Changes in Brain Volume and Cognition in Mice Exposed *In Utero* to ABC/ 3TC-ATV/ RTV

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Workshop on HIV & Women

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University Health Network

UNIVERSITY OF TORONTO

Women and HIV

- 1.5 million HIV+ women become pregnant each year
- Combination antiretroviral therapy (cART) recommended during pregnancy
- Successfully prevent vertical transmission of HIV
- Uncertainty about the potential long-term effects cART-exposed children

Fetal Programming: Developmental Origins of Health and Disease (DOHaD)

Adverse *In utero* Environment

HIV & cART

Insults During Fetal Growth

Low Birth Weight
Preterm

Predisposition to chronic diseases and developmental delays

HIV-Exposed Uninfected (HEU) Children

- Increased susceptibility to infection
- Stunted growth in early life
- Smaller head circumference
- Speech and language delay
- Deficits in cognitive and motor development

HEU and Cognition

Longitudinal development of cognitive, visuomotor and adaptive behavior skills in HIV uninfected children, aged 3–5 years of age, exposed pre- and perinatally to anti-retroviral medications

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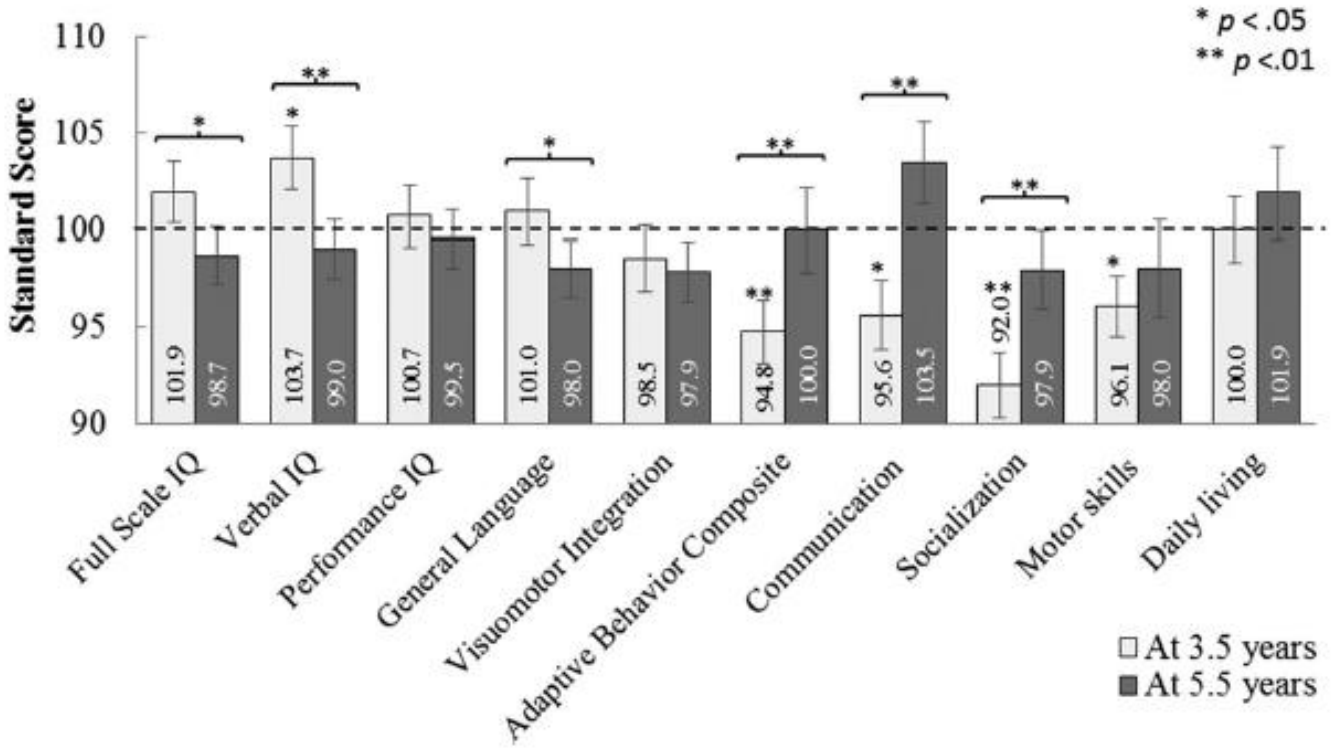


Hypothesis

Perinatal cART exposure alters fetal development, and results in impaired neurological development by adversely affecting the growing brain and nervous system

Consideration

- Delineate the effect of the drugs from HIV
- Timely information
- Test different drug regimen
- Genetically identical—eliminates genetic variations

Objective 1

To assess the impact of *in utero* exposure to cART on fetal brain morphology

Approach

Pregnancy

Female
C57BL/6 mice

GD1

Control

cART

GD15.5

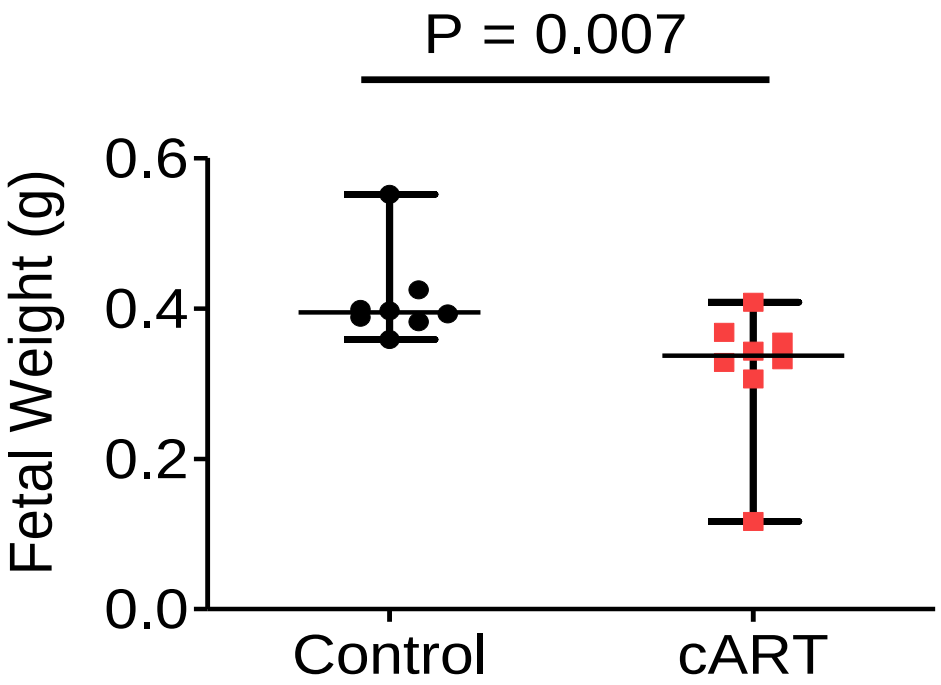
Fetuses

Micro-CT scan

- Volumetric analysis

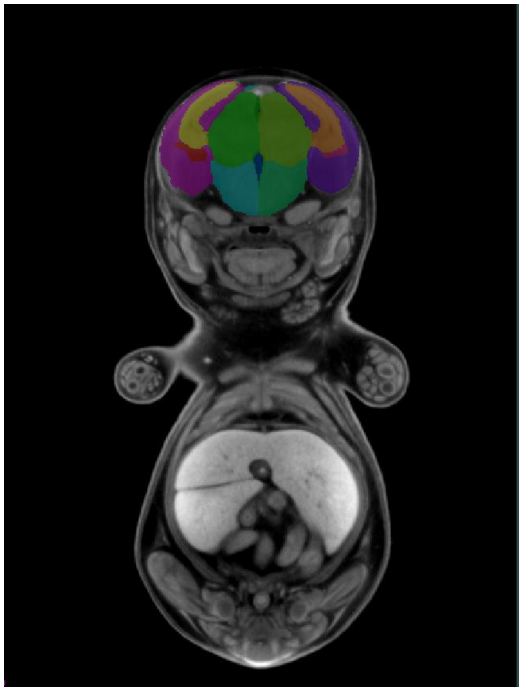
cART=ABC/3TC+ATV/RTV

cART was Associated with Low Fetal Weight in Pregnant c57BL/6 mice

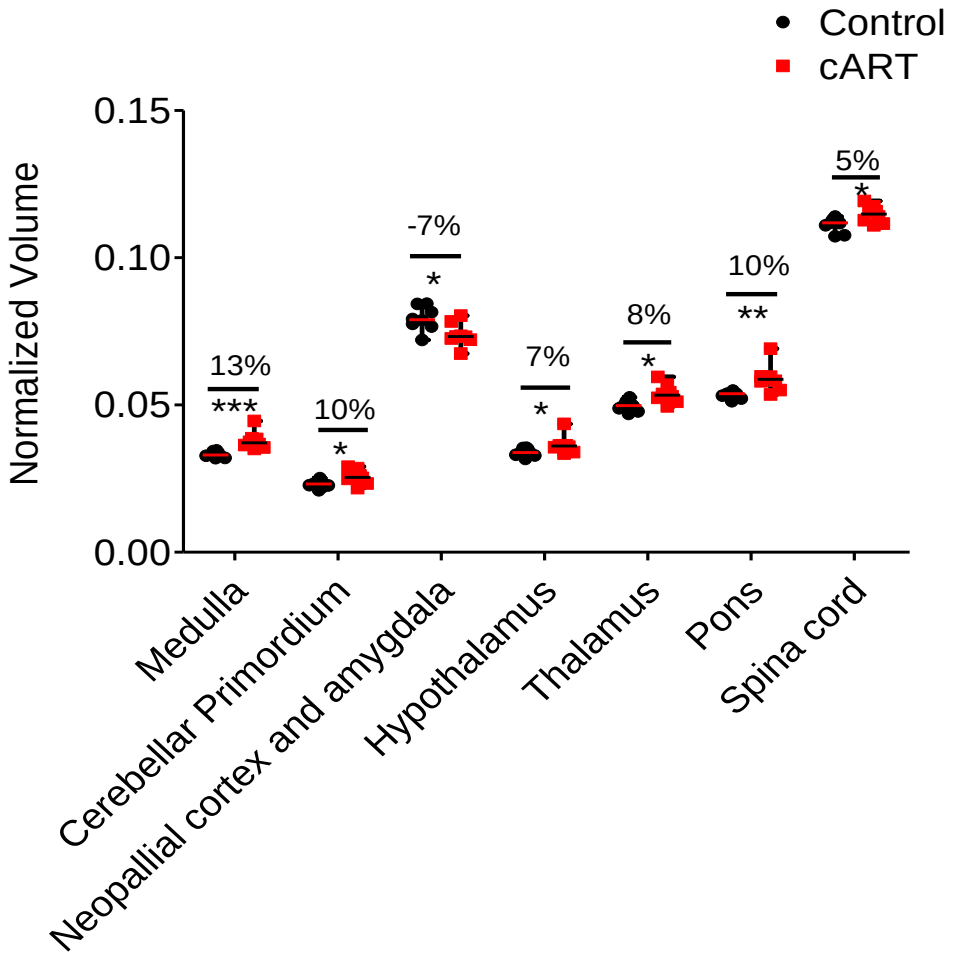


Data = Mean and Range; Statistics = Mann Whitney; n=8 litters/group

cART was Associated with Changes in Volumetric Measurements in different Regions of Fetal Mouse Brain



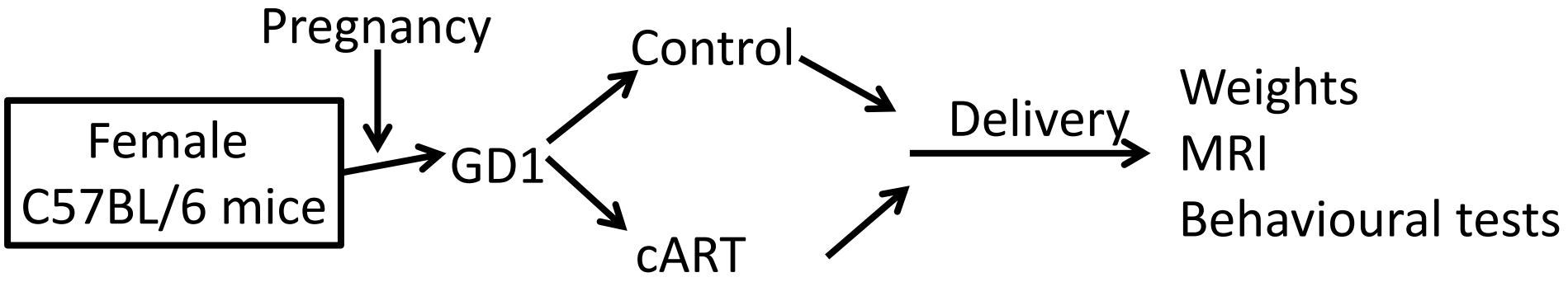
Noecortex and amygdala (purple), thalamus (green), Hypothalamus (blue),



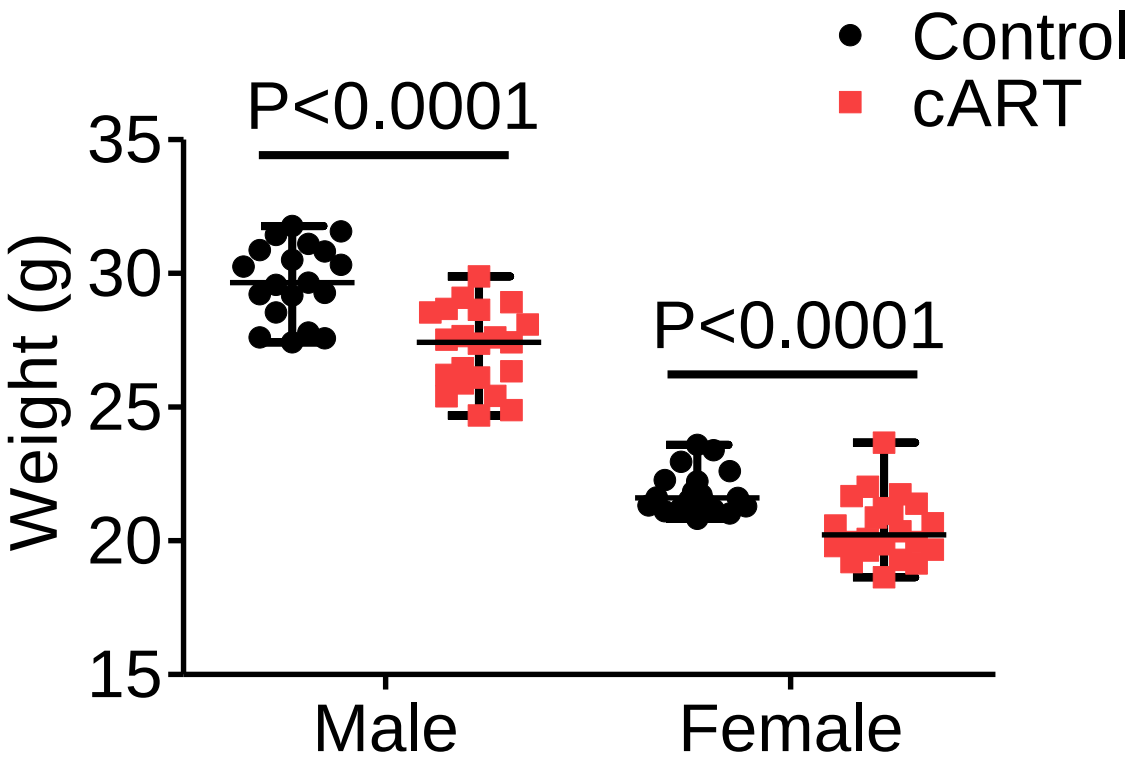
Data = Mean and Range; Statistics = Mann Whitney; n=8

What about adult mice?

Approach

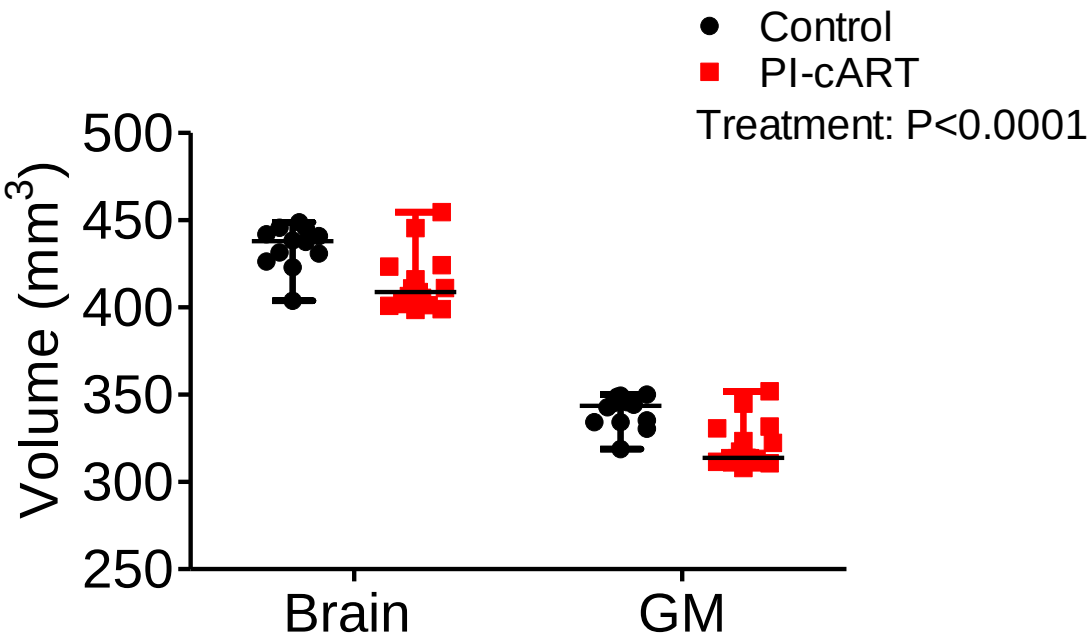

Pregnancy
Female
C57BL/6 mice
GD1
Control
cART
Delivery
Weights
MRI
Behavioural tests

cART Exposed Mice were Smaller than the Controls



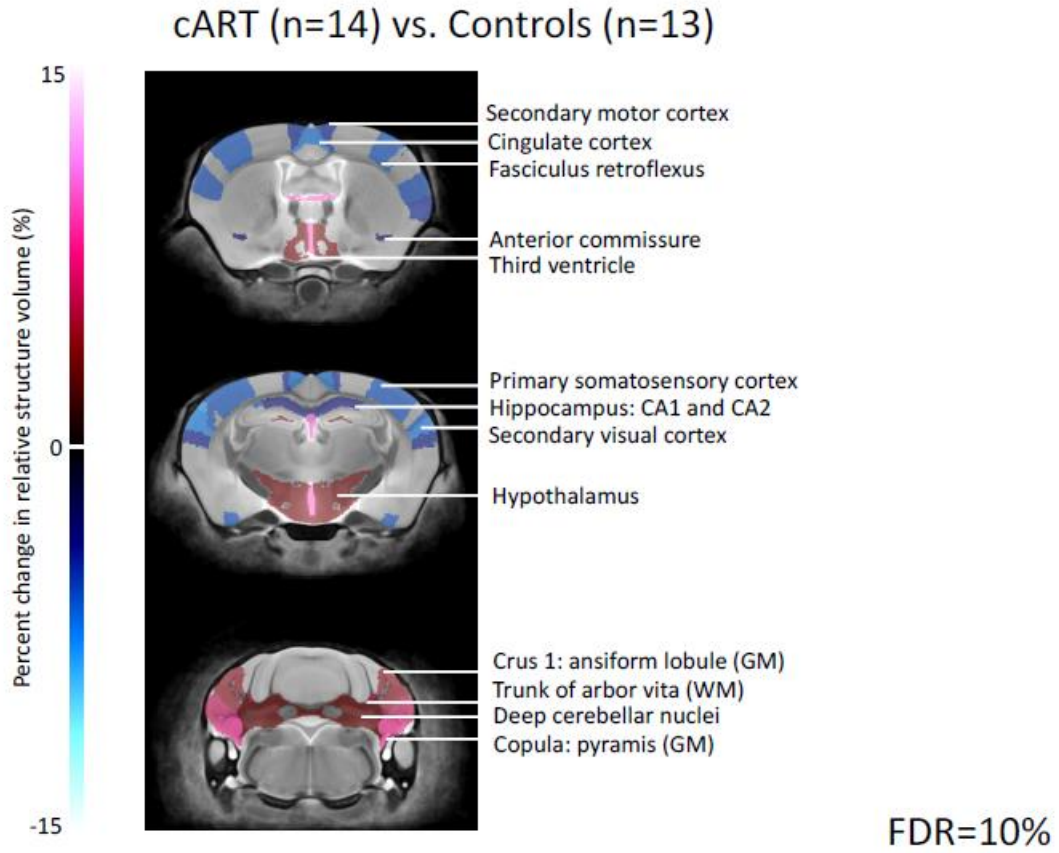
Data = Median and Range; (Two way ANOVA; n= 20-22 per group)

cART-exposed Mice had Smaller Brains than the Controls



Data = Median and Range; (Two way ANOVA; n= 13-18)

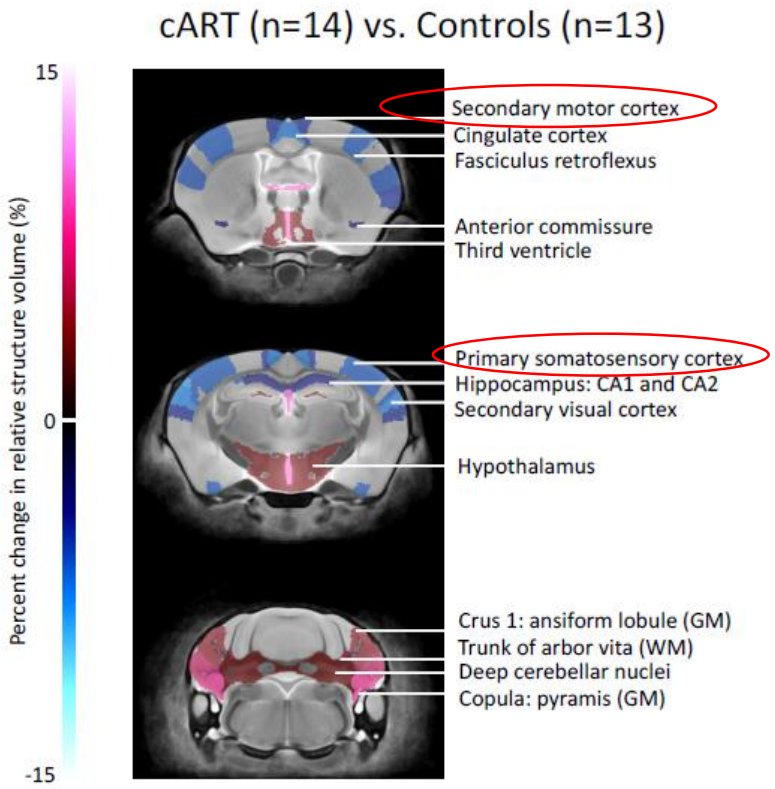
cART was Associated with Changes in Volumetric Measurements in Different Regions of an Adult Mice Brain (MRI)

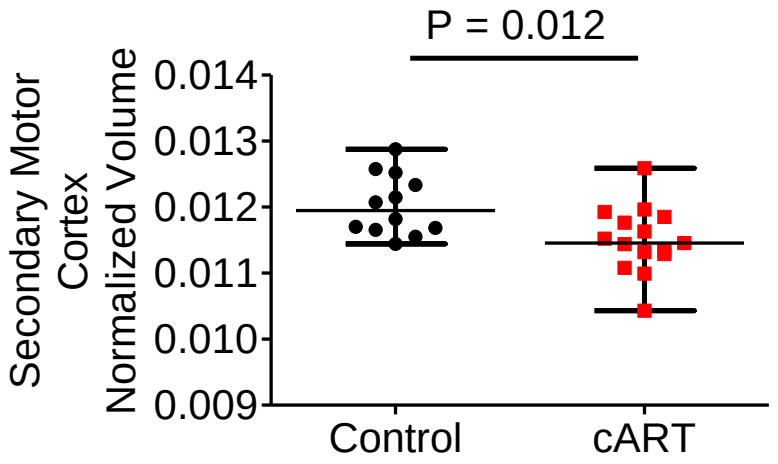


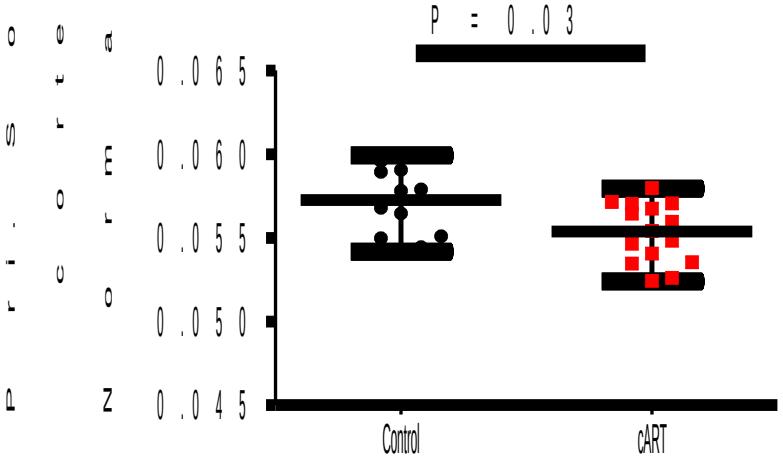
Objective 2

To assess the impact of in utero exposure to cART on cognitive, neurosensory and motor behaviours

cART was Associated with Changes in Volumetric Measurements in Different Regions of an Adult Mice Brain (MRI)



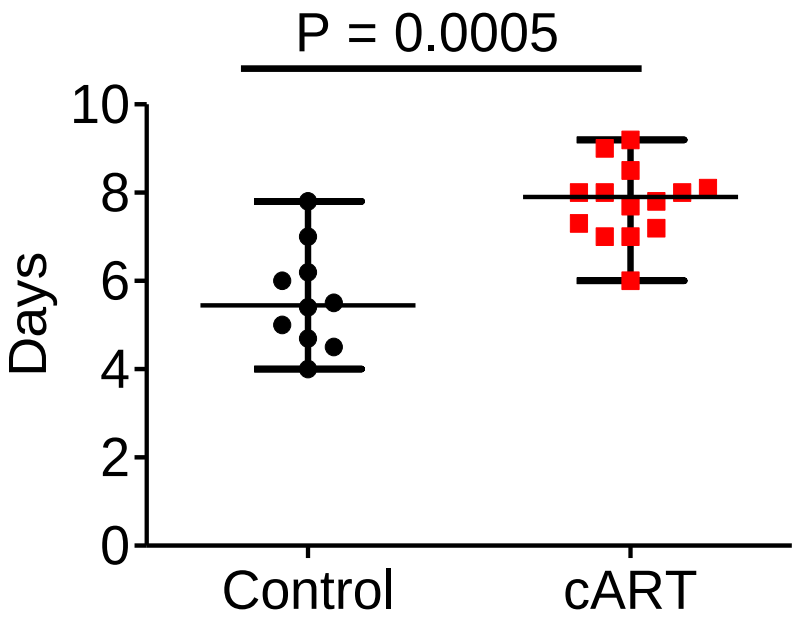


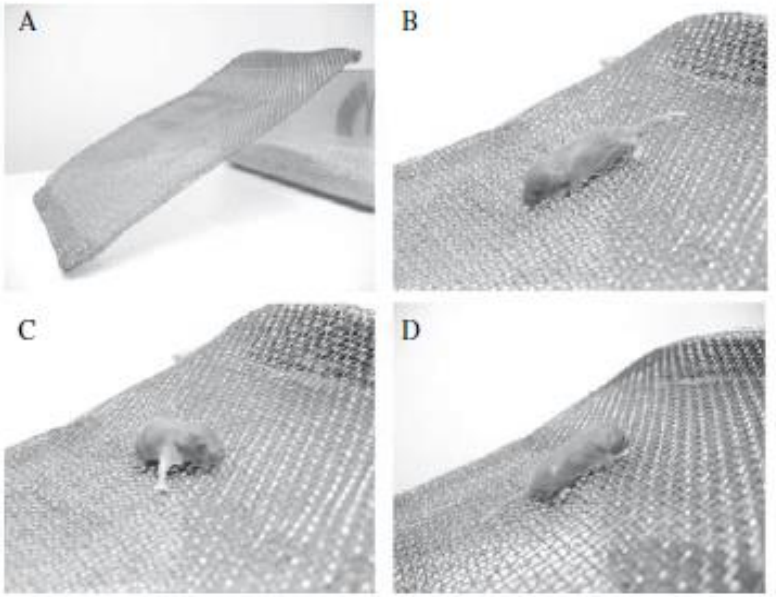


Data = Mean and Range; Statistics = Mann Whitney; n=13-16

Strength and Coordination

The Development of Motor Skills was Delayed in Mice Exposed to cART *In Utero*



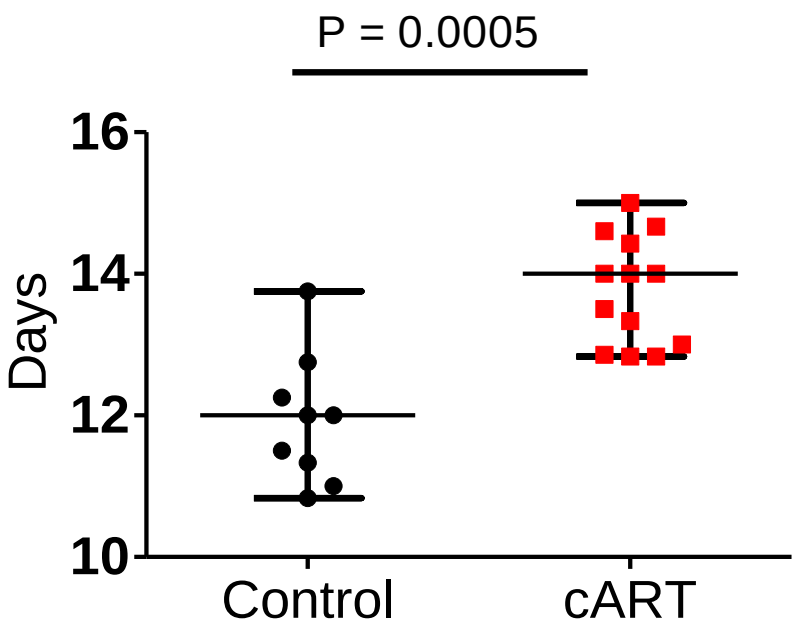


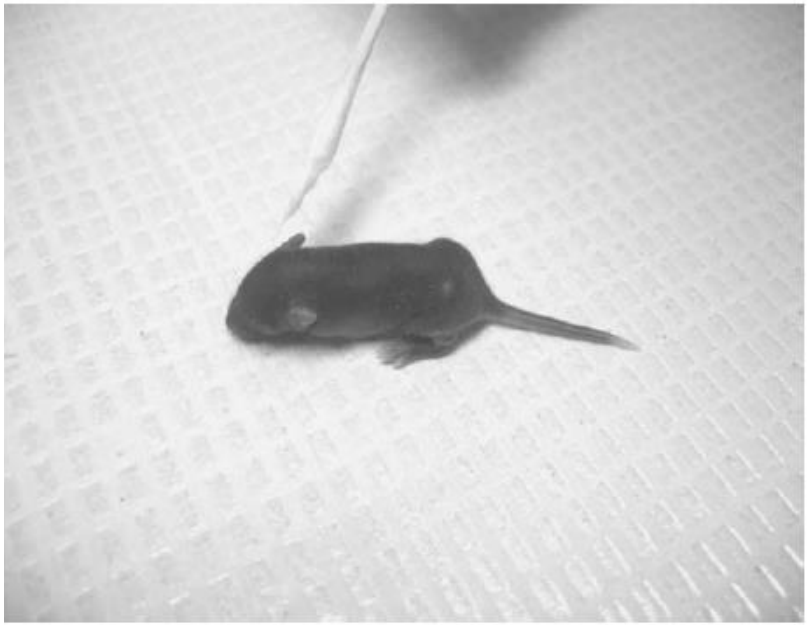
Joanna et al, *Neuromethods, Vol. 39: Neuropeptide Techniques*

Data = Median and Range; (Mann Whitney; n= 10-15 for Litter Average)

Tactile Reflex

The Development of Tactile Reflex was Delayed in Mice Exposed to cART *In Utero*





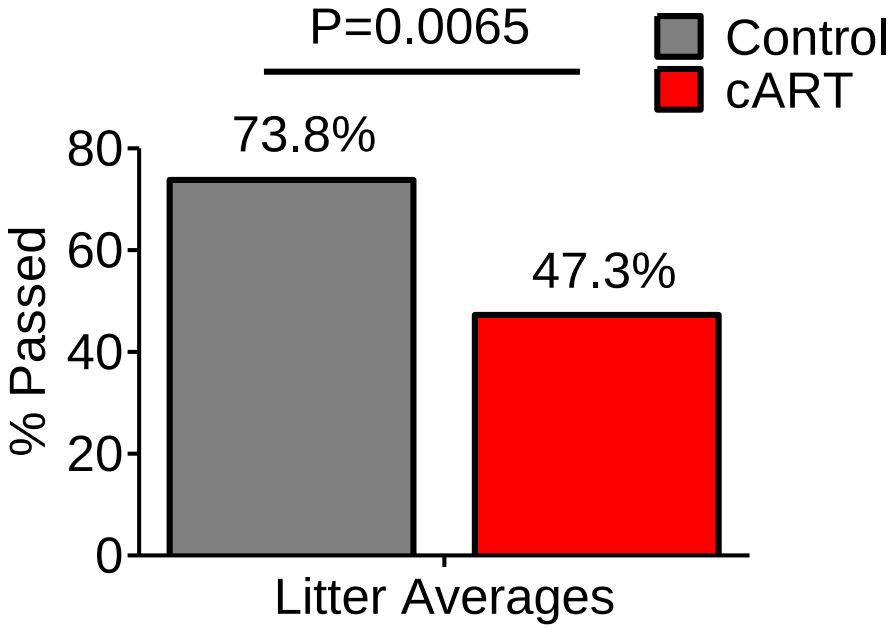
Joanna et al, *Neuromethods, Vol. 39: Neuropeptide Techniques*

Data = Median and Range; (Mann Whitney; n= 10-15 for Litter Average)

Olfactory Reflex

The Development of Olfactory Reflex was Delayed in Mice Exposed to cART *In Utero*

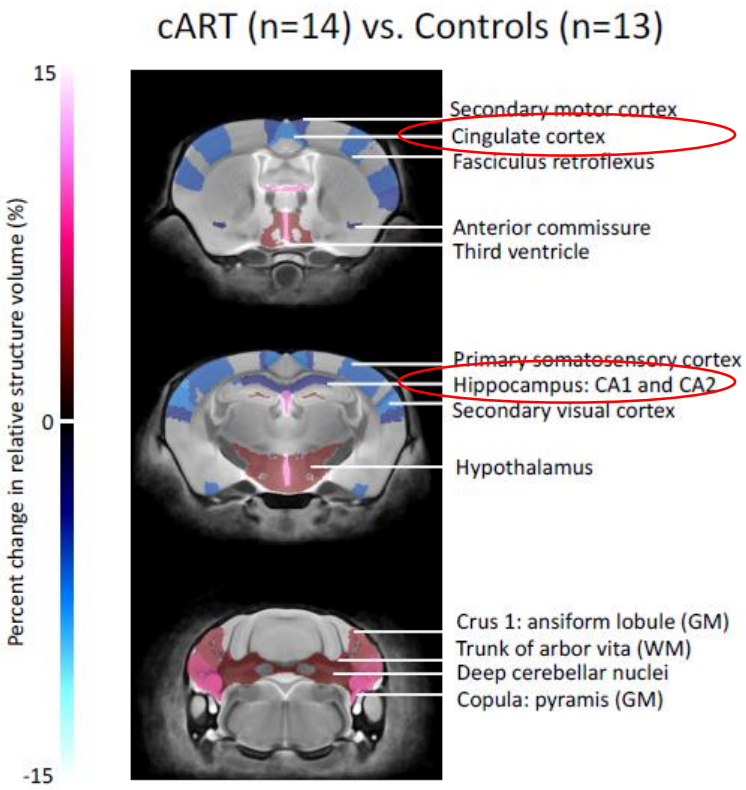
http://www.ssponline.com/shepherds_cob.htm

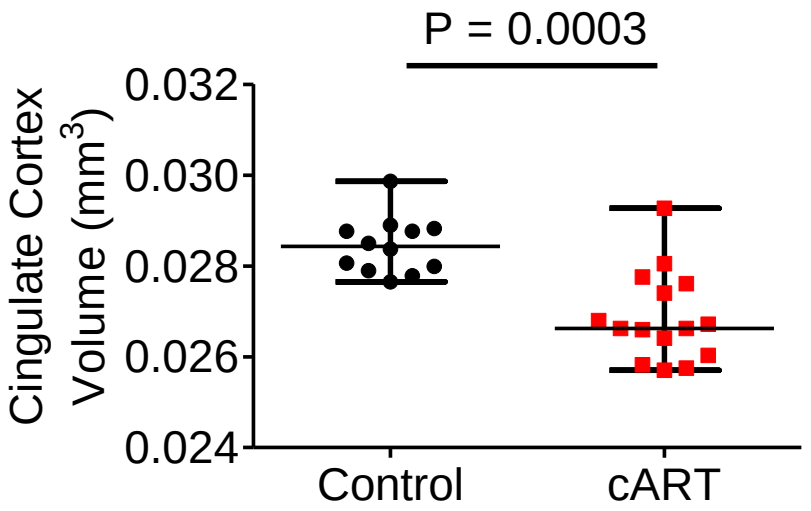


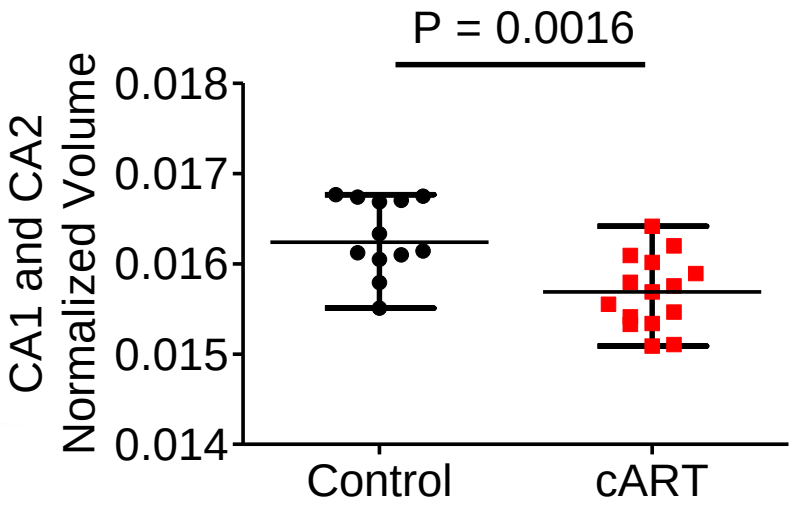
Data = % passed; (Fisher's exact test; n= 10-15 for Litter Average)

Impaired cognitive function

cART was Associated with Changes in Volumetric Measurements in different Regions of an Adult Mouse Brain (MRI)

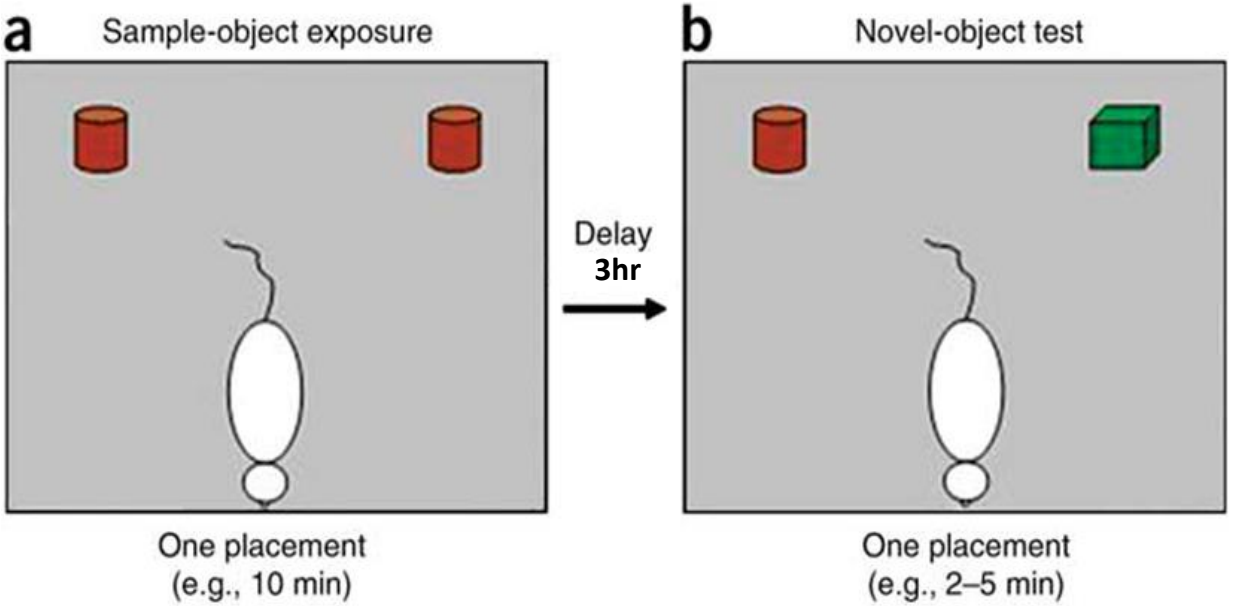




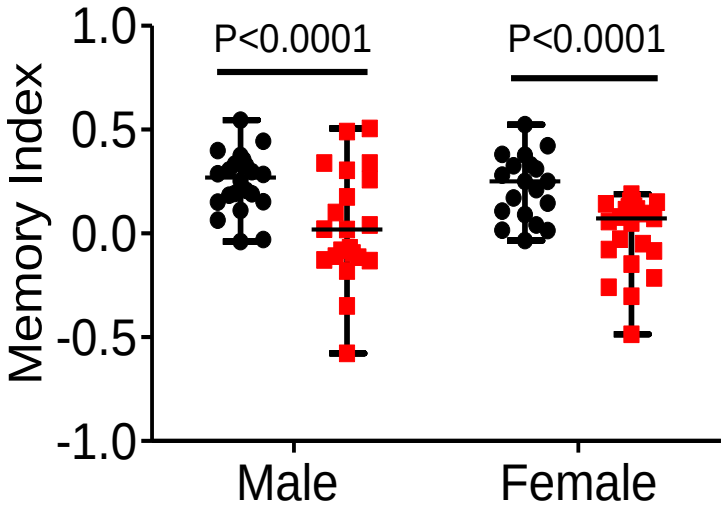


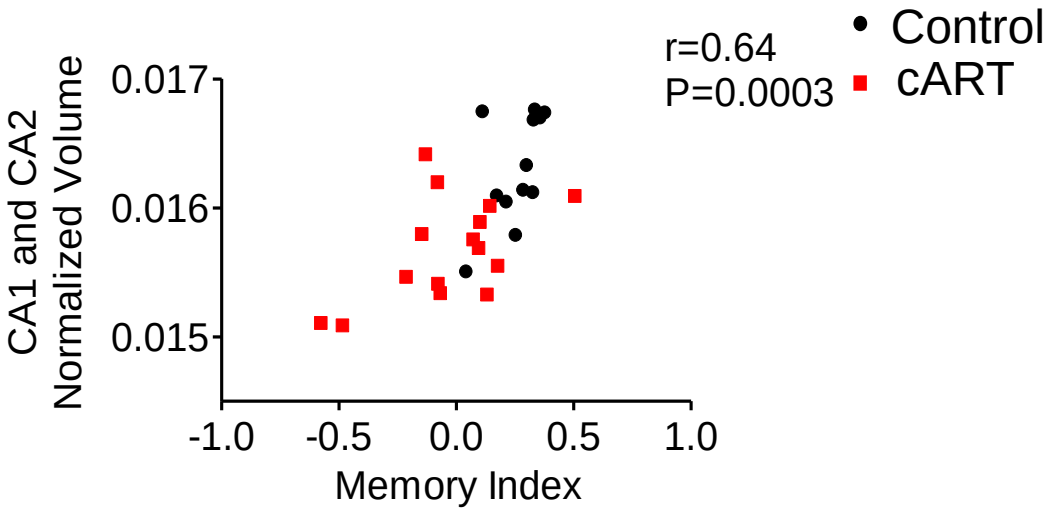
Data = Mean and Range; Statistics = Mann Whitney; n=13-16

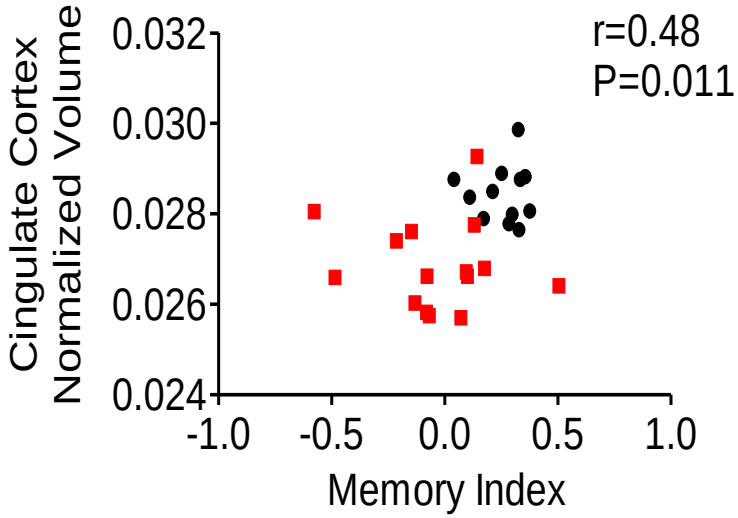
Novel Object Recognition (NOR) Test



In utero Exposure to PI-cART is Associated with Smaller Hippocampus and a Lower Memory Index





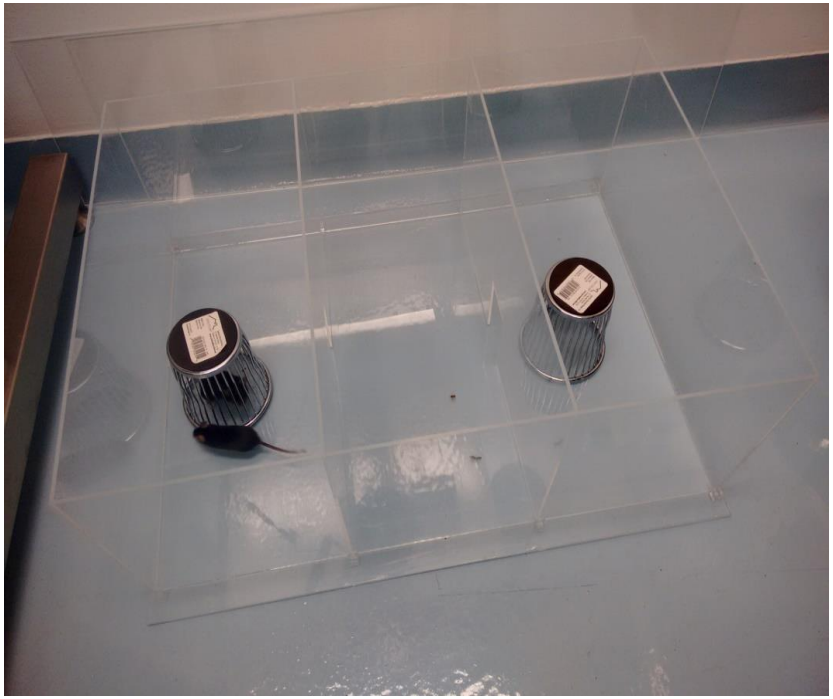


Memory Index=(tn-tf)/(tn+tf)

Data = Median and Range n= 20-22; Statistics = Mann Whitney and Spearman's correlation

Speech and Language Delay

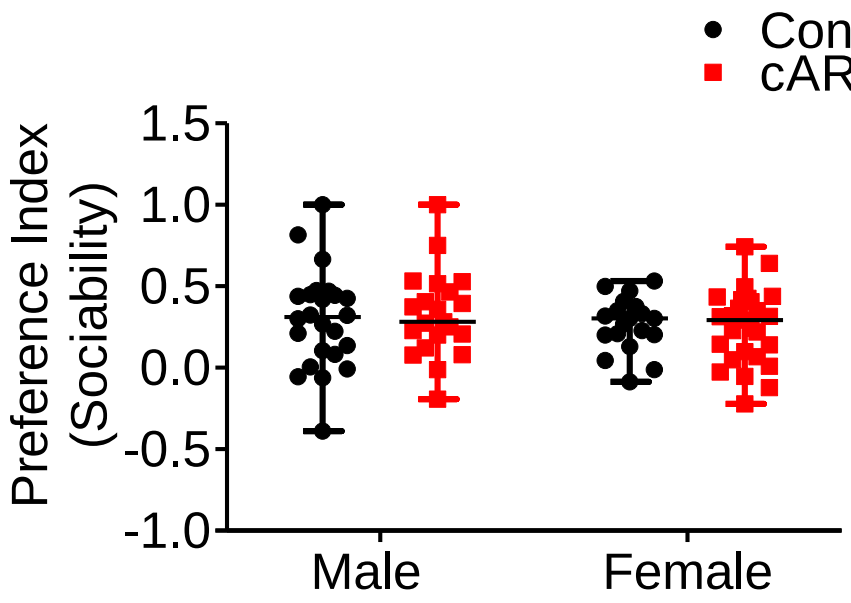
Sociability and Social Novelty Test

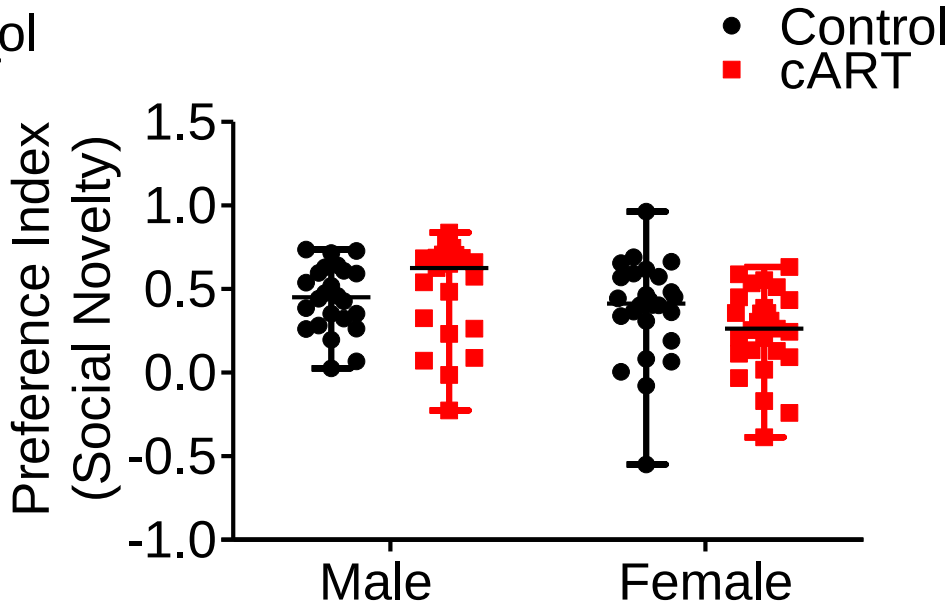


Sociability

Social Novelty

In utero Exposure to cART had no Effect on Social Interaction





Preference Index=(tn-tf)/(tn+tf)

Data = Median and Range n= 20-25; Statistics = Two-way ANOVA

Summary

Compared to control, *in utero* exposure to ABC/3TC+ATV/RTV was associated to with:

- Lower fetal and adult weights
- Changes in volumetric measurement in fetal and adult brains
- Delayed motor, tactile, and olfactory reflexes
- Lower memory index

Conclusion

Our data suggest that the *in utero* exposure to ABC/3TC+ ATV/RTV is associated with volumetric changes in key regions of the brain, developmental delays, and cognitive deficits in a mouse model of pregnancy.

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Collaborators

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- Lisa Yu
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