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# Investigating the gut-brain axis in 4,006 P50 Heterogeneous Stock rats

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Epidemiological studies suggest a gut-brain axis exists whereby gut and brain functions are interconnected. However, epidemiological studies are subject to confounding from unknown environmental and genetic factors. To limit the extent of confounding and to use host genotypes as anchors to infer causality, we investigated the gut-brain axis in laboratory Heterogeneous Stock (HS) rats, focusing on behavioral traits relevant to drug abuse and metabolic phenotypes.

We characterised the gut microbiome of 4,006 rats using 16S sequencing, characterised the gut metabolome of a subset of 1,047 rats using untargeted LC-MS-MS, and took advantage of dense genotypes and hundreds of phenotypes collected, in the same rats, by the NIDA P50 Center for GWAS in Outbred Rats. We tested for differences in gut microbiome/metabolome composition between the three phenotyping centers and subsequently carried all genetic analyses in each center independently to evaluate the generalisability of our findings. We estimated the heritability and carried out the genome-wide association study of individual microbial taxa and metabolites, and leveraged the results of the P50 Consortium for the same analyses done with the phenotypes.

We identified numerous genome-wide significant loci for microbial taxa and metabolites, and in multiple cases loci for a given microbe or metabolite overlapped between the different centers. We focused on those genomic loci influencing microbes and metabolites, microbes and phenotypes, or metabolites and phenotypes. We identified several likely causal genes at associated loci and tested the causal paths linking microbe, metabolite and phenotype, yielding testable hypotheses that we can now follow up on.