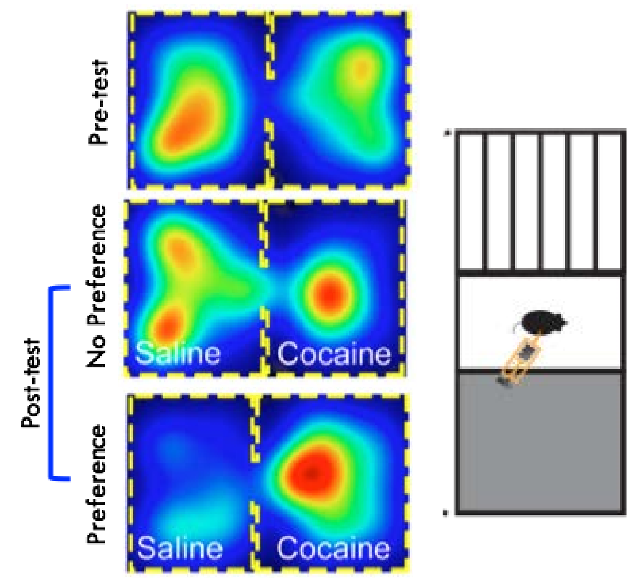
Adolescent social isolation = increase susceptibility to addiction in males

Adolescent Stress Results in Opposite Effects in Males and Females

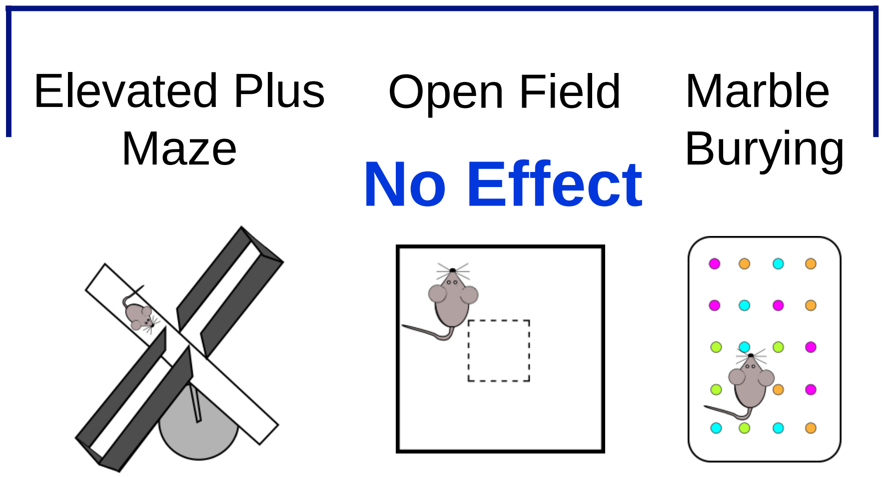
A Adolescent Stress Paradigm



Cocaine Conditioned Place Preference (CPP)

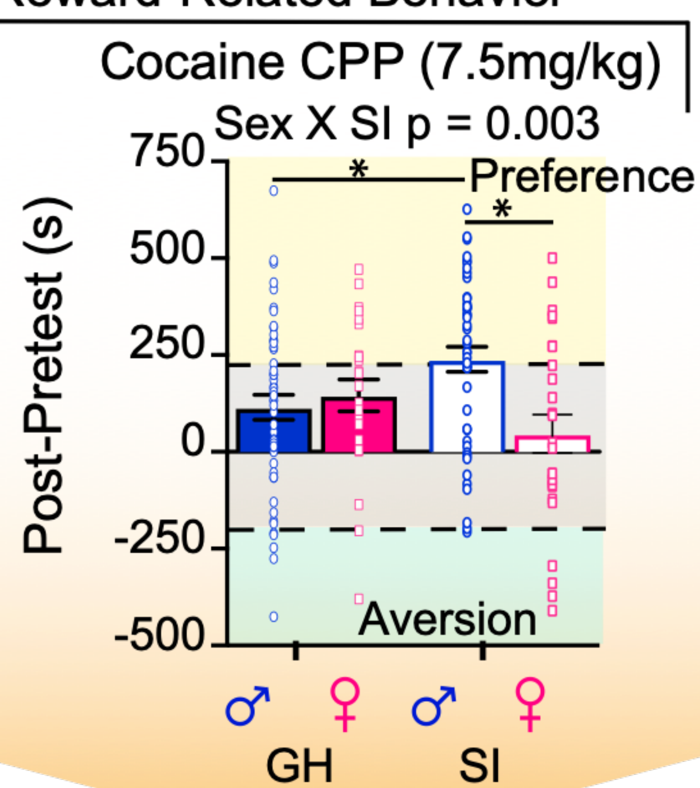


Sexually Dimorphic Behaviors



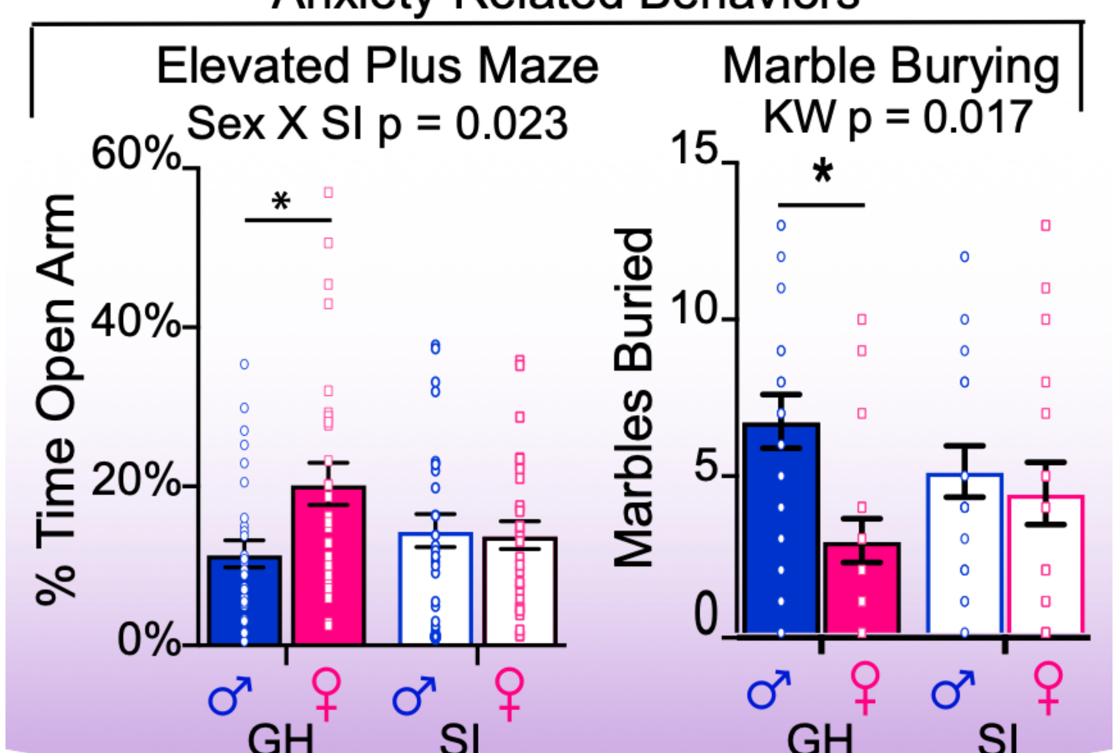
Gain of Sex Differences

Reward-Related Behavior



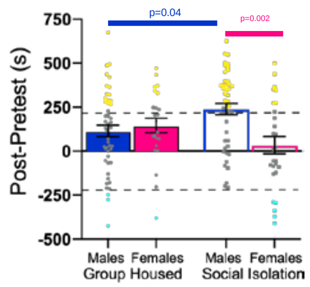
Loss of Sex Differences

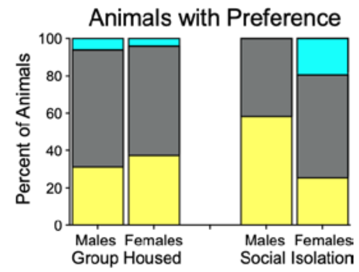
Anxiety-Related Behaviors



Summary

Behavioral Changes after Adolescent SI

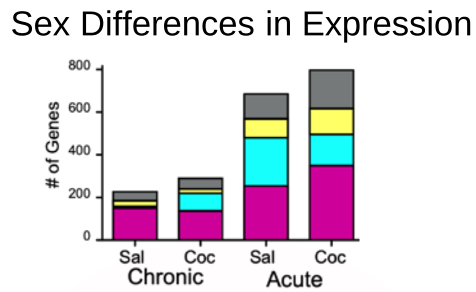


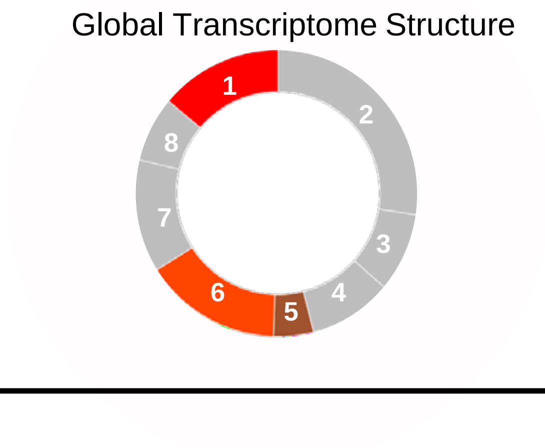


Loss of Baseline Sex Differences

Gain of Sex Differences in Cocaine Response

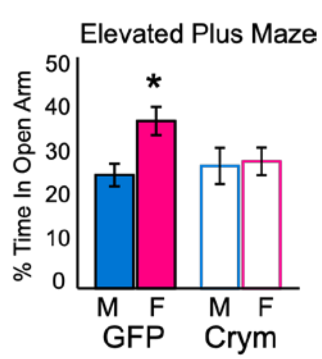
Transcriptional Changes After Adolescent SI

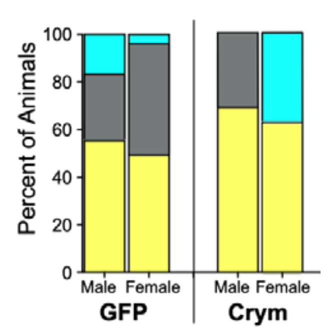




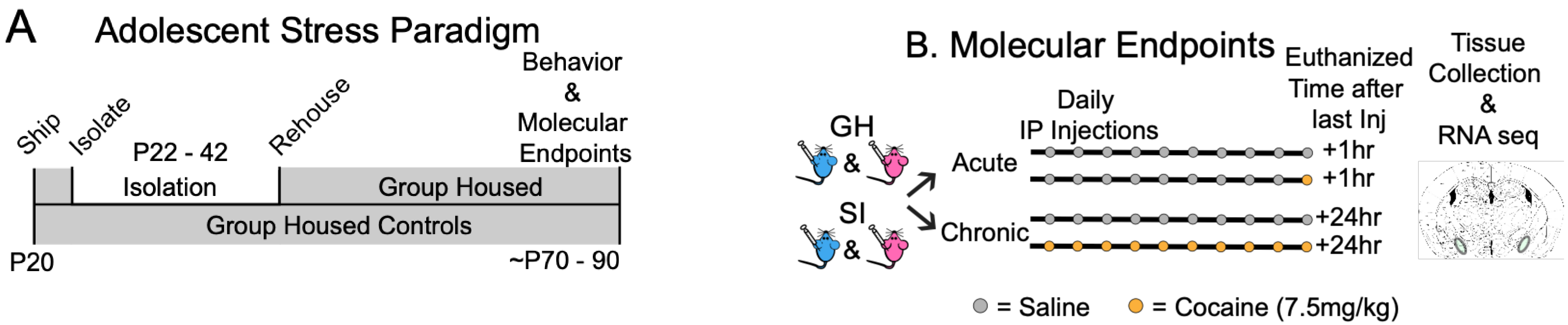
How are sex-specific behavioral responses to cocaine encoded at the transcriptional level?

Behavioral effects of manipulation of conserved key driver in <u>adult</u> meAMY

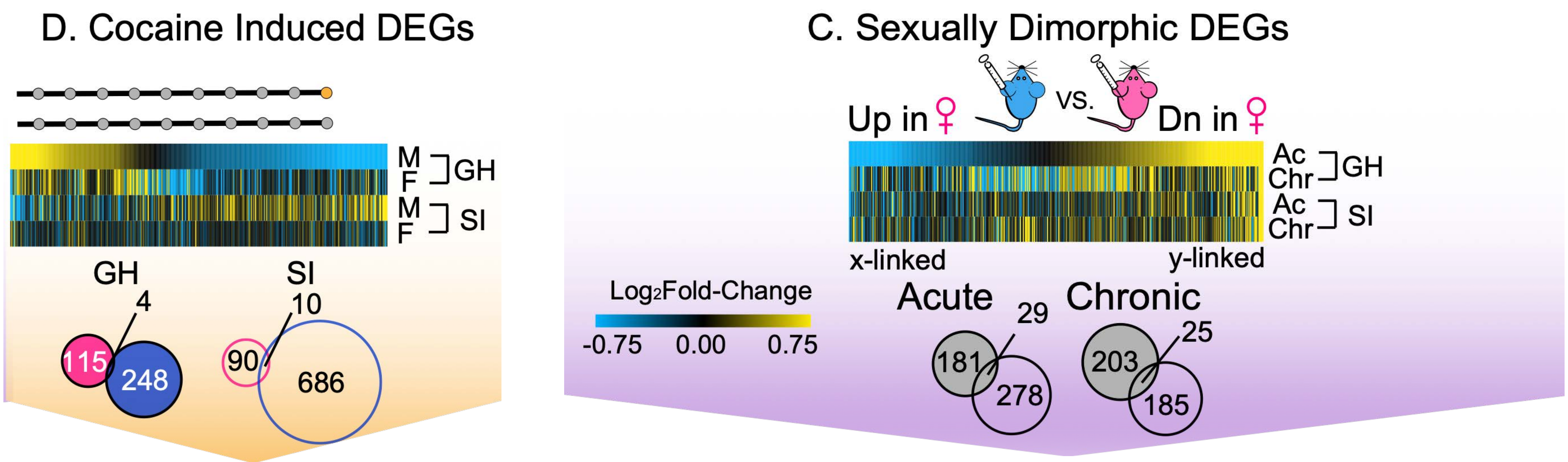




s adolescent social isolation alter the transcriptional response to c



Gain of Sex Differences



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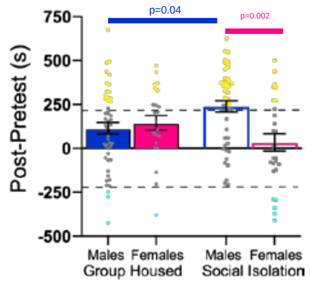

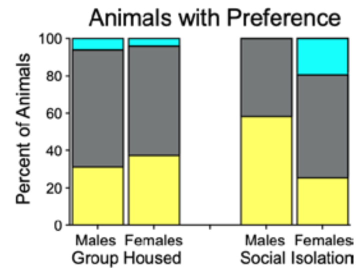

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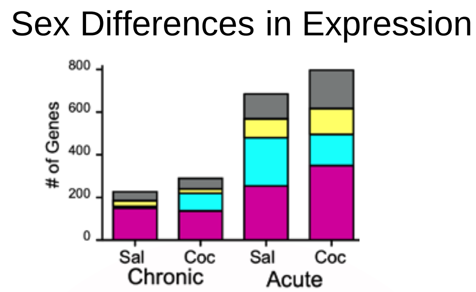

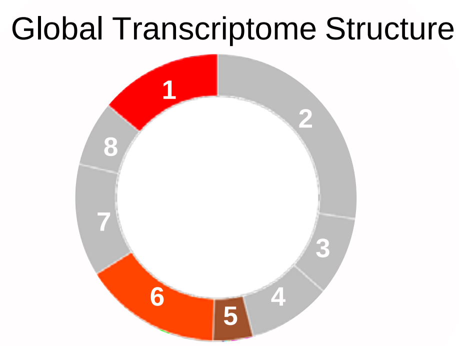

Loss of Baseline Sex Differences

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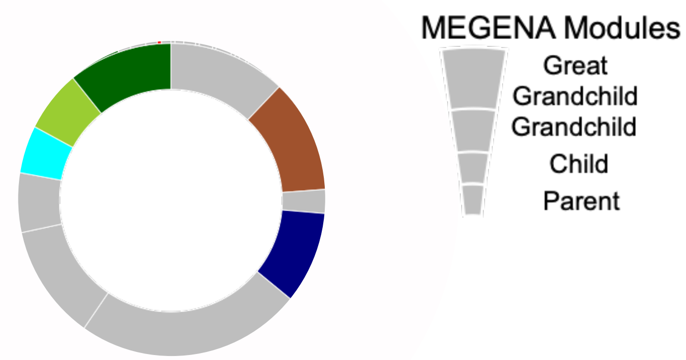
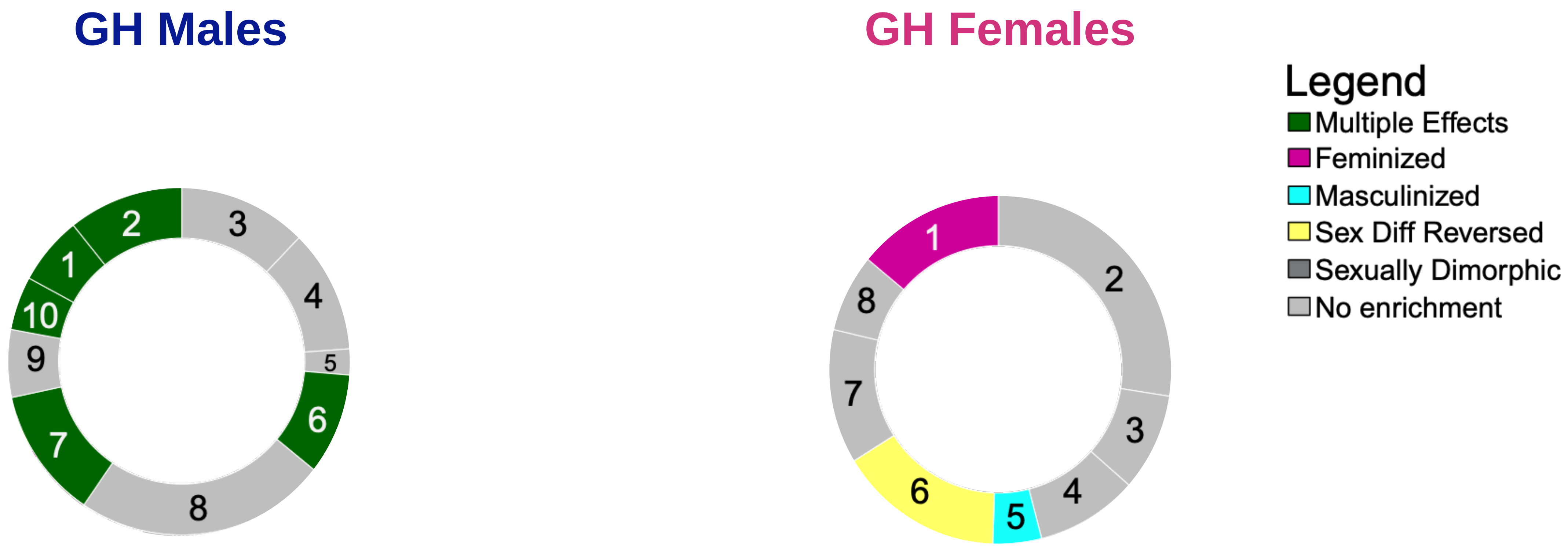
Do these sex differences disrupt global transcriptional structure?

Multi-Scale Embedded Gene Co-Expression Network Analysis (MEGENA) Shows Genes that are Changing Together across the Entire Transcriptome



MEGENA Reveals Global Co-expression is Disrupted by Adolescent SI



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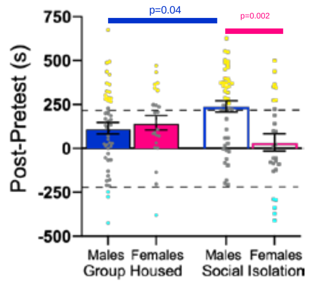

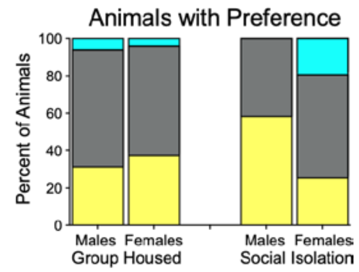

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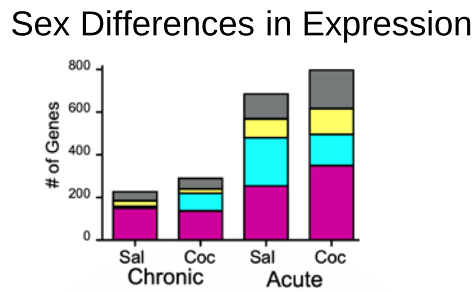
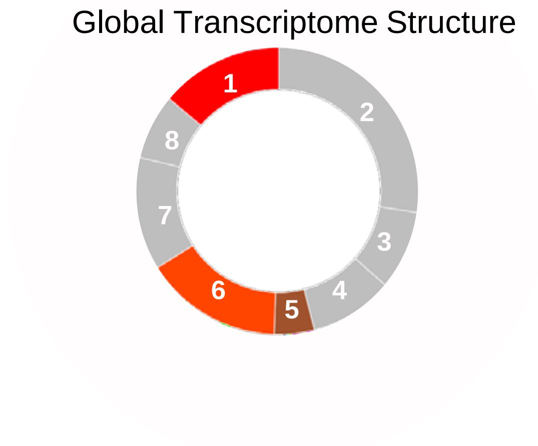




Loss of Baseline Sex Differences

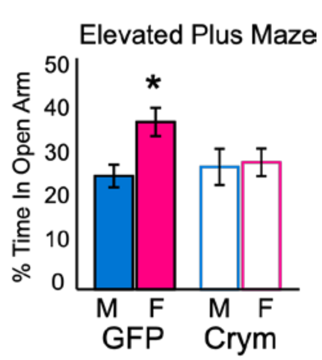
Gain of Sex Differences in Cocaine Response

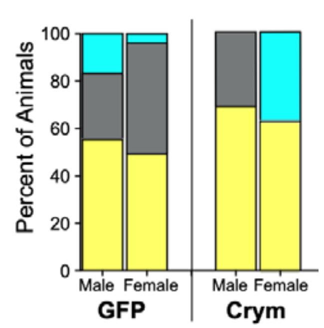
Gain of Sex Difference in Transcriptomic Structure:

SIM = Gain of Structure

SIF = Loss of Structure

Behavioral Effects of manipulation of conserved key driver in <u>adult</u> meAMY

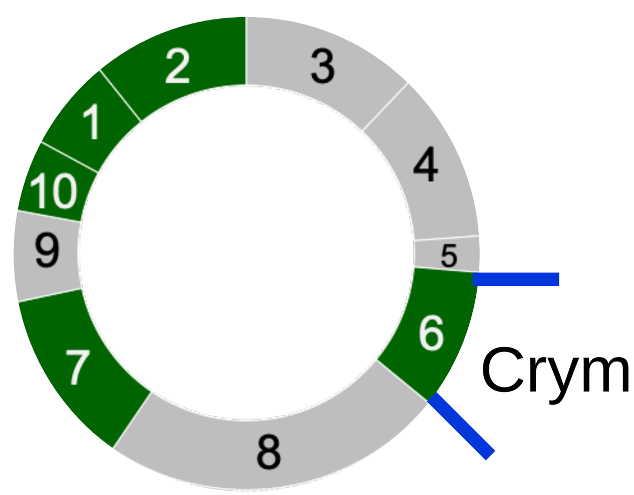




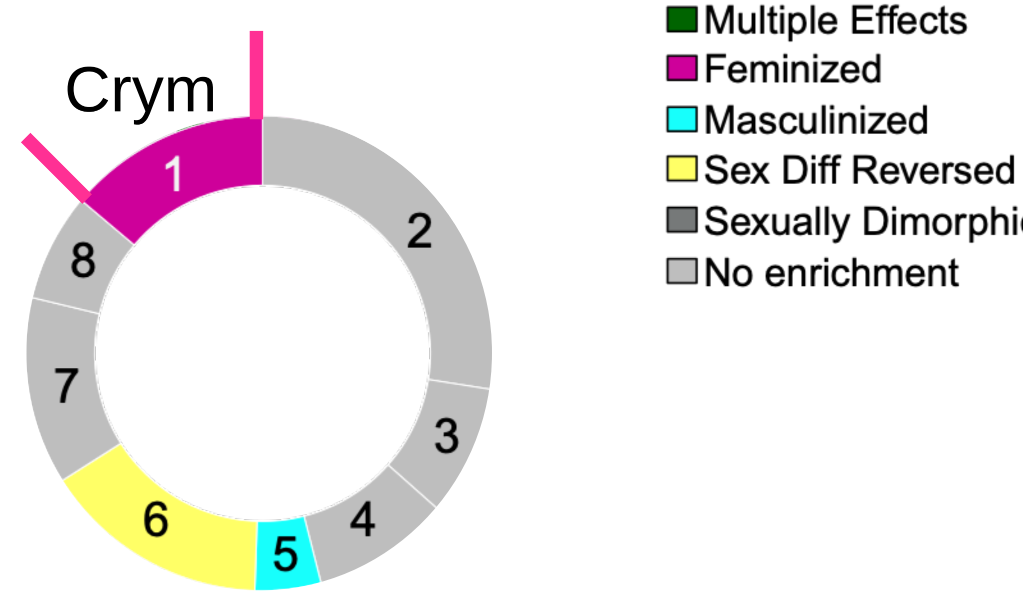
Can we integrate all levels of transcriptional analysis to identify key drivers of sex-specific response to SI?

Can We Leverage Co-Expression Analysis and Pattern Analysis to Identify Targets That Regulate Sex Differences in Reward?

GH Males



GH Females



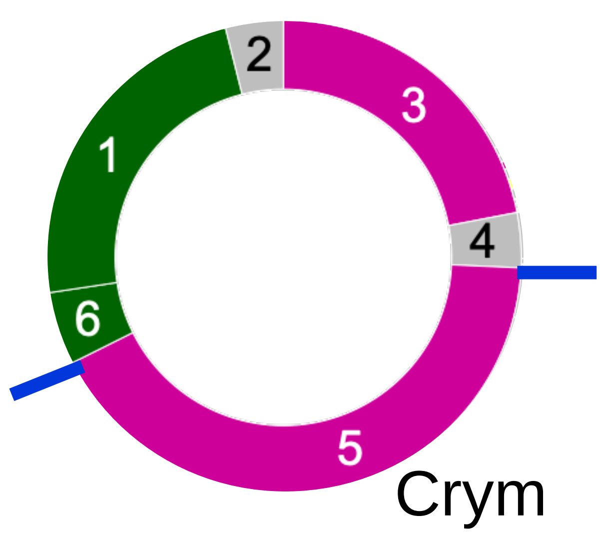
Key Driver:

Conserved across all groups
Modules Enriched in Sexually Dimorphic Genes

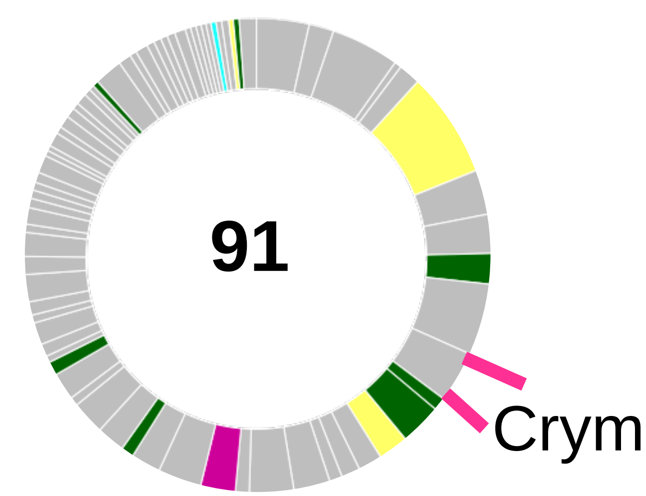
Sex-specific connectivity to genes in module

Key Driver is sexually dimorphic

SI Males

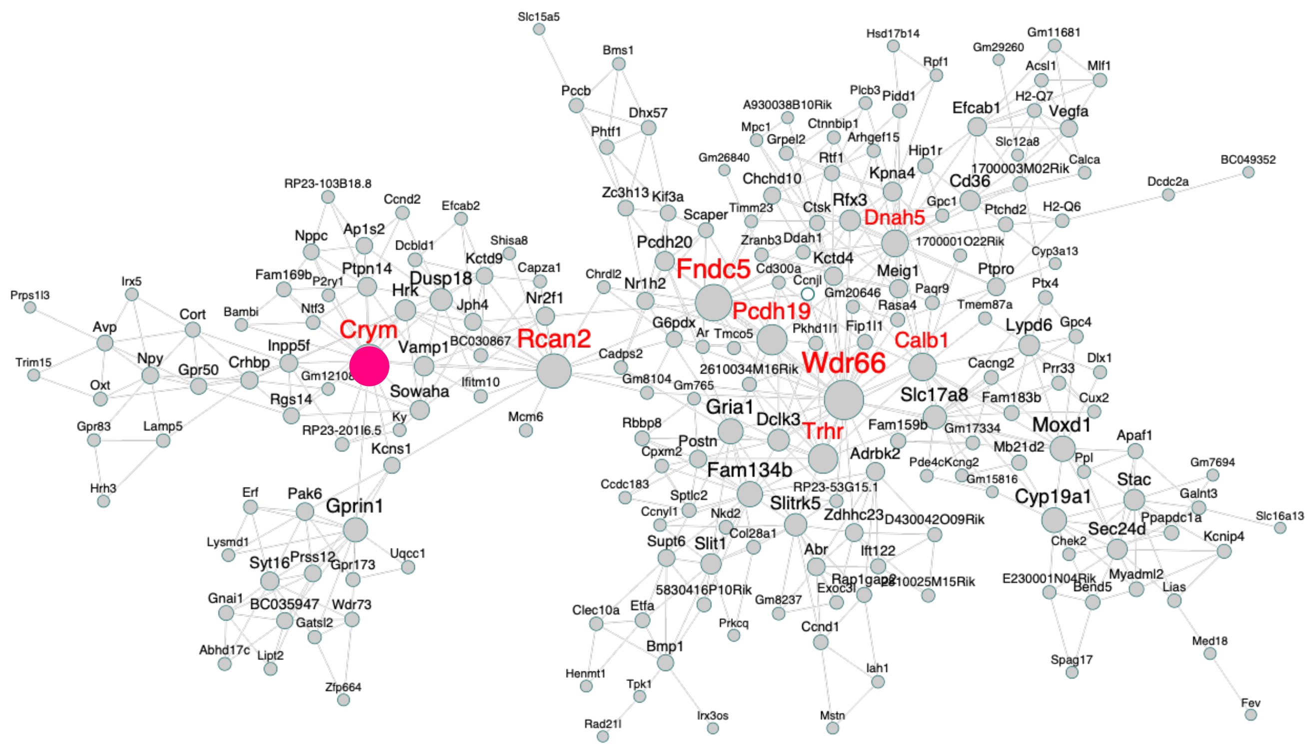


SI Females

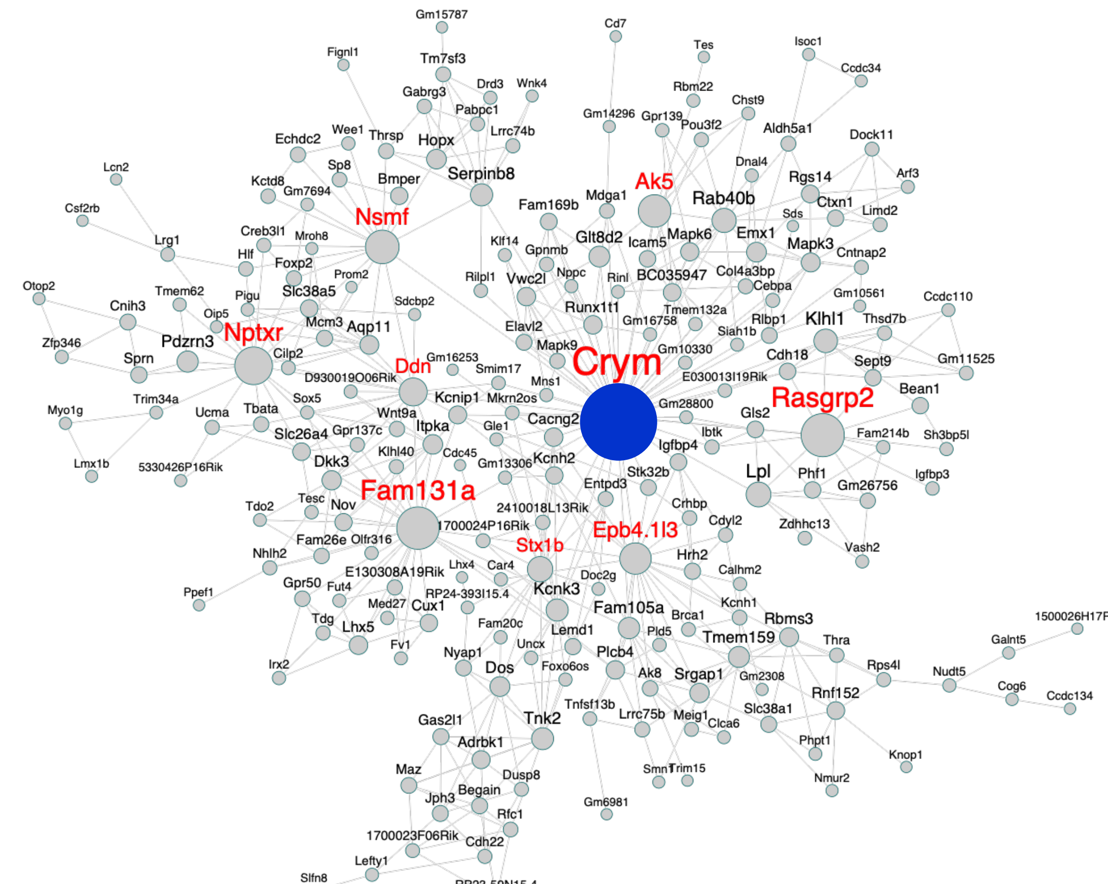


Crystallin mu (Crym) Is a Key Driver in All Groups and Is Differentially Connected in Males and Females

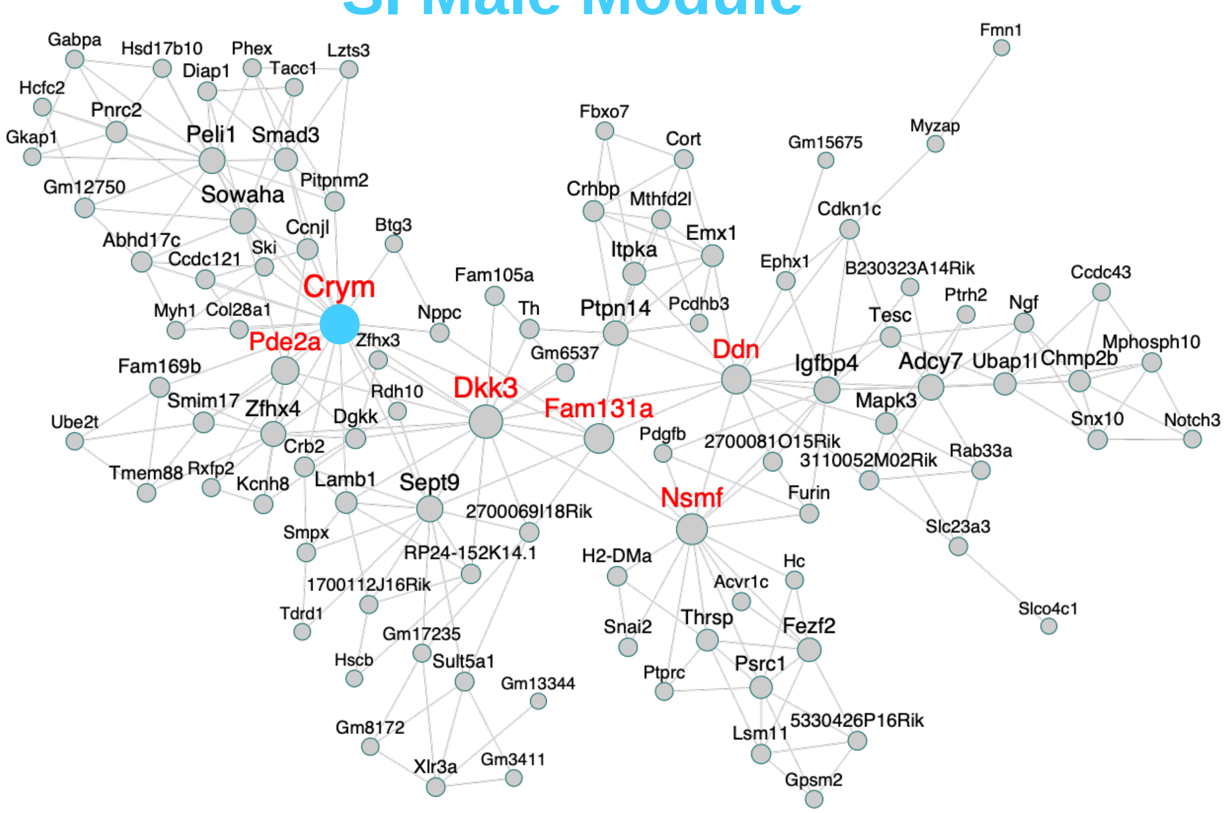
GH Female Module



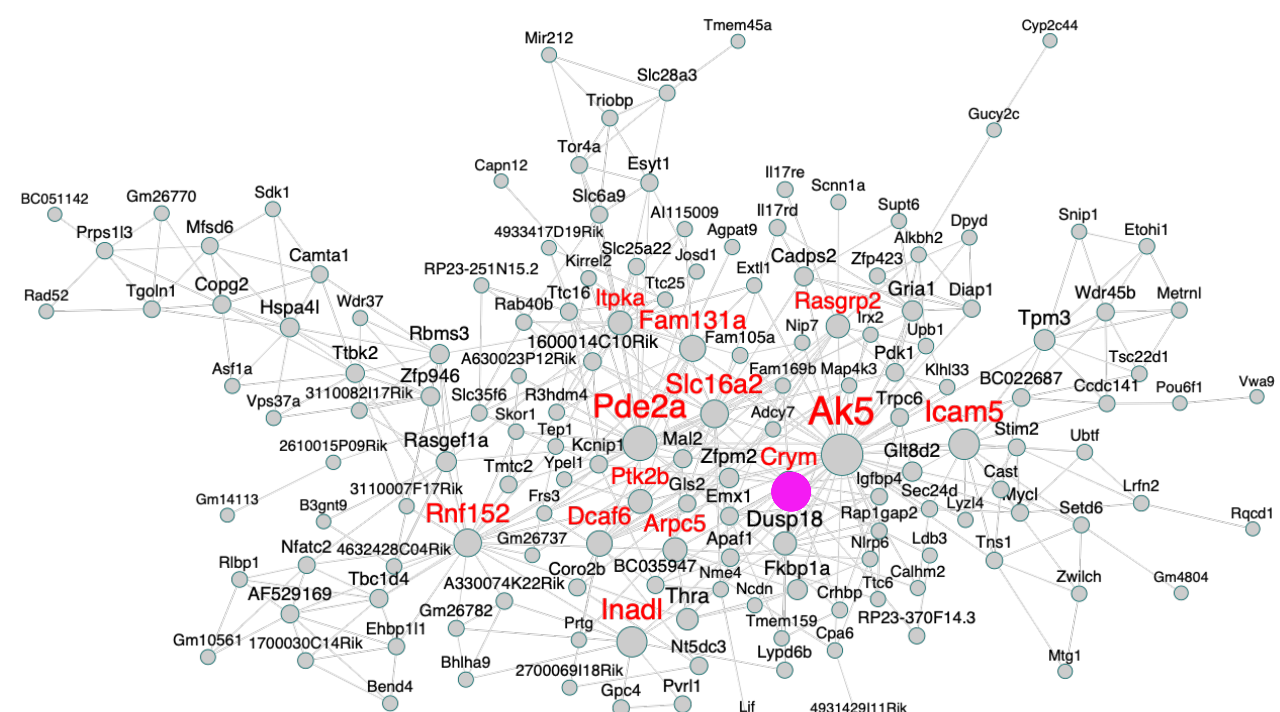
GH Male Module



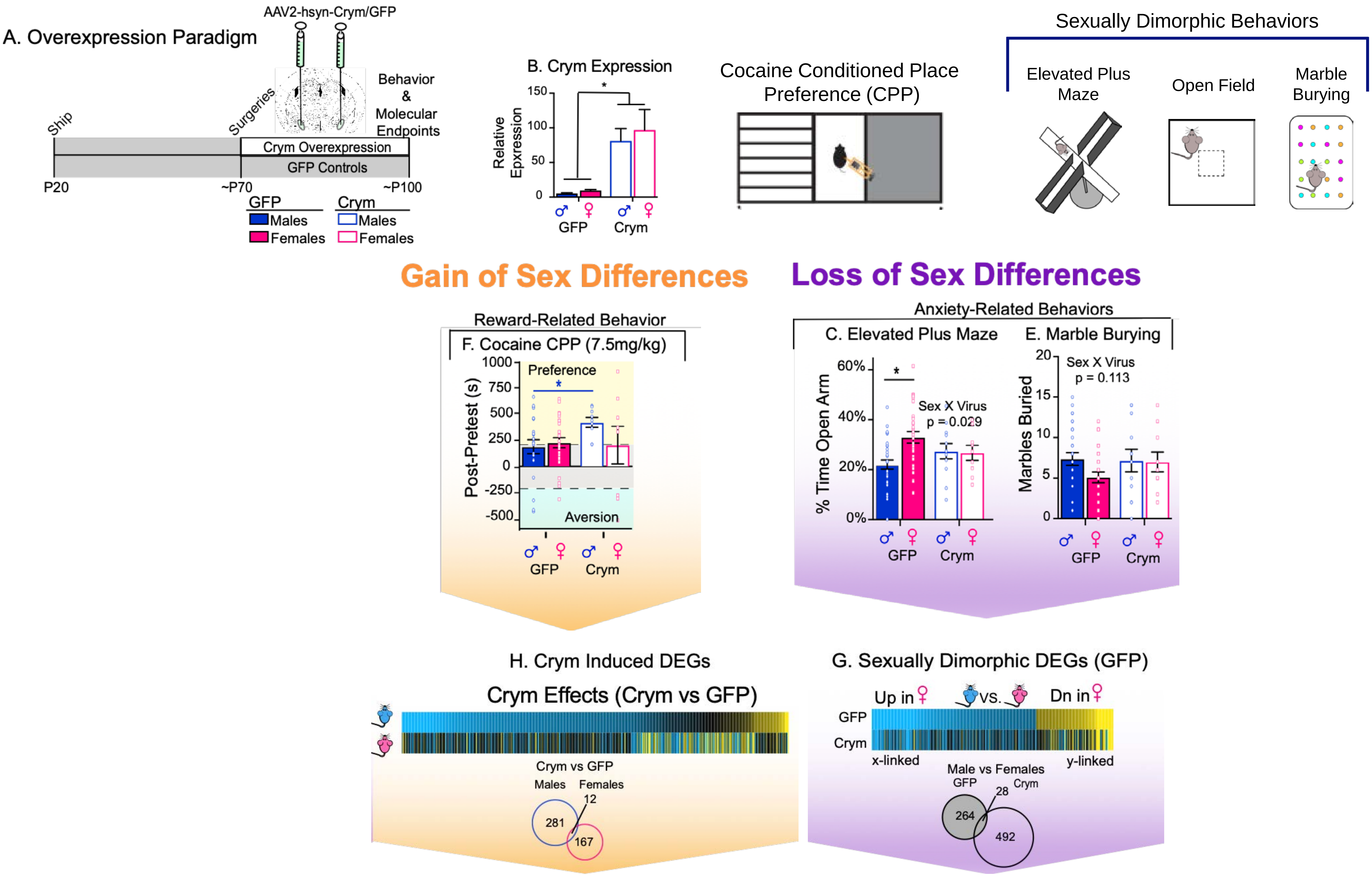
SI Male Module



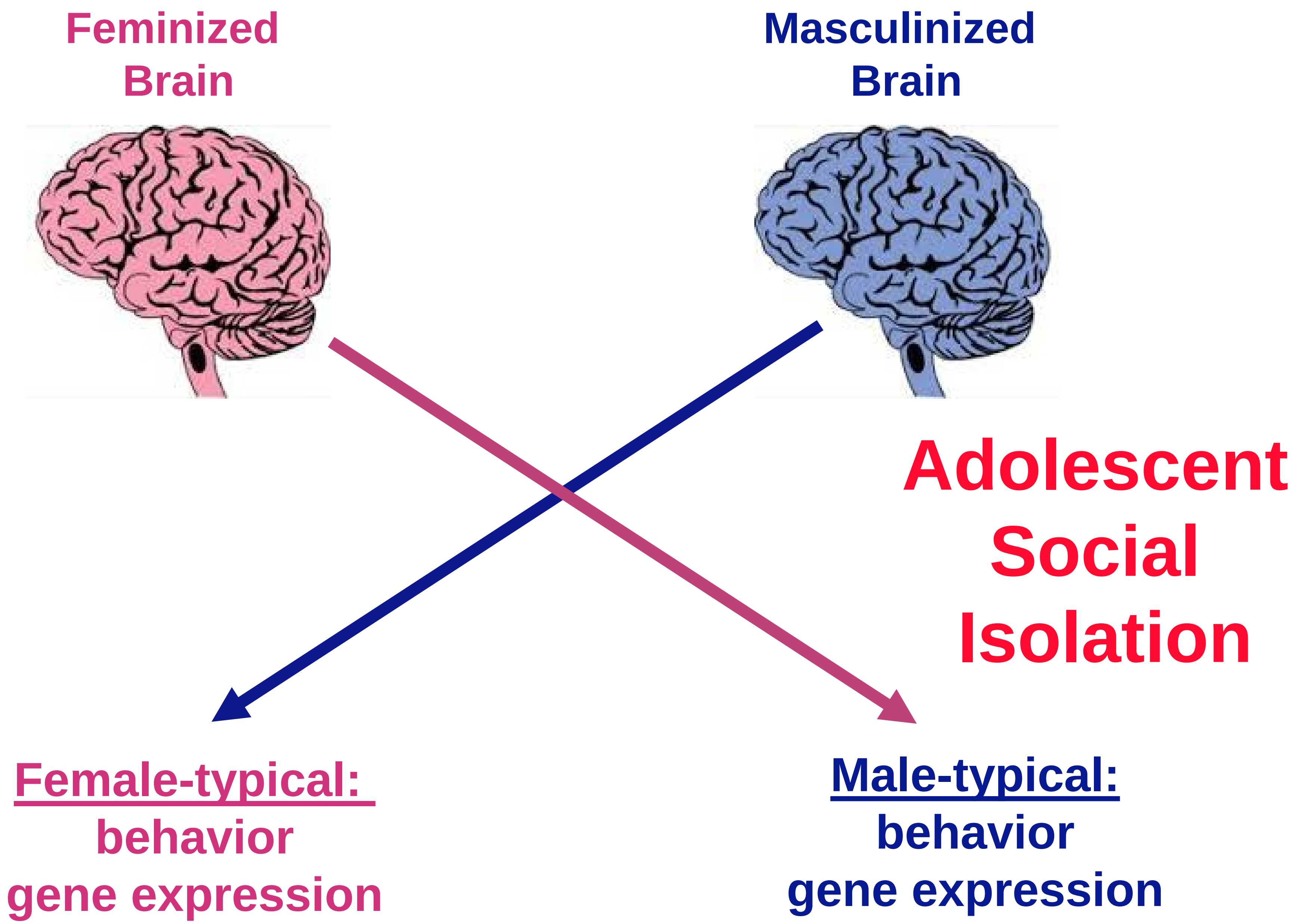
SI Female Module



Overexpression of Crym in the MeAMY Results in Sex-Specific Effects on Behavior



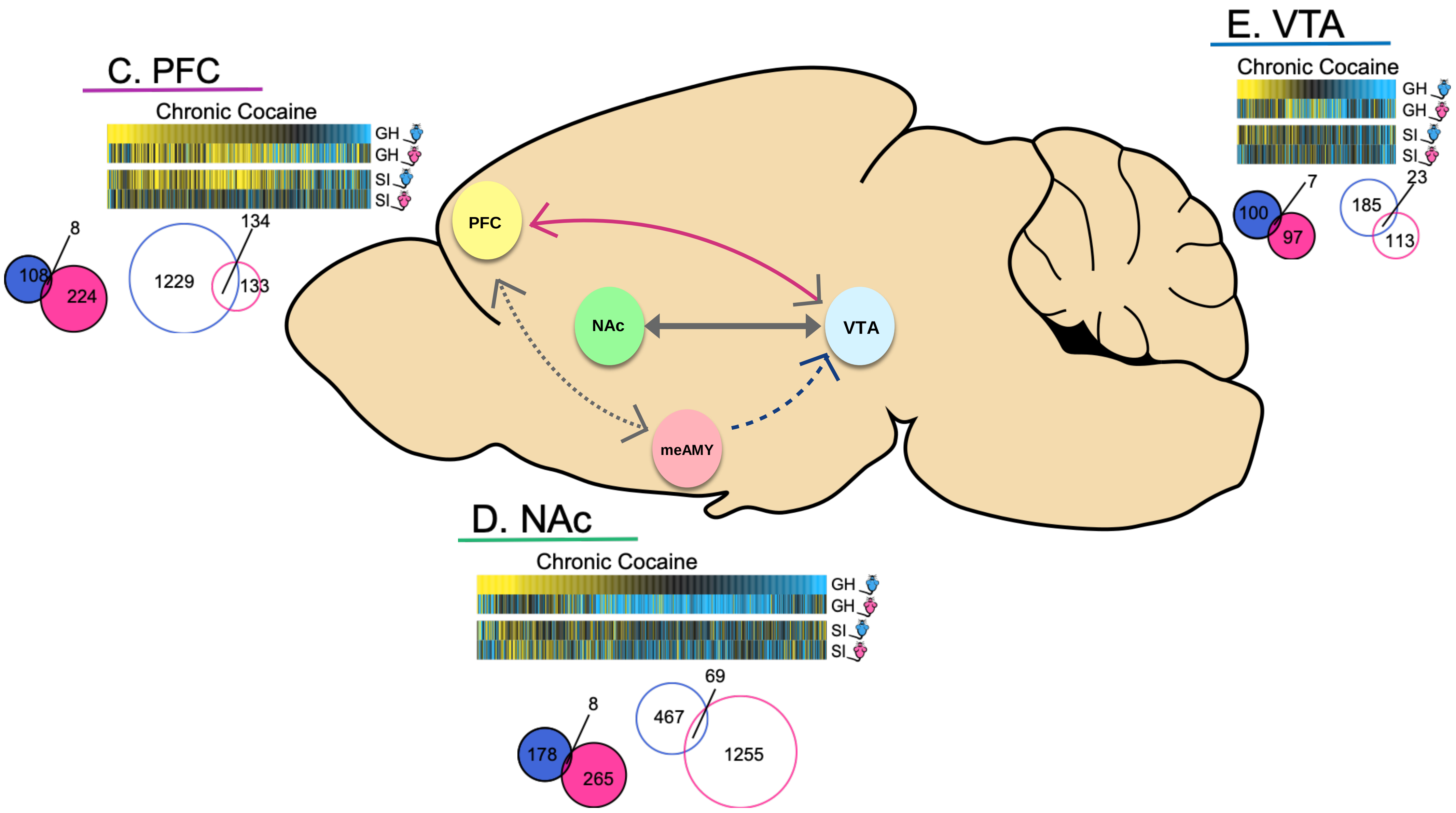
Conclusion: meAMY is Crucial for Regulating Sex-Specific Response to Cocaine in Adulthood



Establish the meAMY as a key regulator of sex-specfic reward-associated behaviors in adulthood at the circuit and molecular level.

Identify both sex-specific and sex-independent regulators of vulnerability to addiction-related behaviors

Using Disrupted Model of Sex-Specific Behaviors We can Understand Basic Mechanisms of Sex-Specific Transcription



Acknowledgments:

Nestler Lab:

Eric Nestler, MD, PhD

Hope Kronman

Ashley Cunningham

Peter Hamilton, PhD

Orna Issler, PhD

Yentl Van der Zee

Stephen Pirpinias

Ezekiell Mouzon

~~Casey Lardner~~

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Matthew Zucker

Janet Kim

Sonia Lombroso

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Marianne Seney, PhD (PITT)

Ryan Logan, PhD (PITT; Jackson Labs)

Andrew Wolfe, PhD (Johns Hopkins)

Georgia Hodes, PhD (Virginia Tech)

National Institute on Drug Abuse
Advancing Addiction Science

NIDA–K99DA042100 (DMW)

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Allison Milian

National Institute on Drug Abuse
Advancing Addiction Science

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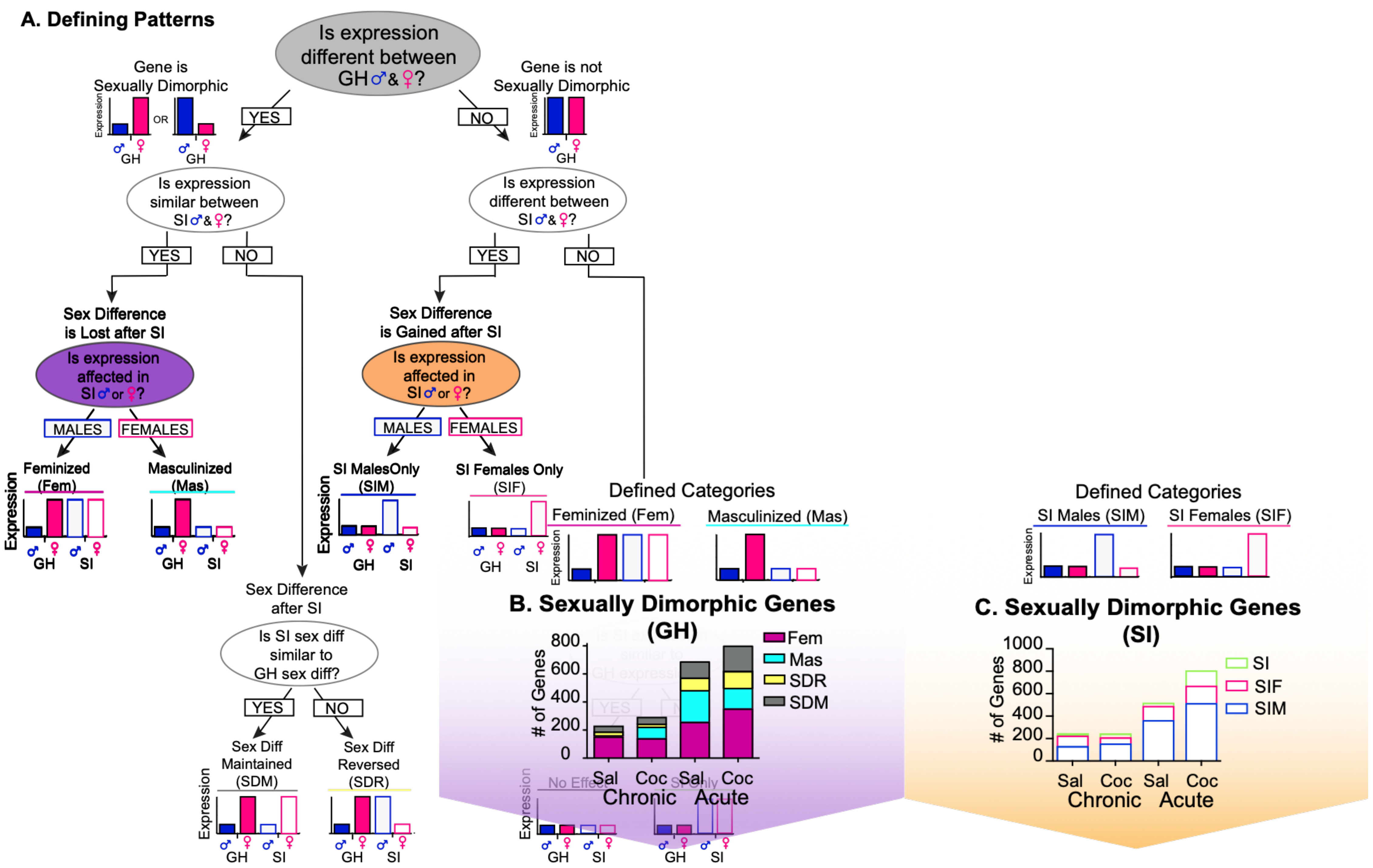
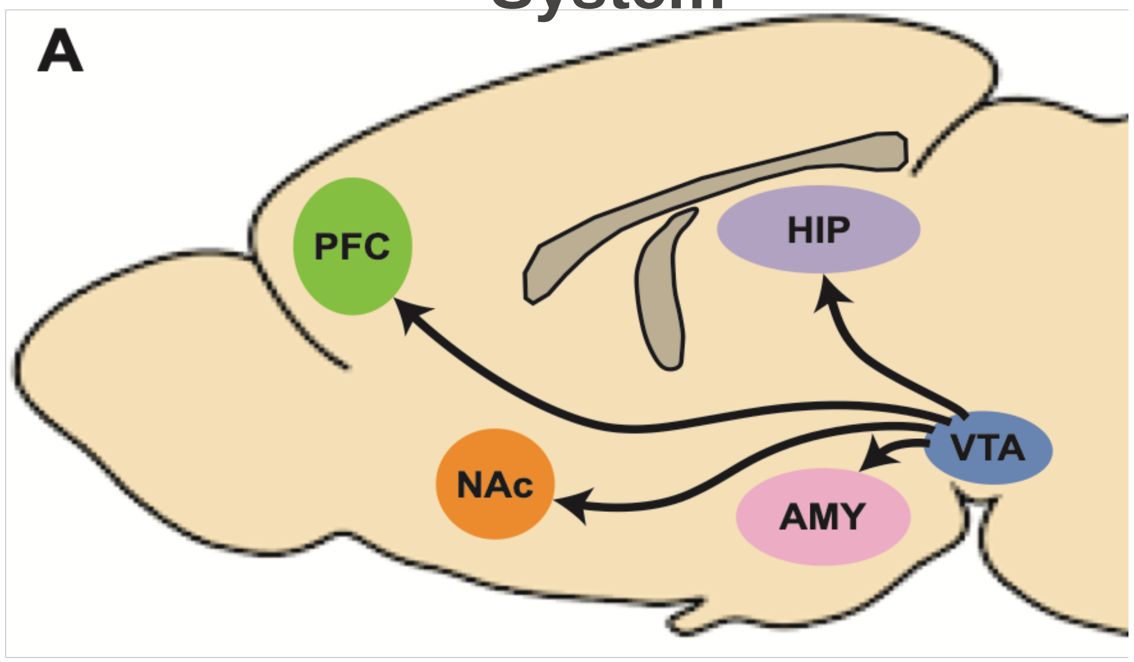
OREGON HEALTH & SCIENCE UNIVERSITY

Does adolescent SI alter baseline sex differences and how can we account for those differences in the analysis?



Development of Mesocorticolimbic Dopamine Circuitry is Coupled with Hormone Changes During Adolescence

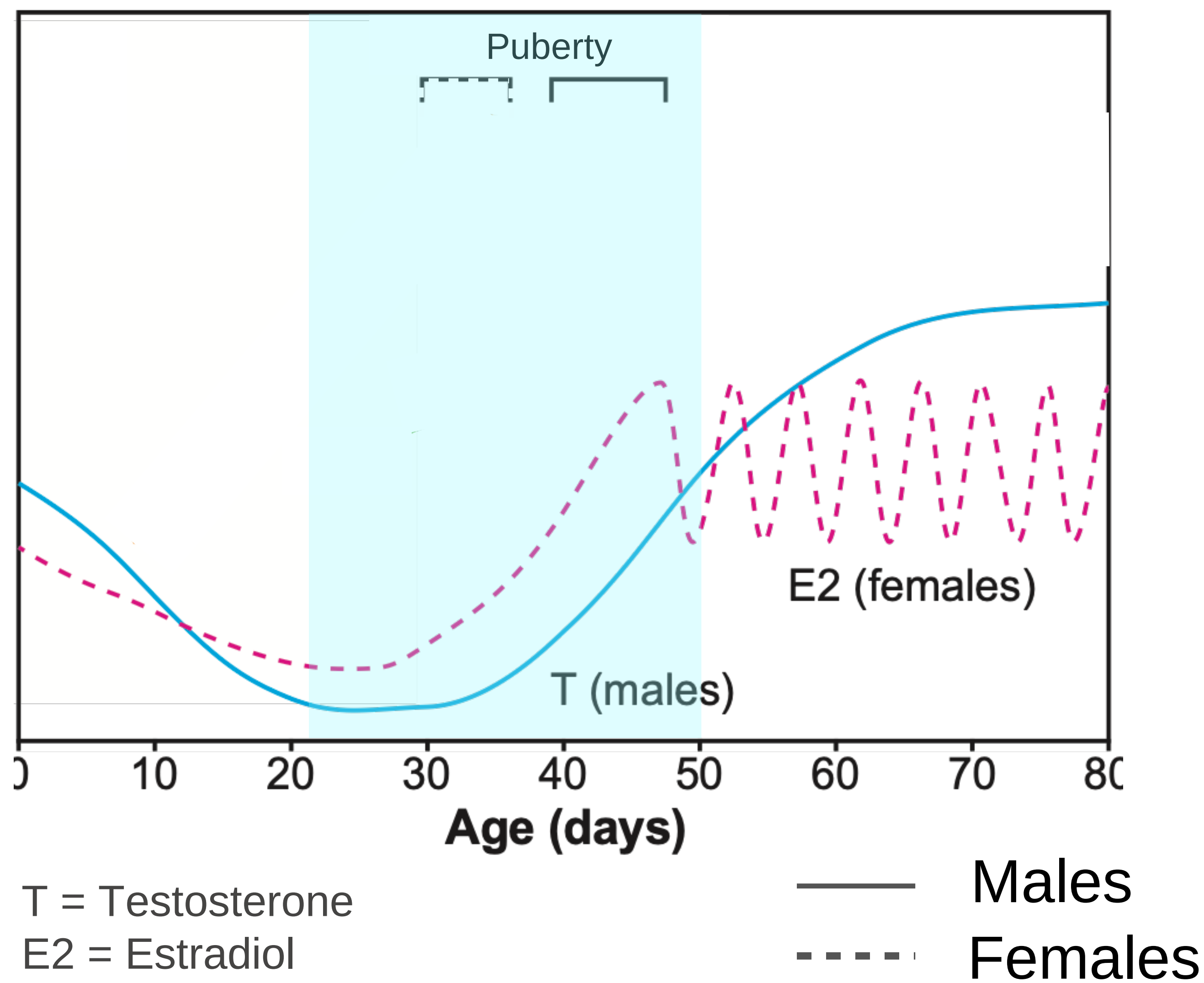
Mesocorticolimbic Dopamine System



Walker DM et al., 2018 J. Neuroscience

- **Perturbations during this period could alter DA signaling and function.**
- **Sex differences in adolescent development means that stress could have sex-specific effects on DA function in adulthood**

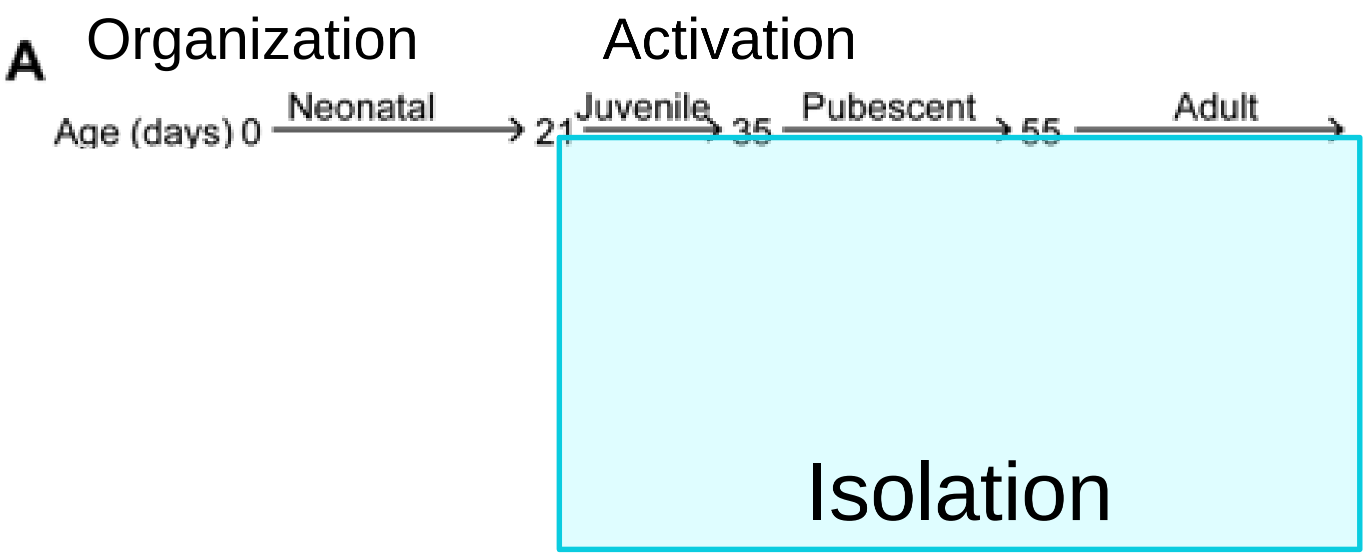
Dopamine Changes Across Adolescence



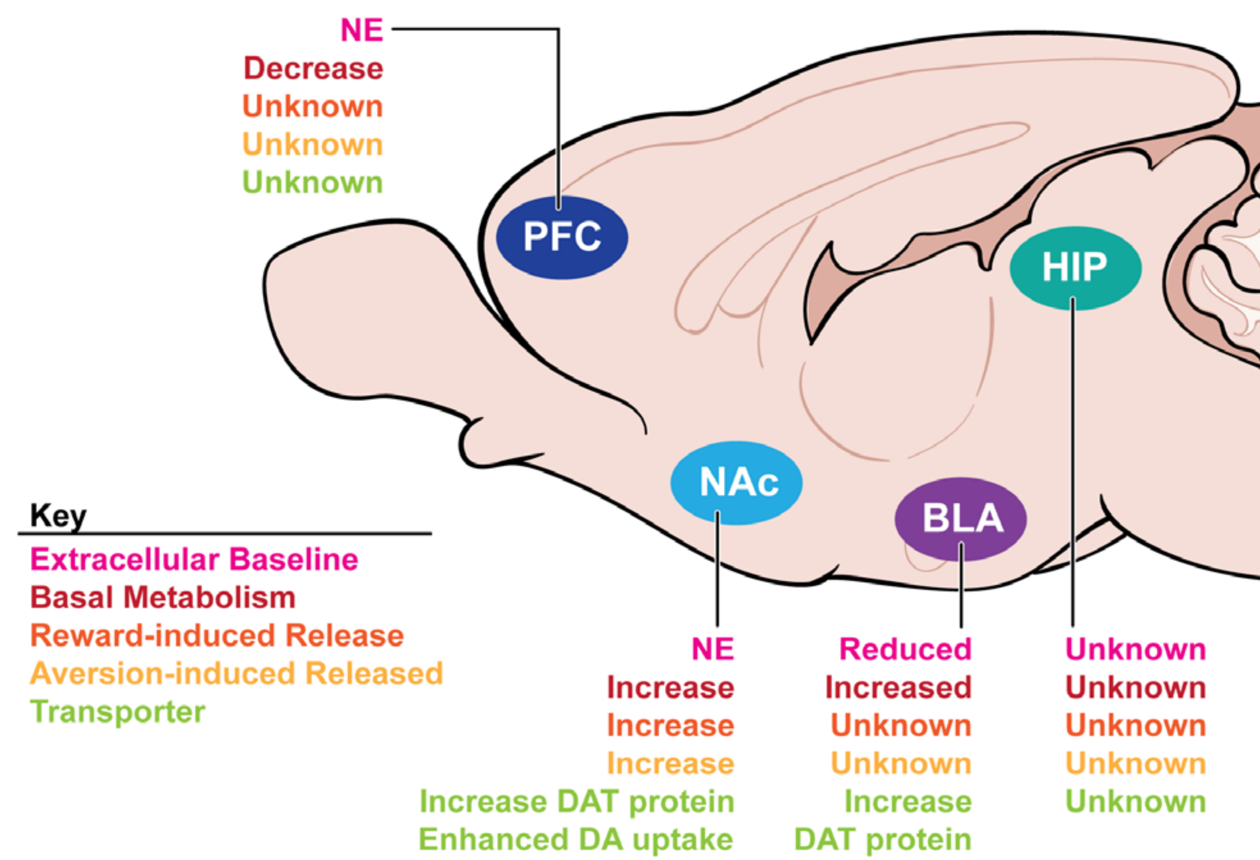
PFC = Prefrontal Cortex; NAc = Nucleus Accumbens; VTA = Ventral tegmental Area; HIP = Hippocampus

Walker DM et al., 2018 J. Neuroscience

Adolescent Social Isolation Stress (SI) as Preclinical Model of Addiction Susceptibility

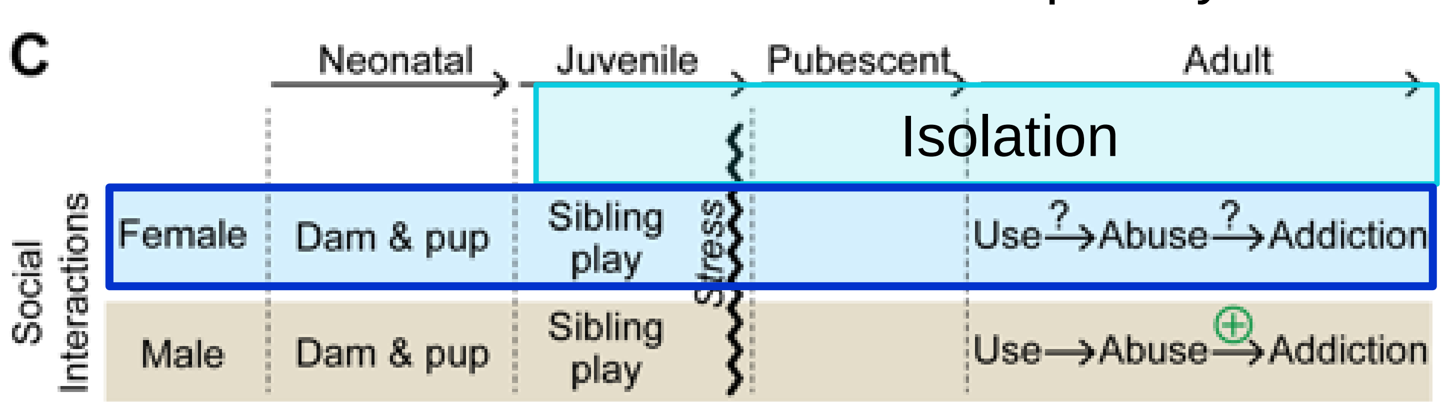


Social Isolation Alters DA Dynamics in the Reward Circuitry



NE = No Effect; DA = Dopamine
DAT= Dopamine Transporter

Social Isolation Increase Addiction Susceptibility in Males



Can't separate effects of long-term isolation vs adolescent specific effects

Few studies examine females

Walker DM et al, 2019 Frontiers in Behavioral Neuroscience

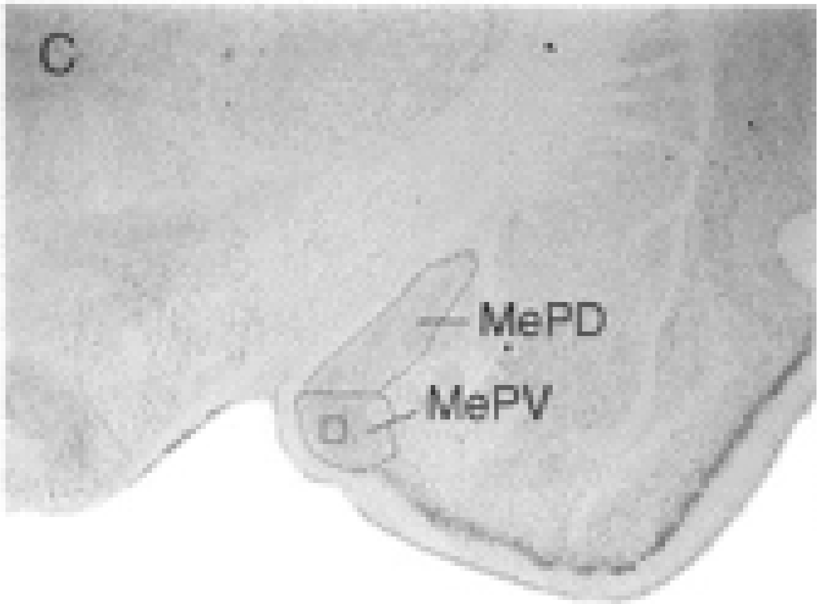
The Medial Amygdala Regulates Behaviors the Emerge During Adolescent Development

Feeding

Social Behavior

“Play” Behavior

(Reviewed in, Knapska E et al., 2007)



- **Sexually Dimorphic (M>F)**
- **Organized by Pubertal Testosterone Surge in Males**

(DeLorme et al., 2012)

- **Adolescent Social Isolation Results in a Smaller Medial Amygdala in Male Rats.** **(Cooke, BM et al., 2012)**
- **Little is Known Regarding its Response to Drugs of Abuse**