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Dimension Reduction and Cluster Analysis of Mouse Microbiome Data for Understanding Heterogeneity of Addiction

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Background: Substance use disorders are heterogeneous. Gut bacteria alterations can be a key to identify the mediators or moderators in the pathways of SUD etiology. Subtyping analyses for SUD have not used microbiome features. Identifying mouse groups showing concurrent patterns in both gut microbiome and addiction-related behaviors may help refine SUD classification.

Hypothesis: Gut microbiome interacts with SUD and associated novelty behaviors through multiple mechanisms.

Method: Uniform manifold approximation and projection (UMAP) reduces data dimensions nonlinearly to reveal grouping structures. UMAP was applied to data of 74 genera from feces of 341 Diversity Outbred mice between ages of 8-12 weeks – who were tested on open field exploration, hole board exploration, and novelty preference followed by intravenous cocaine self-administration (IVSA) – to group mice and examine concurrent cluster validity on 30 novelty behavioral and 9 IVSA features.

Results: Three clusters were identified: clusters 1 (n=77) and 2 (n=100) had novelty scores, respectively, below and above the overall sample means whereas cluster 3 (n=164) was around the sample means. Cluster 1 had the most distinguishable IVSA patterns where mice had very high reinstatement after inactive lever presses during the initial session and tended to have below-average response to large dosage of 1mg/kg but above-average response to smaller dosage e.g., 0.32mg/kg. The most significant microbiome genus that distinguishes the clusters was *Lactobacillus* ($p<0.005$) together with four top genera of *unclassified Porphyromonadaceae*, *Barnesiella*, *unclassified Lachnospiraceae*, and *unclassified Bacteroidales* ($p< 0.05$).

Conclusion: Integrating gut microbiome with behavior is promising to differentiate characteristics of cocaine use disorder.