An integrated analysis of the transcriptomic effects observed following wildland firefighter relevant occupational exposures in the pre-frontal cortex of male mice

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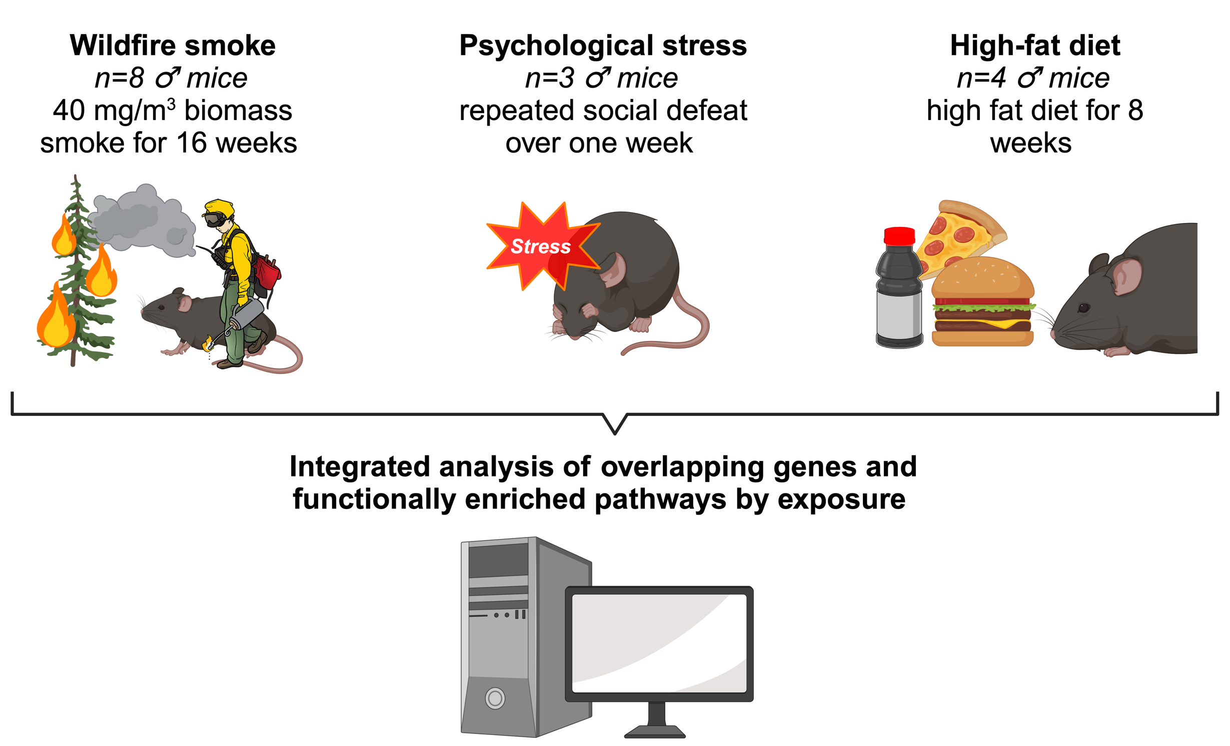
Introduction

- Wildfires are rapidly increasing in frequency and intensity following trends of climate change across the globe necessitating unprecedented levels of fire mitigation strategies
- Wildland firefighters (WLFF) are on the frontlines of these events, risking exposure to several occupational factors (e.g., wildfire smoke, poor nutrition, sleep deprivation, etc.) which are well studied in the context of cardiopulmonary health; however, recent public health literature suggests that the effects of these exposures extend to the central nervous system (CNS)
- Here, we sought to investigate effects of combined WLFF-relevant exposures in the male mouse pre-frontal cortex (PFC) using bulk RNAseq

Graphical Abstract

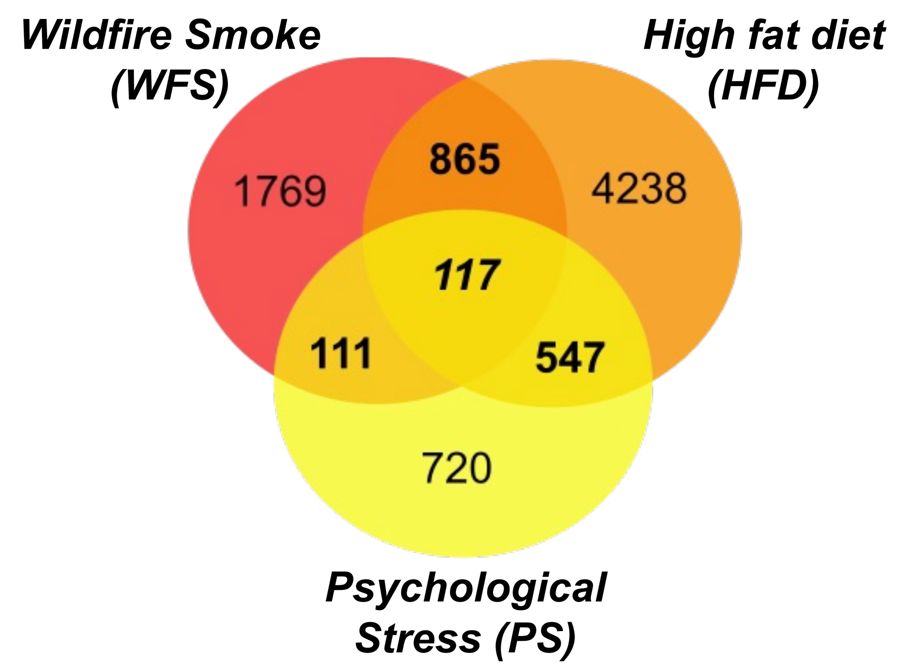


Methods

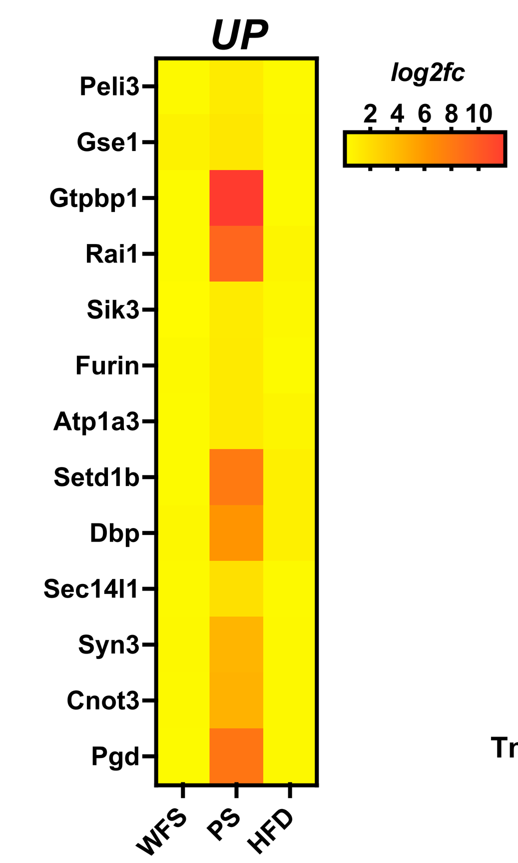
- Three parent studies were identified through a search of published literature and data repositories examining male mouse PFC for WLFF-relevant exposures: wildfire smoke (WFS), high fat diet (HFD), and psychological stress (PS)
- We performed an integrated analysis of the combined 8,367 differentially expressed genes (DEGs) as reported in each parent study to determine conserved directionality across study populations
- Subsequently, functional enrichment analysis was performed by assembling a Protein-Protein Interaction (PPI) network map of the 117 overlapping DEGs and conducting pathways analysis of the same transcripts using the PANTHER Overrepresentation Test of the Reactome database
- Secondary pathways analysis occurred via the Gene Ontology (GO) database examining for DEGs shared between two WLFF-relevant exposures; only results for WFS and HFD are graphically represented due to lack of enriched pathways in other analyses

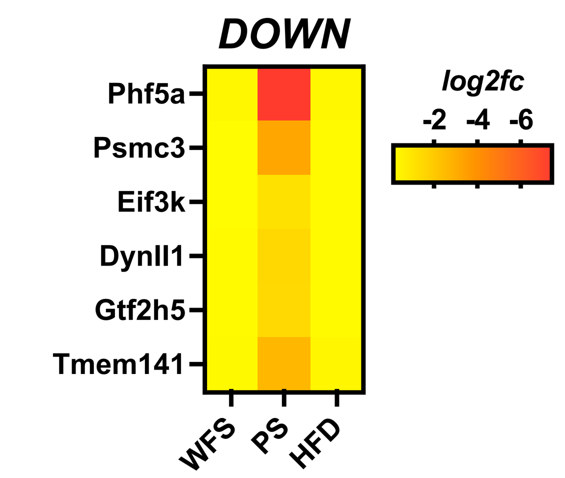
Results

Venn Diagram DEG Overlap Analysis

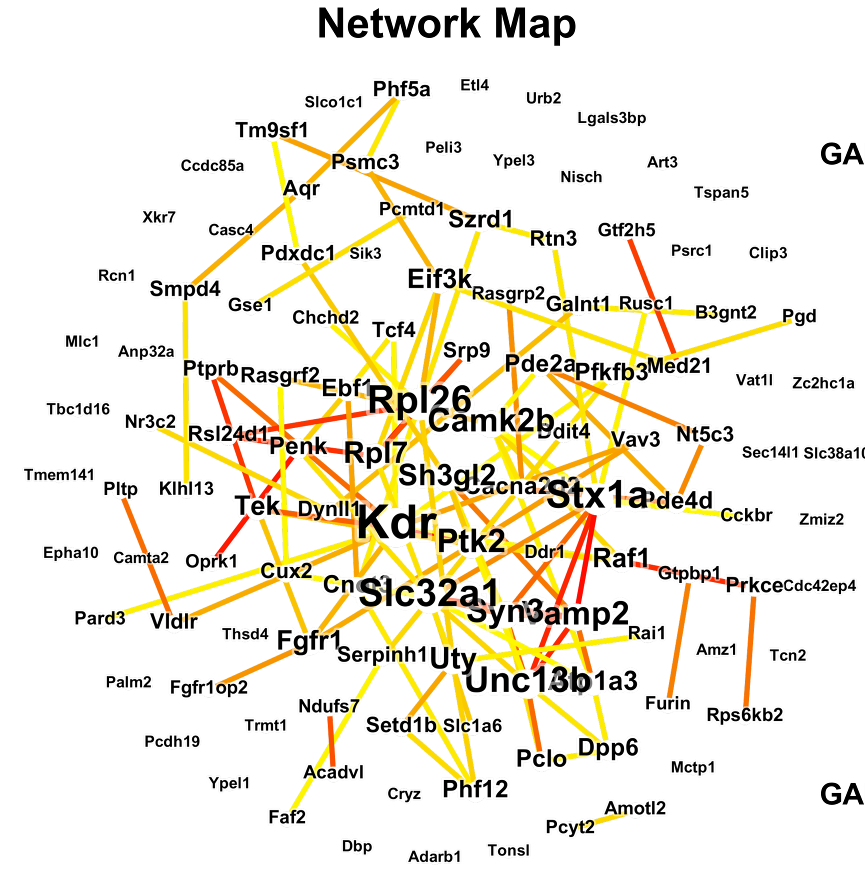


Heatmaps Depicting Concordantly Increased or Decreased Transcripts

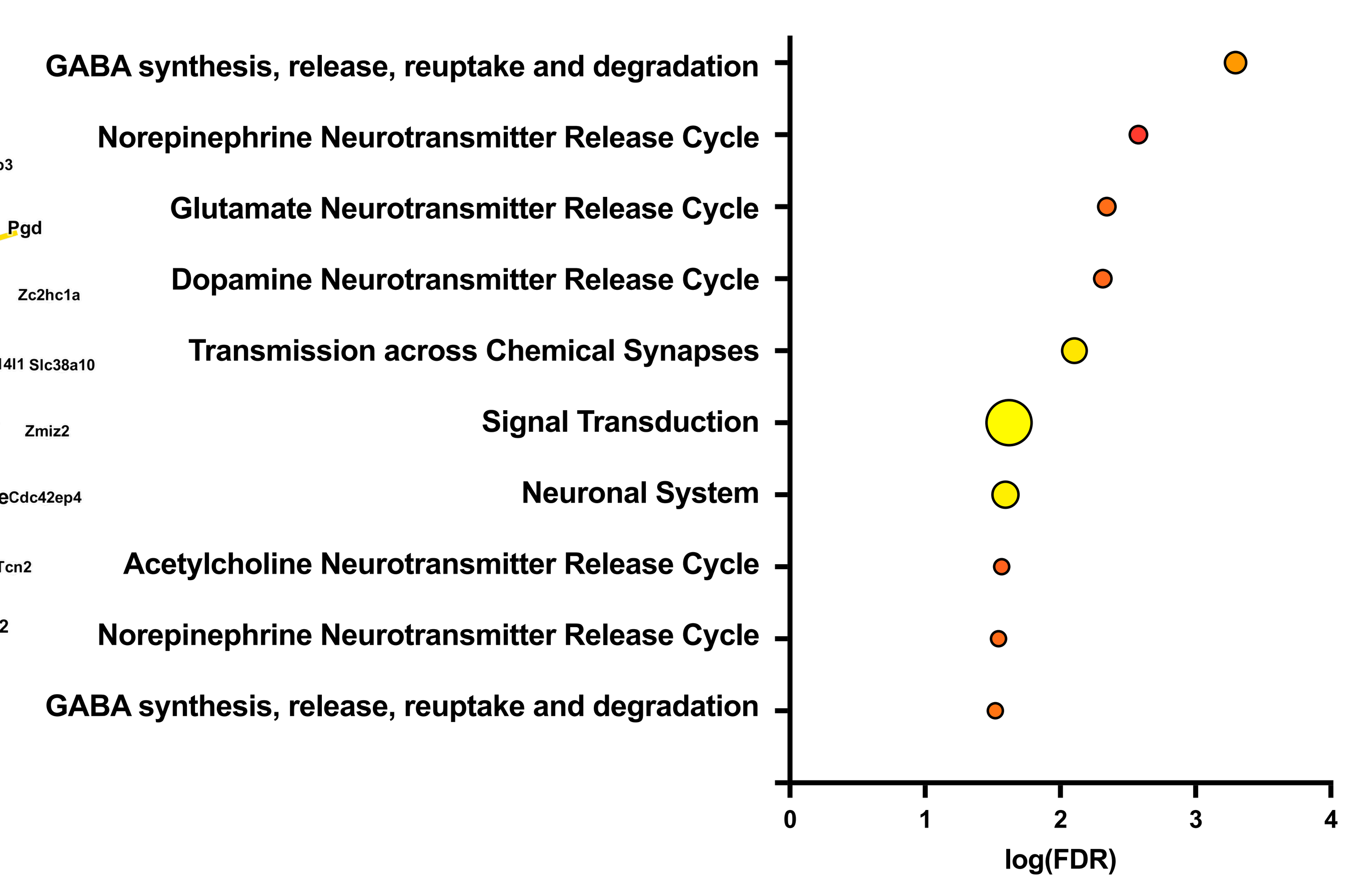




Protein-Protein Interaction Network Map



Reactome Pathways Functional Enrichment Analysis



GO Pathways Analysis of WFS and HFD

Figure 1 (top left). Venn diagram depicting overlapping DEGs across all three WLFF-relevant exposures.
Figure 2 (top right). Heatmaps constructed to visualize conserved directionality across 117 overlapping DEGs where 6 transcripts were concordantly decreased and 13 transcripts were concordantly increased.
Figure 3 (Middle left). PPI network map assembled using the STRING database highlighting central nodes with a high degree of interrelated connection.
Figure 4 (middle right). Bubble plot demonstrating the 10 significantly enriched Reactome pathways by FDR.
Figure 5 (bottom left). Tree map reporting GO Biologic Process (BP) terms significantly enriched across shared DEGs between WFS and HFD datasets. Positive correlation between size of box and strength of association; boxes of same color correspond with familial GO BP term classification

Discussion/Implications

- WLFF encounter many occupationally relevant health hazards which have been reported in epidemiologic literature in the context of the cardiopulmonary system and have been subsequently mechanistically explored in isolation in molecular toxicology literature
- This is the first attempt to characterize gene expression changes that are associated with multiple WLFF-relevant exposures by performing an integrated analysis of mouse model data in the CNS to attempt to broadly represent shared toxicologic profiles
- We found that 117 DEGs overlap between the three studies (6 consistently up, 13 consistently down, and 98 with directional discordance) which we further examined for functional enrichment and found significant differences in pathways relevant to synaptic transmission, including specific neurotransmitter metabolism and release profiles
- Additionally, PPI network analysis revealed a central hub that confirms pathways analysis findings related to neurotransmission and secondary nodes suggesting differences in cellular signaling and neuroplasticity
- The results reported here motivate subsequent studies of these factors using multi-hit models to tease out directionality and causality of potential synergistic mechanisms in the context of WLFF occupational health effects; similarly, experiments collecting peripheral tissue in tandem with CNS samples will allow for biomarker assessment

Acknowledgements

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  - https://www.researchgate.net/publication/377592393_WFS_MOUSE_TRANSCIPTOMIC_DATA
  - https://www.frontiersin.org/articles/10.3389/fgene.2019.00083/full
  - https://www.hindawi.com/journals/bmri/2019/7505260/#materials-and-methods

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