

Alterations in Brain Microstructure and Functional Networks

Following Schizophrenia-Linked Changes in EIF4EBP2

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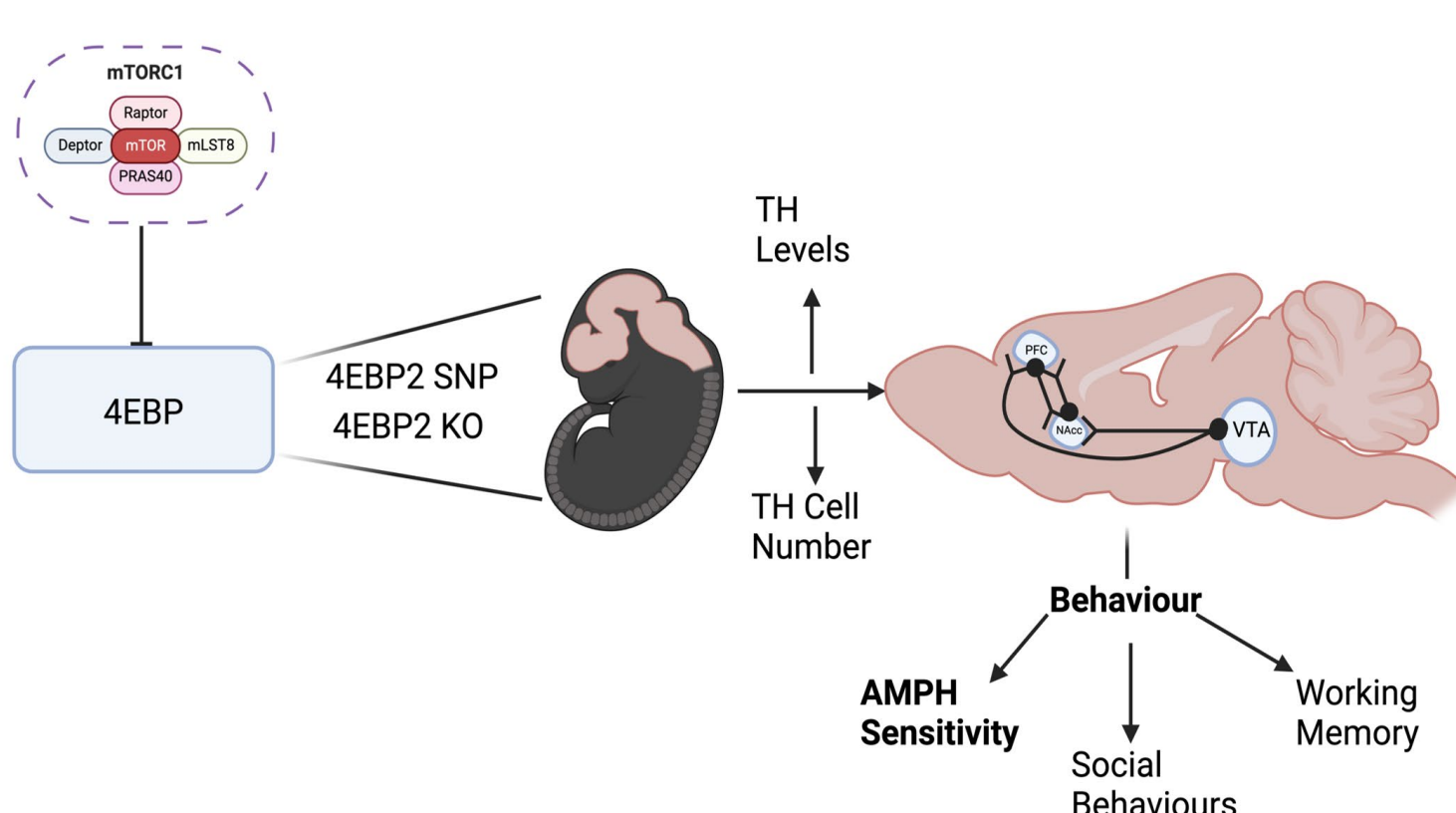


Background/Methods

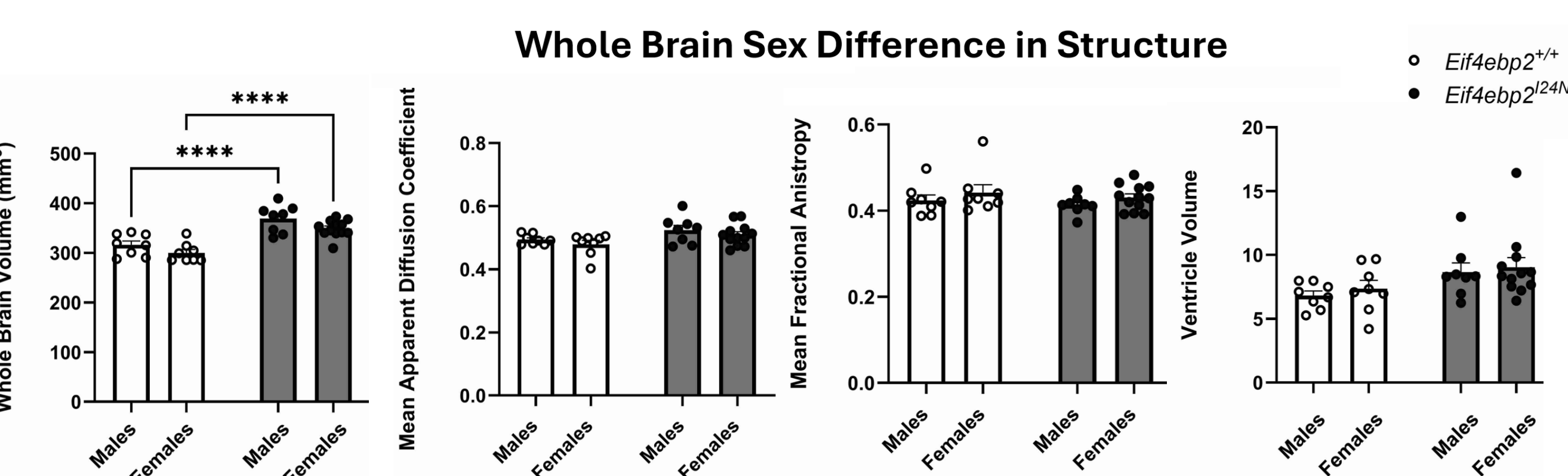
Schizophrenia is a psychiatric condition characterized by certain structural and functional brain abnormalities. Despite such findings being prevalent in neuroimaging studies, there has been limited research in the genetic-linked risk factors associated with such changes. In this study, we examined how a schizophrenia-linked mutation in EIF4E-binding Protein 2 (EIF4EBP2), a regulator of neuronal protein translation, alters brain structure and function at the preclinical level.

Methods

- Adult male and female knock-in and wild-type C57BL/6 mice (N = 34, sex split)
- Diffusion Weighted Imaging (DWI), Voxel Based Morphometry (VBM), Ventricular Mapping
- d-amphetamine phMRI challenge (2.5 mg/kg males and 2.2 mg/kg females)
- Measured brain activation 25-30 minutes after injection
- Performed stimulus-based functional connectivity analysis

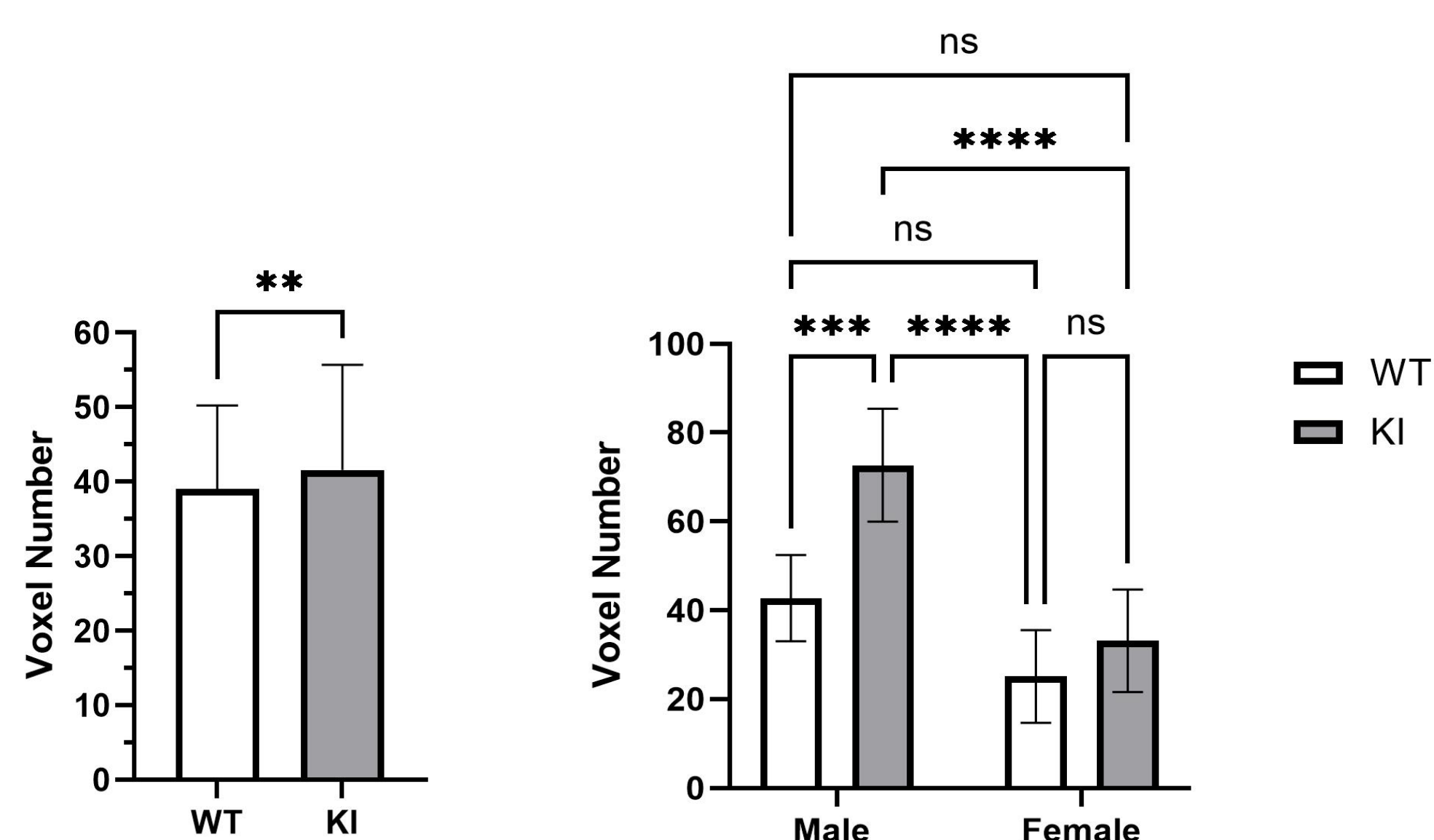


Whole-Brain Structural Results



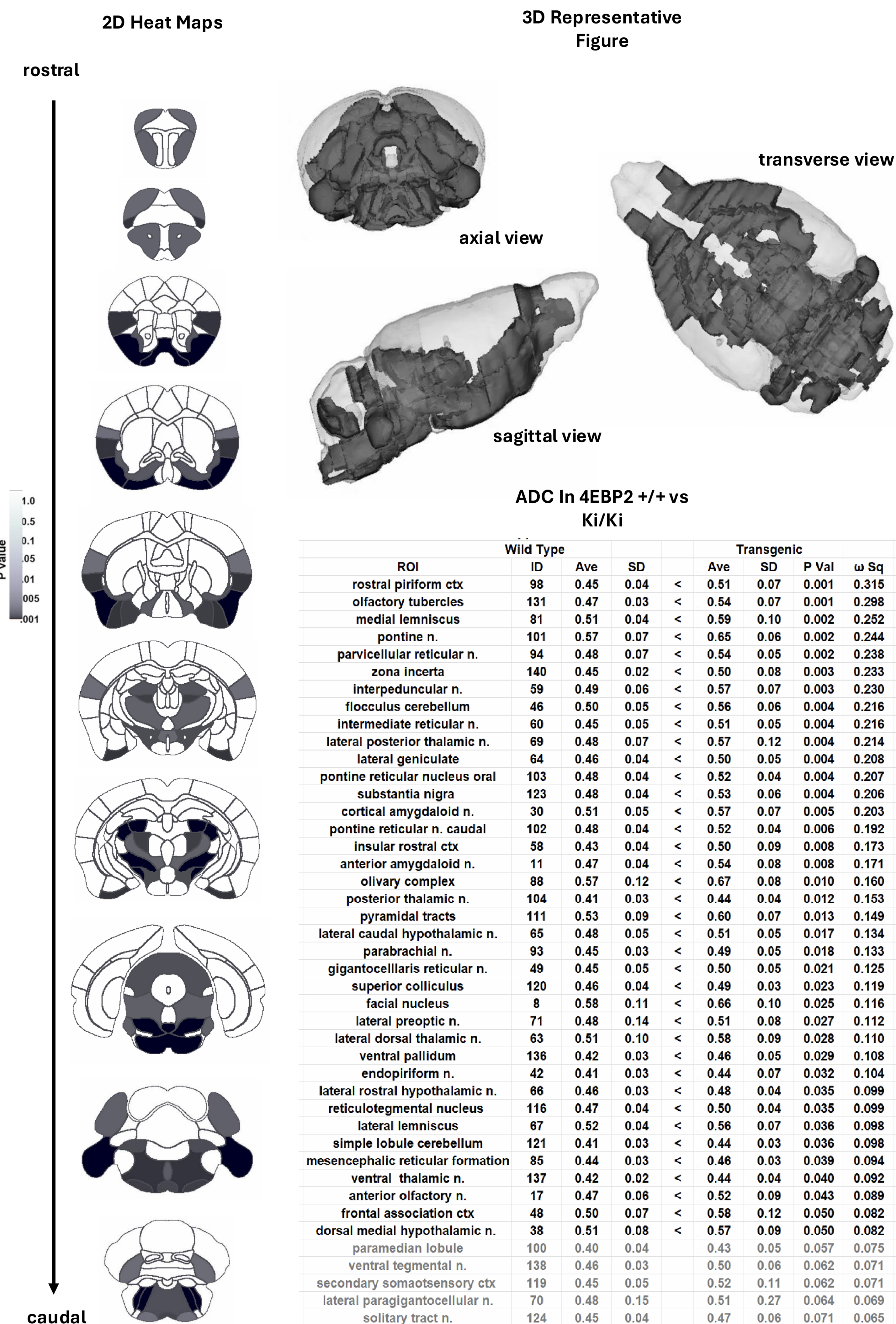
Whole-Brain phMRI Results

Whole Brain Combined and Sex-Specific BOLD phMRI Activation



Region-Based DWI Results

Increases in Apparent Diffusion Coefficient in 4EBP2 SNP Mouse Model



Discussion

Structural

- **VBM:** Measures differences in the volume of neuronal cell bodies
 - Males showed significantly larger difference in whole brain volumes between genotypes than females
- **DWI:** Whole brain ADC and FA values were similar between both sexes and across genotypes, but regional differences in ADC values were found:
 - Lateral rostral regions → **sensory integration and processing**
 - Medial caudal regions → **dopaminergic signaling**
- **Ventricular Mapping:** KI mice showed increased ventricle volume compared to WT mice (*)

Functional (phMRI)

- Observed male-dominated changes in positive BOLD while on amphetamine
- Positive BOLD was heightened in KI > WT (**)
- Behavior analysis supports neuroimaging findings

Conclusion & Future Directions

- EIF4EBP2's role in regulating neuronal protein translation may lead to the structural and functional brain changes associated with schizophrenia.
- There is a sex-specific effect in both structure and functional responses, with a heavy lean towards male-dominant changes.
- Future directions include analyzing stimuli-based functional connectivity to understand resting brain networks that may contribute to differences in sensitivity responses

Acknowledgements

Amphetamine: National Institute of Drug Abuse
Project Funding: Carleton University, Ekam Imaging

