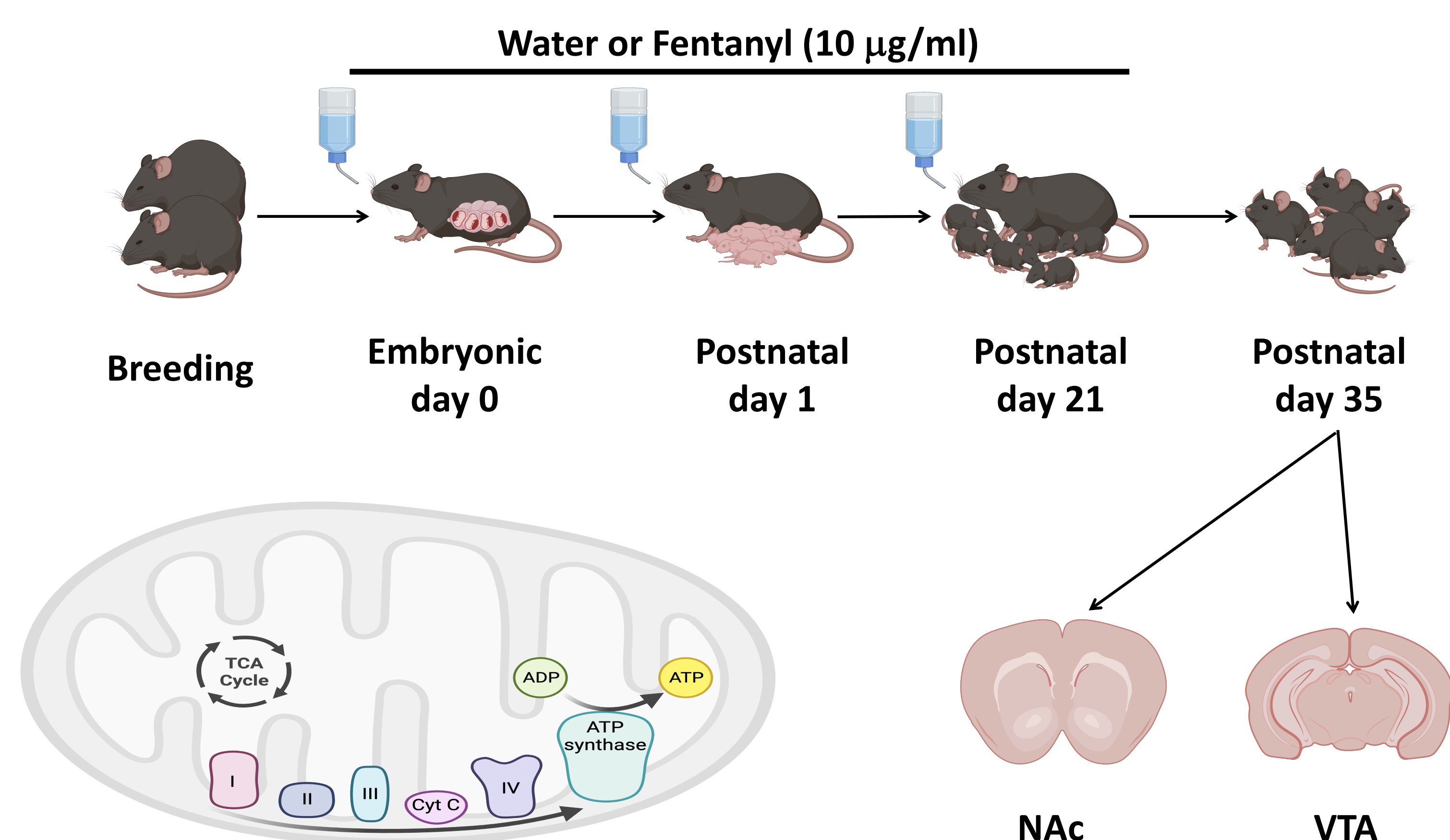


## INTRODUCTION

- Fentanyl exposure is driving opioid-related overdose deaths due to its enhanced potency compared to heroin and other opioids.
- Opioid use during pregnancy predisposes babies to withdrawal symptoms, premature births, decreased birth weight and body size, and, in extreme cases, stillbirth and infant death.
- Opioids cross the placental barrier, entering fetal circulation and the central nervous system where they can impact fetal brain development.
- Long-term consequences of prenatal and perinatal opioid exposure include dysregulated stress reactivity, altered glucocorticoid levels, hyperactivity, impulsivity, and aggression.
- Our previous work demonstrates Complex I genes are upregulated in perinatal fentanyl exposed adolescent male nucleus accumbens (NAc) and female primary somatosensory cortex (S1) but were downregulated in the ventral tegmental area (VTA) of both sexes.
- These findings suggest an increase in active protein synthesis and cellular energy production in S1 and NAc and a decrease in cellular energy production in the VTA.
- While mitochondria have been examined in adult exposure to used substances in rodents, there is little information about mitochondrial processes in conditions of drug exposure in utero.

## BACKGROUND



## MITOCHONDRIAL GENES IN NAC AND VTA

Electron transport chain (ETC) genes that are differentially enriched in NAc and VTA of perinatal fentanyl exposed mice

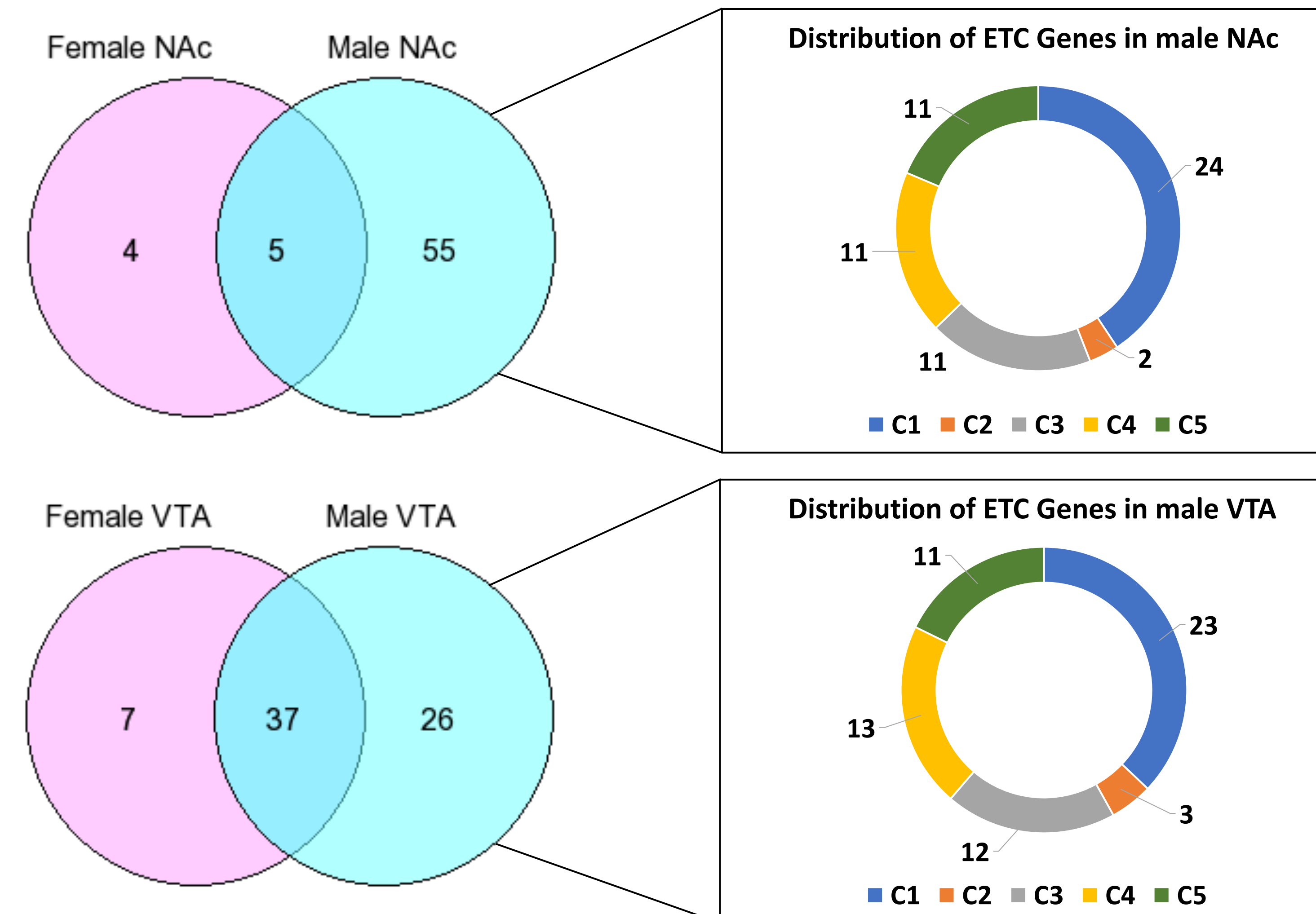


Figure 1. Venn diagram (left) demonstrating ETC differentially enriched genes (DEGs) in NAc and VTA upon perinatal exposure of fentanyl. A majority of the DEGs belong to complex I in both brain regions (right).

## ETC GENES ARE COUNTER-REGULATED IN NAC AND VTA

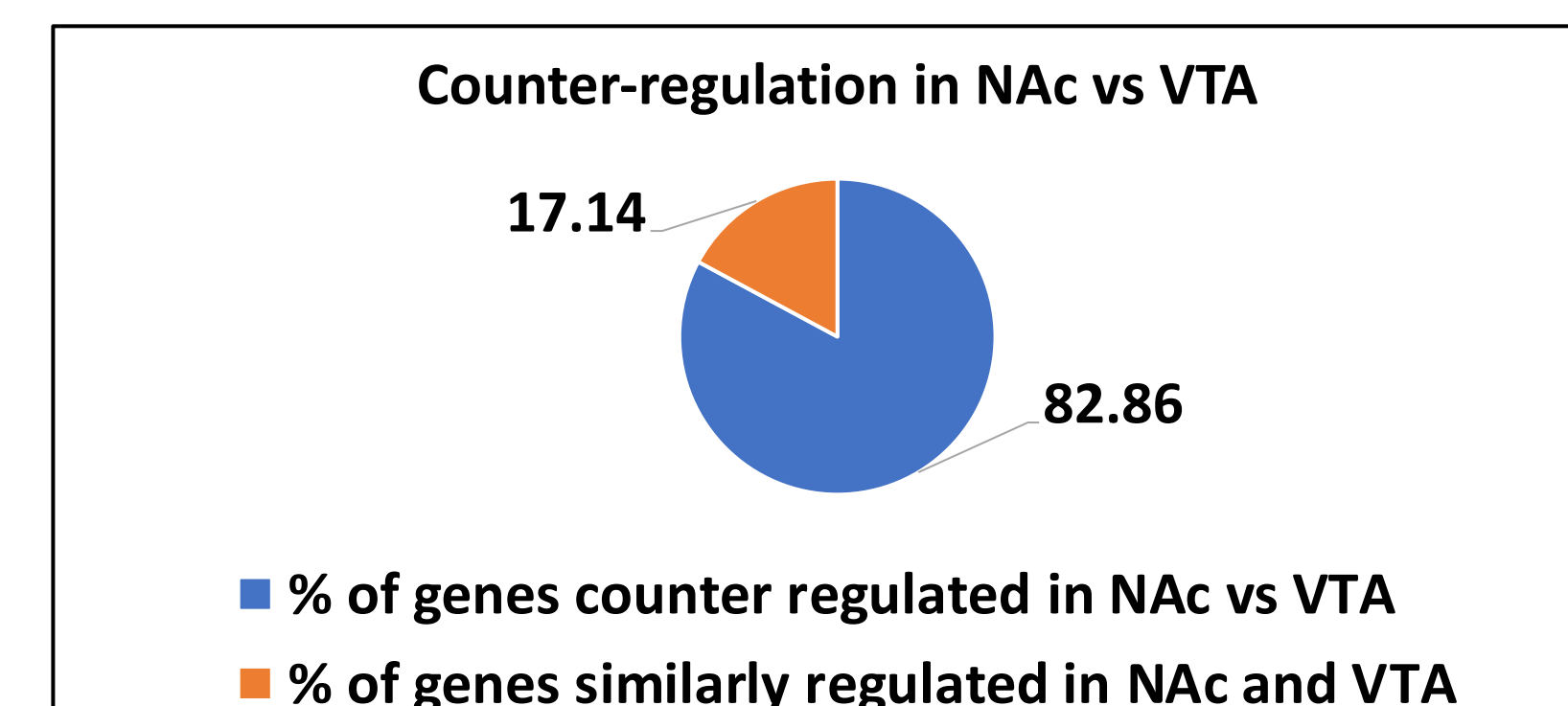
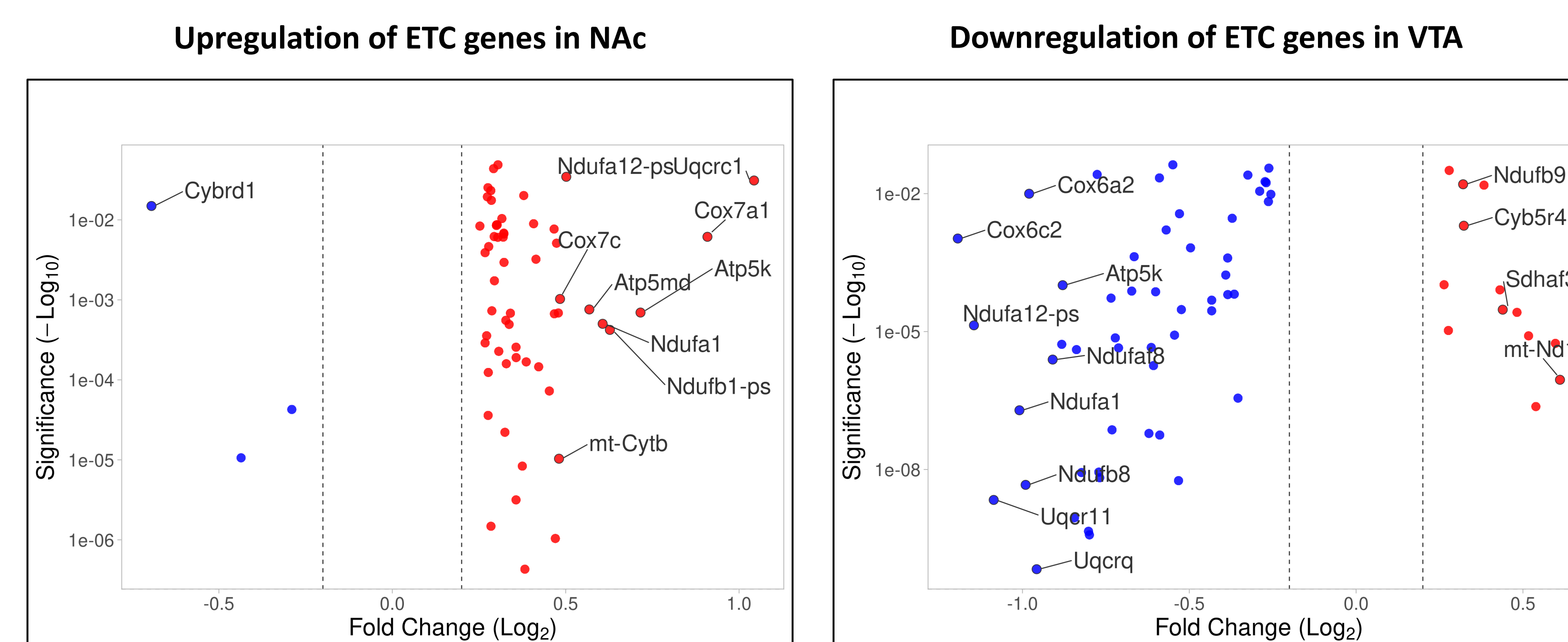


Figure 2. Volcano plots of transcriptomic data (top) suggests counter-regulation of ETC genes in NAc and VTA. A majority of the genes out of the total ETC genes are discordant in NAc and VTA (bottom)

## REGULATION OF MITOCHONDRIAL COMPLEXES GENES

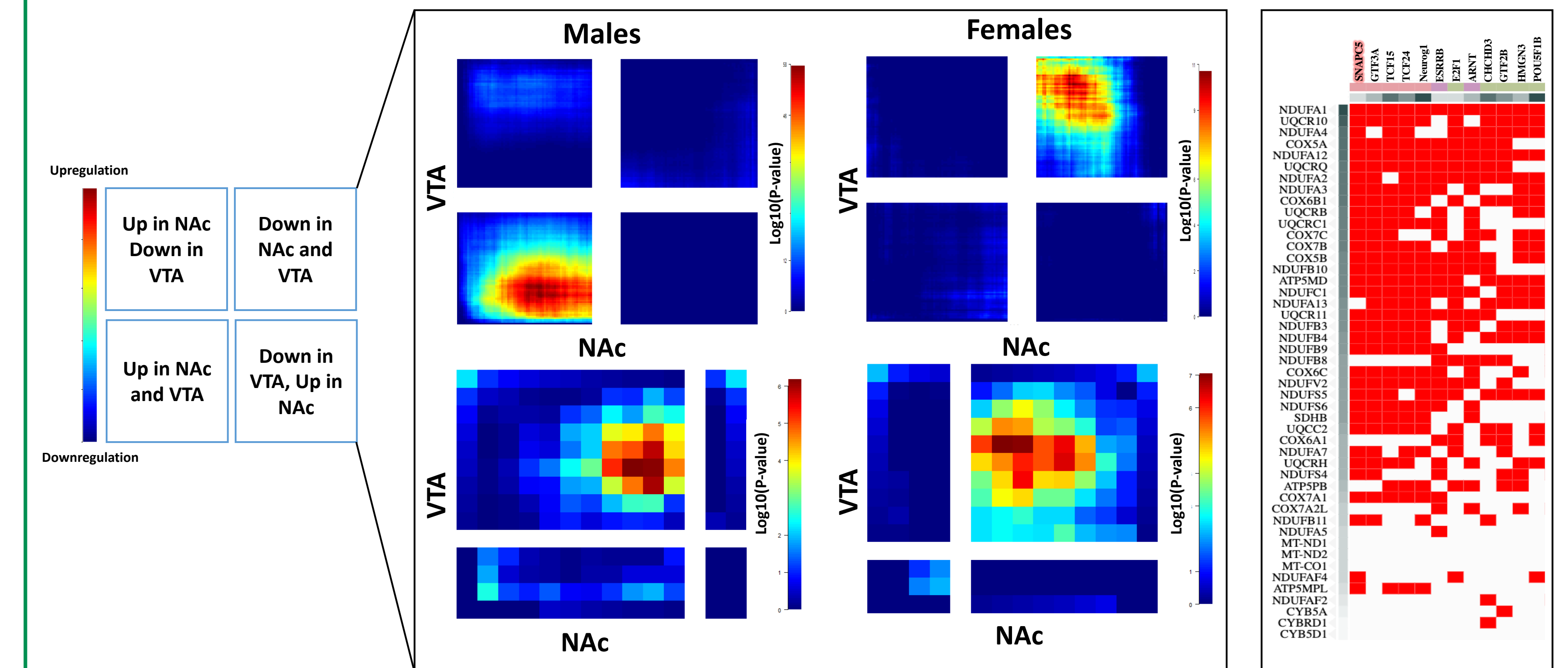


Figure 3. Rank-rank hypergeometric overlap (RRHO, left) shows relative regulation of mitochondrial genes in NAc and VTA. Transcription factor enrichment analysis identified SNAPC5 as potential regulator of concordant mitochondrial genes

## CONCLUSION

- Mitochondria-specific analysis of a transcriptomic dataset obtained from adolescent mice born exposed to fentanyl during the perinatal fentanyl period suggests discrete energetic pathways are regulated in reward circuit regions.
- ETC genes are counter-regulated in NAc and VTA in mice with perinatal fentanyl exposure.
- SNAPC5 is a potential bidirectional regulator of ETC transcripts in NAc and VTA of perinatal fentanyl exposed mice.

## FUTURE DIRECTIONS

- Validate and identify ETC gene expression in NAc and VTA, as well at prefrontal cortex (PFC) at postnatal time points until adulthood using nanostring.
- Examine mitochondrial OXPHOS and energy metabolism in these regions by performing a Seahorse experiment in perinatal fentanyl exposed mice.
- Examine region-specific downregulation of SNAPC5 to study its downstream effect on mitochondrial regulation in NAc and VTA

## FUNDING and References

- Funding: NIH GRANT - R01DA038613, R01DA054905
- Olusakin, J., Kumar, G., Basu, M. *et al.* Transcriptomic profiling of reward and sensory brain areas in perinatal fentanyl exposed juvenile mice. *Neuropsychopharmacol.* 48, 1724–1734 (2023). <https://doi.org/10.1038/s41386-023-01639-8>