Inflammation, Microbiota, and the Enteric Neuro-Immune Interface: Mechanisms Shaping Behavior and Cognition

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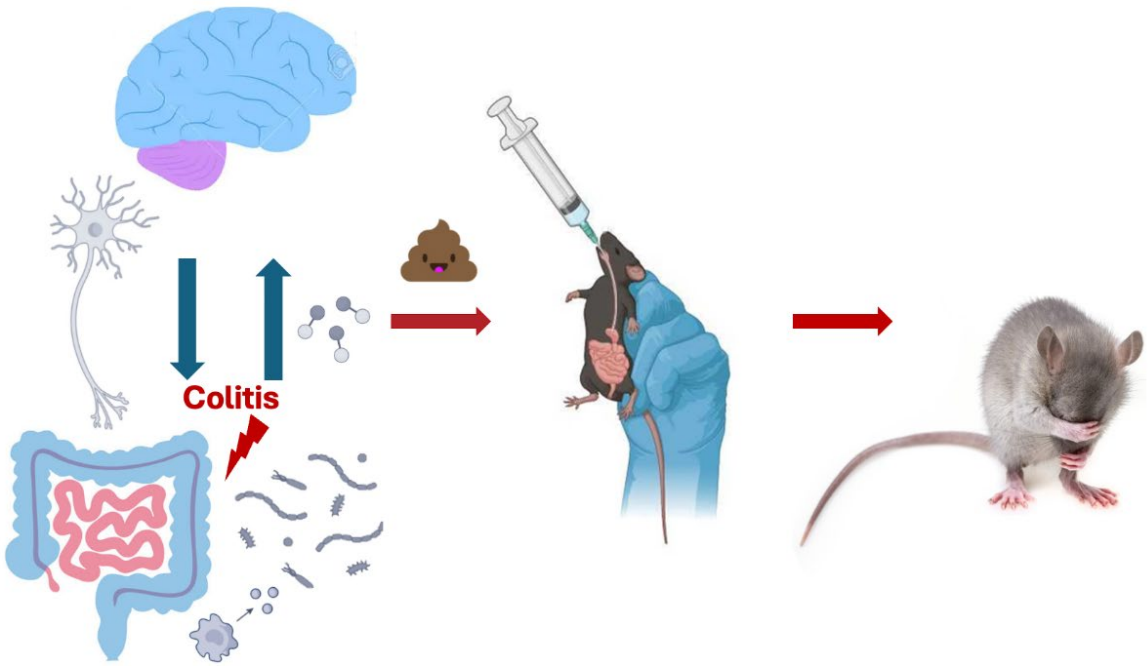
Graphical abstract:



Background and preliminary data:

Inflammatory bowel diseases (IBD) are frequently associated with psychiatric comorbidities, including anxiety, depression, and cognitive impairment. Meta-analyses report ~20% prevalence of anxiety and ~15% prevalence of depression among IBD patients, as well as measurable deficits in executive function (Neuendorf et al., 2016). These findings highlight the clinical relevance of gut–to–brain signaling in chronic intestinal inflammation. Conversely, evidence also supports the reverse direction of this interaction: psychological stress can exacerbate intestinal inflammation. It was recently demonstrated (Schneider et al., 2023) that the enteric nervous system acts as a relay of psychological stress, with enteric glial cells activating proinflammatory programs in the gut. This establishes a mechanistic link by which stress signals from the central nervous system

aggravate mucosal immune responses, thereby reinforcing the concept of a bidirectional gut–brain axis.

To this end, experimental studies provide evidence for a causal role of the intestinal microbiota: microbiota from colitic mice transfer anxiety-like behavior and impaired cognition to germ-free recipients, even in the absence of active inflammation (unpublished work by iDfellow J.-P. Sutter). Additionally, others and we have made fundamental contributions to intestinal immunology, demonstrating how T cell plasticity and cytokine regulation shape mucosal and systemic inflammation (Bedke et al., Gut 2024). These discoveries underscore the strong interdependence between the microbiota, immune system, and host homeostasis.

Together, these data suggest that intestinal inflammation persistently reprograms microbiota–immune–ENS pathways, which drive long-term behavioral and cognitive changes. Conversely, stress-related signals can feed back to exacerbate gut inflammation. However, the mechanistic details and the question of reversibility remain an open question and will be investigated in this project.

Hypothesis

We hypothesize that stress and intestinal inflammation induce durable alterations in the gut microbiota and immune system that persist beyond clinical remission, and that these changes impair behavior and cognition via ENS-dependent neuro-immune signaling. Specifically, we propose that altered microbiota-derived metabolites and inflammatory immune responses converge on the ENS, which in turn modulates vagal and central neuronal activity. This process may explain the persistence of anxiety- and cognition-related deficits after intestinal disease has clinically resolved.

Aims and Work Programme

Aim 1A: Longitudinal analysis of behavior under colitis

We will employ established models of DSS-induced colitis in C57BL/6 wild-type mice. Behavioral assays will systematically cover anxiety-like responses (Elevated Plus Maze, Open Field), social interaction (Three-Chamber Test), and cognition (Novel Object Recognition, Object Location Memory). Testing will be performed at multiple time points, from early inflammation, peak colitis, to the remission phase. This longitudinal approach will determine whether stress and inflammation produce overlapping or distinct behavioral trajectories and whether deficits persist beyond the inflammatory episode.

Aim 1B: Microbiota and immune correlates of behavioral change

Parallel to behavioral testing, fecal samples will be collected for 16S rRNA sequencing, metagenomic profiling, and metabolomics. Immune cell repertoires will be analyzed from mesenteric lymph nodes, blood, and intestinal tissues using multiparameter flow cytometry and cytokine quantification by ELISA. Particular attention will be paid to monocyte infiltration, T-cell subset polarization, and proinflammatory cytokines such as IL-17A, TNF, and IL-6. Correlation analyses will identify microbial and immunological signatures predictive of persistent behavioral alterations. Functional relevancy of microbial alterations will be tested using fecal microbiota transplantation into germ-free mice and the translational relevancy will be investigated using patient-derived microbiome models.

Aim 2: Role of the enteric nervous system in gut–brain signaling

We will assess the contribution of the ENS using pharmacological interventions that target specific neuronal and glial pathways, including capsaicin-sensitive afferents and peptide receptor agonists/antagonists. Immunohistochemistry and confocal microscopy will be applied to visualize activation markers such as GFAP and cFOS in enteric neurons and upstream targets. This will clarify how ENS activation integrates inflammation-induced changes and transmits them to the brain.

Aim 3: Integrative multi-omics and causal mechanisms

A central goal is to integrate data across behavioral, microbial, immunological, and ENS readouts. Bioinformatic pipelines will be developed to combine sequencing data, metabolite profiles, and immune cell signatures with longitudinal behavior. Causal mechanisms will be tested by pharmacological manipulation of candidate pathways identified in Aims 1–2. By unifying multimodal data in the same experimental animals, this project reduces risk of bias and increases mechanistic clarity.

Long-term Aim

The long-term vision is to establish a mechanistic framework for how intestinal inflammation shape brain function, and vice versa, through the enteric neuro-immune interface. By identifying microbial, immune, and ENS pathways that mediate persistent behavioral changes, this work seeks to pave the way for targeted interventions that improve (mental health) outcomes in IBD.

References

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