# Deep Metabolic Profiling for Tissue-Specific Responses Against SARS-CoV-2 Variants in Hamster Models

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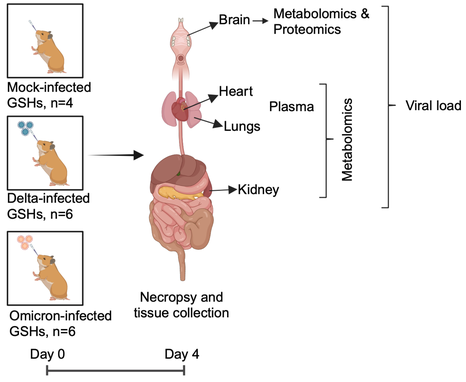
**Urvinder Kaur Sardarni**[1], Anoop Ambikan[2], Arpan Acharya[1], Samuel D. Johnson[1], Rajesh Rajaiah[1], Kabita Pandey[1], Ujjwal Neogi[2], Siddappa N. Byrareddy[1]
[1]University of Nebraska Medical Center, Omaha, Nebraska, USA, [2]Karolinska Institute, Stockholm, Sweden

## BACKGROUND

- As of February 2024, the global impact of COVID-19 remains profound, with over 774 million confirmed cases and an estimated 7.02 million fatalities[1].
- While SARS-CoV-2 initially targets the respiratory system, its presence and effects extend beyond the lungs[2].
- Our previous study showed a distinct immunometabolic response in the lungs of the Golden Syrian Hamsters (GSH) during acute infection by the delta and omicron variants[3]. This underscores the importance of understanding the variant-specific alterations in metabolic regulations across various organs affected by COVID-19.
- Furthermore, emerging evidence underscores the neurological implications of COVID-19[4], necessitating a deeper understanding of the brain damage caused by different SARS-CoV-2 variants.

## METHODS

We intranasally infected GSH with SARS-CoV-2 delta and omicron variants and performed viral load, metabolomics of the brain, heart, kidney, and plasma, and whole-brain proteomics. We used lung metabolomics from our earlier study[3].




## RESULTS

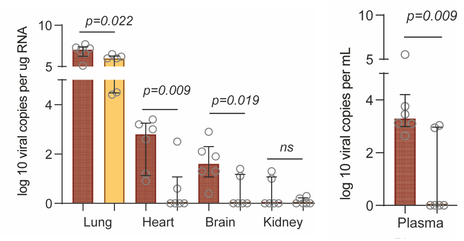



**Fig 1:** Bar graph showing the viral load in different tissues and plasma infected with delta (red) and omicron (yellow) variants.

**Multi-omics analyses revealed distinctive metabolic responses between the delta and omicron variants, with the former demonstrating dysregulation in synaptic transmission proteins associated with neurocognitive manifestations**

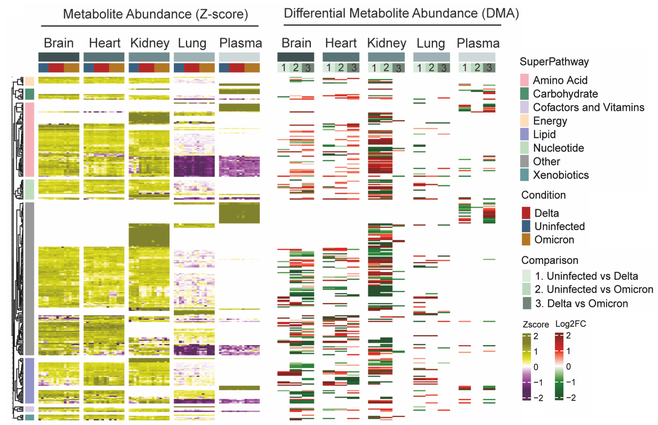



**Fig 2:** Heatmap visualization of metabolite abundance in each tissue. The heatmap shows the enrichment pattern of metabolites and related log2 fold changes of enrichment. Rows are metabolites significantly enriched (p.adj<0.1) in any tissues, and columns are samples

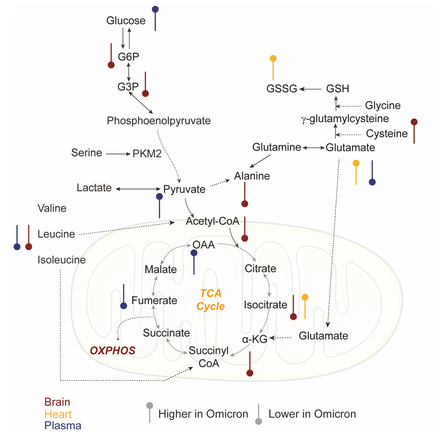



**Fig 3:** Schematic diagram of metabolic reactions showing dysregulation of key metabolites in omicron compared to delta variant infected tissues.

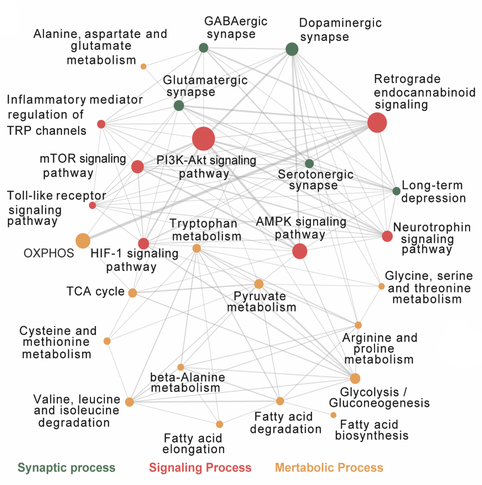



Fig 6: Network visualization of significantly enriched pathways in delta compared to omicron-infected brain samples. Edges represent protein overlap between the corresponding pair of pathways. Edge width is relative to the number of proteins overlapping between the paths. Node size is relative to the number of significantly regulated proteins in the corresponding pathways.

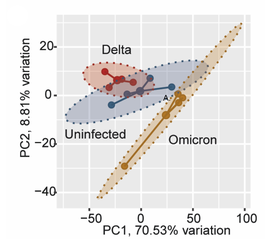



Fig 4: PCA plot displaying the protein profile in the brain of naïve, delta and omicron hamsters. The ellipse represents 90% confidence space, and the lines connect each sample with the corresponding centroid.

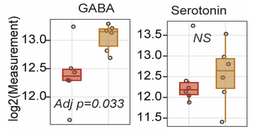



Fig 5: Box plot showing the level of γ-Aminobutyric acid (GABA) and serotonin in the brain tissue of delta (red) and omicron (yellow) infected hamsters.

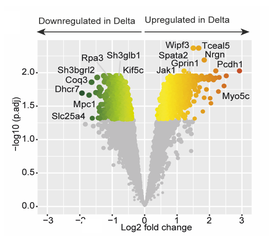



Fig 7: Volcano plot visualizing differential expression analysis results of synaptic proteins in delta compared to omicron infected brain. Significantly regulated (p.adj < 0.05) key synaptic proteins are labeled.

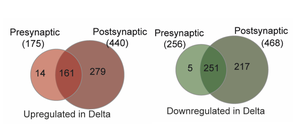



Fig 8: Venn diagram of pre- and post-synaptic proteins upregulated and downregulated in delta compared to omicron-infected brain .

## CONCLUSIONS

- Our study investigates the complex host responses triggered by SARS-CoV-2 variants using the GSH model.
- Omicron variant shows reduced viral burden in the lungs, heart, brain, plasma, and intestine compared to the delta variant.
- These variants induce distinctive metabolic regulations in various tissues and plasma.
- Further, brain proteomics indicate dysregulation of synaptic transmission, plasticity, and imbalance of excitatory and inhibitory signals within the brain in a variant-specific manner.
- The observed dysregulation of post-synaptic proteins, coupled with the presence of markers linked to neurodegenerative disorders, underscores the potential neurological repercussions of COVID-19.
- Our findings warrant further investigations to determine if metabolic and proteomic dysregulation observed at acute infection persist in post-recovery from COVID-19 symptoms and their role in developing neurocognitive impairments as reported in PASC patients.

## REFERENCES

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## AUTHOR CONTACT INFORMATION

Name: **Urvinder Kaur Sardarni**
Email Id: **usardarni@unmc.edu**