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**Influence of the microbiome on novelty behavior and cocaine addiction in mouse models.**

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The microbiome is implicated in many diseases including those of the brain and behavior. Most microbes are in the gut but are capable of remotely affecting tissues through metabolites released into circulation or activation of systemic responses like inflammation. Neurotransmitters can also be produced by bacteria or their host synthesis influenced by bacteria. The gut-brain axis provides additional means of microbe-brain communication through effects on the enteric nervous system or vagus nerve. There is ample reason to believe the microbiome is not invisible to neural and behavioral processes and could play a significant role. We seek to relate specific microbes to novelty behaviors, intravenous self-administration of cocaine, and other addiction assays. We use Diversity Outbred and Collaborative Cross mice to allow genetic analysis as well as microbiome and behavioral analysis. A set of novelty behaviors were measured in two cohorts of DO mice as well as microbiome structure including taxonomic enumeration of bacteria, abundances of microbial genes and pathways, and metatranscriptional analysis to provide functional views of genes. An elaborate suite of correlation analyses are being performed, and a number of specific microbes have been identified as significantly associated with the various behaviors. Because the microbiome is manipulatable, we are able to test whether a correlation reflects a causal relation of the microbiome and behavior. Treatment with antibiotics to deplete the microbiome can affect a behavior (see presentation by Jason Bubier) and restoration of the microbiome or even a single bacterial species can then be tested to prove causation.