268, 113426. https://doi.org/10.1016/j.socscimed.2020.113426.

Fernández-Castañeda, A., Lu, P., Geraghty, A.C., Song, E., Lee, M.-H., Wood, J., O'Dea, M.R., Dutton, S., Shamardani, K., Nwangwu, K., et al. (2022). Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation. Cell *185*, 2452–2468.

Geraghty, A.C., Gibson, E.M., Ghanem, R.A., Greene, J.J., Ocampo, A., Goldstein, A.K., Ni, L., Yang, T., Marton, R.M., Pasca, S.P., et al. (2019). Loss of Adaptive Myelination Contributes to Methotrexate Chemotherapy-Related Cognitive Impairment. Neuron *103*, 250–265.e8. https://doi.org/10.1016/j.neuron.2019.04.032.

Gibson, E.M., and Monje, M. (2021). Microglia in Cancer Therapy-Related Cognitive Impairment. Trends Neurosci. *44*, 441–451. https://doi.org/10.1016/j.tins.2021.02.003.

Gibson, E.M., Nagaraja, S., Ocampo, A., Tam, L.T., Wood, L.S., Pallegar, P.N., Greene, J.J., Geraghty, A.C., Goldstein, A.K., Ni, L., et al. (2019). Methotrexate Chemotherapy Induces Persistent Tri-glial Dysregulation that Underlies Chemotherapy-Related Cognitive Impairment. Cell *176*, 43–55. e13. https://doi.org/10.1016/j.cell.2018.10.049.

Honigsbaum, M. (2013). "An inexpressible dread": psychoses of influenza at fin-de-siecle. Lancet *381*, 988–989. https://doi.org/10.1016/s0140-6736(13)60701-1.

Monje, M.L., Toda, H., and Palmer, T.D. (2003). Inflammatory blockade restores adult hippocampal neurogenesis. Science *302*, 1760–1765. https://doi.org/10.1126/science.1088417.

Steadman, P.E., Xia, F., Ahmed, M., Mocle, A.J., Penning, A.R.A., Geraghty, A.C., Steenland, H.W., Monje, M., Josselyn, S.A., and Frankland, P.W. (2020). Disruption of Oligodendrogenesis Impairs Memory Consolidation in Adult Mice. Neuron *105*, 150–164.e6. https://doi.org/10.1016/j.neuron.2019.10.013.

Villeda, S.A., Luo, J., Mosher, K.I., Zou, B., Britschgi, M., Bieri, G., Stan, T.M., Fainberg, N., Ding, Z., Eggel, A., et al. (2011). The ageing systemic milieu negatively regulates neurogenesis and cognitive function. Nature *477*, 90–94. https://doi.org/10.1038/nature10357.

Breaking down a gut-to-brain circuit that prevents malabsorption

Brooke C. Jarvie[1,2] and Zachary A. Knight[1,2,3,*]
[1]Department of Physiology, University of California, San Francisco, San Francisco, CA 94158, USA
[2]Kavli Institute for Fundamental Neuroscience, University of California, San Francisco, San Francisco, CA 94158, USA
[3]Howard Hughes Medical Institute, University of California, San Francisco, San Francisco, CA 94158, USA
*Correspondence: zachary.knight@ucsf.edu
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The ileal brake is an important reflex that ensures proper absorption of nutrients. This involves intestinal GLP-1 release, which recruits an enteric-sympathetic-spinal pathway to inhibit gastric motility and appetite. This visceral alarm system could be targeted to treat obesity and gastrointestinal dysfunction.

The transit of food through the gastrointestinal tract must be properly timed so that nutrients can be safely and efficiently absorbed. During a normal meal, most macronutrients are absorbed before they reach the most distal part of the small intestine, known as the ileum. However, this normal pattern of digestion can be disrupted by bariatric surgery, certain diseases, or the rapid consumption of very large meals. In these scenarios, the accumulation of excess food in the ileum triggers an alarm reflex known as the "ileal brake" that decreases gastrointestinal motility and powerfully inhibits appetite, thereby allowing time for nutrients to be absorbed (Maljaars et al., 2008). In this issue of *Cell*, Zhang et al. identify the neural circuit that mediates this response to digestive emergencies in a mouse model. In doing so, they reveal a web of interactions between gut hormones and enteric, sympathetic, and spinal neurons that together regulate gastric emptying and aversive responses to food (Zhang et al., 2022; Figure 1).

The hormone GLP-1 is released by enteroendocrine cells in the intestine in response to the detection of ingested nutrients and functions to inhibit gastric emptying and food intake (Figure 1, enteroendocrine cells in blue). Although GLP-1 is expressed at many sites in the intestine, it is enriched in the ileum, making it an attractive candidate to mediate the ileal brake (Larsson et al., 1975). Indeed, Zhang et al. show that direct infusion of GLP-1 into the ileum can decrease gastric motility and appetite and cause a remarkable doubling of stomach volume. They further showed, using either optogenetics or chemogenetics, that these responses are phenocopied by direct stimulation of the ileal cells that produce GLP-1, indicating that endogenous GLP-1 release from the ileum is sufficient to mimic the ileal brake.

The authors next investigated how the release of ileal GLP-1 triggers these responses. Vagal afferents, which are sensory neurons that densely innervate the intestine and provide a direct link from the gut to brain, are thought to be the principal gut sensors of GLP-1 (Brierley and de Lartigue, 2022). However, Zhang et al. show that ileal GLP-1 is instead detected by enteric neurons (the resident neurons of the gastrointestinal tract) and specifically by a specialized subset of enteric neurons known as intestinofugal cells that project to the abdominal sympathetic ganglia (Figure 1, shown in red). These ganglia provide sympathetic input

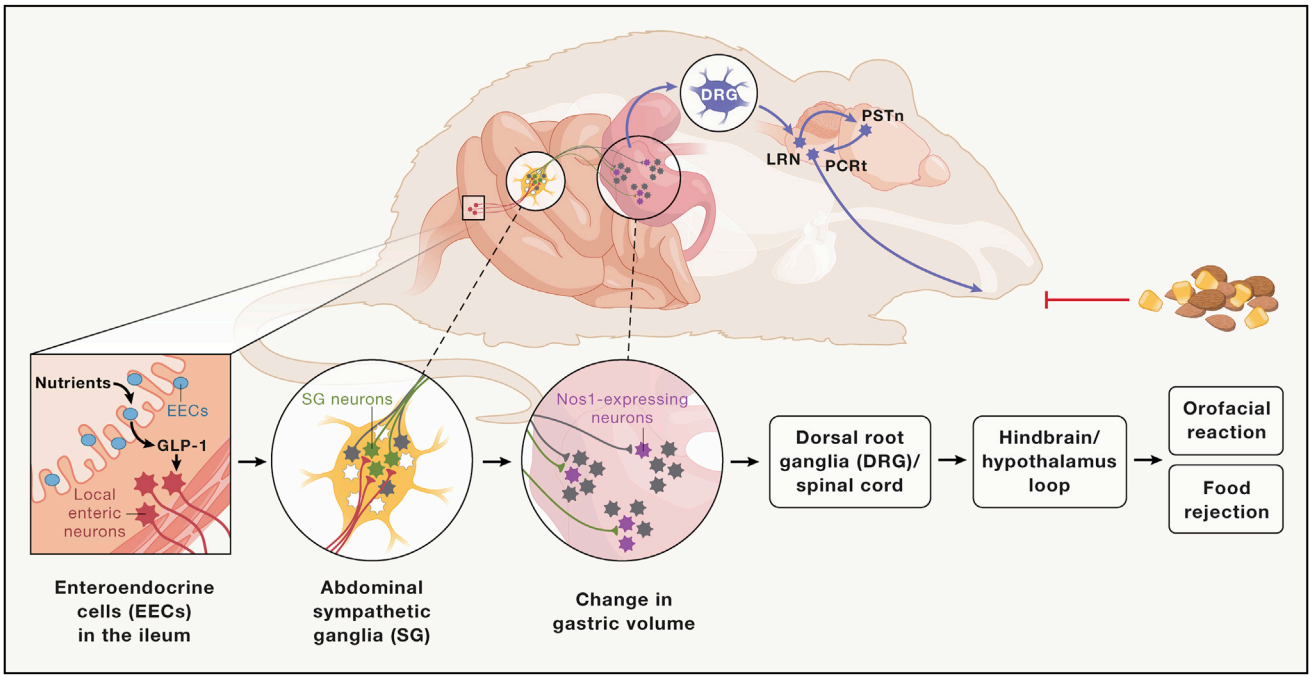

Figure 1. The gastrointestinal neural circuit mediating the ileal brake

Nutrients are sensed by enteroendocrine cells (EECs) in the ileum, which release GLP-1. GLP-1 activates local enteric neurons (red) that project to the abdominal sympathetic ganglia (SG). The downstream SG neurons (green) in turn project to the stomach to innervate inhibitory Nos1-expressing neurons (purple) and increase gastric volume. These gastric changes are then relayed via sensory afferents with cell bodies in dorsal root ganglia (DRG) to the spinal cord and ultimately to the lateral reticular nucleus (LRN) in the hindbrain. This information is further transmitted to the parasympathetic nucleus (PSTn), the pontine parvocellular reticular formation (PCRt), and then the jaw to inhibit food intake.

to the gastrointestinal tract to help coordinate digestion (Furness et al., 2014). Accordingly, the authors find that the sympathetic neurons that receive input from the ileum in turn project to the stomach (Figure 1, shown in green), where they target inhibitory Nos1-expressing neurons, which are known to control motility by relaxing smooth muscle (Figure 1, shown in purple) (Costa et al., 2021). Thus, this provides a multi-step pathway by which the ileum and stomach can communicate to inhibit gastric emptying. Importantly, stimulation or ablation of any node in this circuit either mimics or prevents, respectively, the effects of ileal GLP-1 infusions.

Although an enteric intestinofugal pathway explains how ileal GLP-1 can affect the stomach, information still needs to reach the brain to control feeding. To explore this, the authors used an anterograde viral tracer starting from the stomach to map out the afferent pathway. They first showed that spinal, but not vagal, afferents are required for the inhibition of food intake following ileal GLP-1 administration, revealing surprisingly that there are two distinct neural pathways (spinal and vagal) by which GLP-1 communicates with the brain to regulate feeding. They then traced a circuit from the spinal cord to the lateral reticular nucleus in the medulla, which in turn projects to the parasubthalamic nucleus in the hypothalamus (Figure 1). The authors showed that both the lateral reticular nucleus and the parasubthalamic nucleus respond to gastric distension, and the parasubthalamic nucleus also responds to ileal GLP-1. Given that negative visceral or sensory sensations such as nausea or bitter taste cause animals to display stereotyped facial expressions like gaping (Dolensek et al., 2020), the authors hypothesized that these brain regions might promote similar negative orofacial responses. Indeed, ileal GLP-1 infusion and activation of the parasubthalamic nucleus both induced a gaping response. To complete the circuit, the authors identified a projection from the parasubthalamic nucleus to the pontine parvocellular reticular formation in the hindbrain, a premotor nucleus that innervates the jaw and oral cavity. Thus, this reveals a gut-to-jaw pathway that is linked to the robust inhibition in feeding caused by the ileal brake.

It is important to note that none of the manipulations in the study affected feeding, gastrointestinal motility, or glucose homeostasis at baseline, indicating that GLP-1 in the ileum (and the circuit it activates) are unlikely to signal normal satiation, but rather function as a gastrointestinal defense system against malabsorption. Although some macronutrients reach the ileum following a normal meal (Keller et al., 1997), it is unclear whether this reaches sufficient concentrations to trigger ileal GLP-1 and activate the circuitry described here. However, in the case of bariatric surgeries, elevated levels of nutrients do reach the ileum, and this circuit could help explain why these surgeries are so effective at reducing appetite (Maljaars et al., 2008). In addition, pharmaceutical interventions aimed at different nodes of the enteric-sympathetic-spinal pathway could help

ameliorate symptoms of gastroparesis and other disorders associated with dysregulated gastrointestinal motility. It will be interesting to investigate how this circuit is modulated by the many inputs that can affect GLP-1 release, including circulating peptides, inflammatory stimuli, and the vagus nerve (Brierley and de Lartigue, 2022; Lebrun et al., 2017).

A unique finding of this study is that enteric and spinal neurons can interact with each other to control appetite and behavior, an idea that has been proposed but not clearly demonstrated. Although it is well established that spinal and vagal efferents can synapse on enteric neurons, enteric neurons are not thought to communicate directly with sensory afferents (Furness et al., 2014). Zhang et al. provide a mechanism for how this communication can occur indirectly, providing a framework for exploring how visceral signals can reach the brain. This study also challenges the conventional wisdom that neural gut-brain signaling is mediated almost entirely by the vagus nerve. Given the complexity of these unexplored visceral circuits, there is much that remains to be learned about how they modulate digestive functions and feeding.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

Brierley, D.I., and de Lartigue, G. (2022). Reappraising the role of the vagus nerve in GLP-1-mediated regulation of eating. Br. J. Pharmacol. *179*, 584–599. https://doi.org/10.1111/BPH.15603.

Costa, M., Spencer, N.J., and Brookes, S.J.H. (2021). The role of enteric inhibitory neurons in intestinal motility. Auton. Neurosci. *235*, 102854. https://doi.org/10.1016/J.AUTNEU.2021.102854.

Dolensek, N., Gehrlach, D.A., Klein, A.S., and Gogolla, N. (2020). Facial expressions of emotion states and their neuronal correlates in mice. Science *368*, 89–94. https://doi.org/10.1126/SCIENCE.AAZ9468/SUPPL_FILE/AAZ9468S3.MP4.

Furness, J.B., Callaghan, B.P., Rivera, L.R., and Cho, H.J. (2014). The enteric nervous system and gastrointestinal innervation: Integrated local and central control. Adv. Exp. Med. Biol. *817*, 39–71. https://doi.org/10.1007/978-1-4939-0897-4_3/FIGURES/7.

Keller, J., Rünzi, M., Goebell, H., and Layer, P. (1997). Duodenal and ileal nutrient deliveries regulate human intestinal motor and pancreatic responses to a meal. Am. J. Physiol. Gastrointest. Liver Physiol. *272*, G632–G637. https://doi.org/10.1152/AJPGI.1997.272.3.G632.

Larsson, L.-I., Hoist, J., H~kanson, R., and Sundler, F. (1975). Distribution and Properties of Glucagon Immunoreactivity in the Digestive Tract of Various Mammals: An Immunohistochemical and Immunochemical Study, pp. 281–290.

Lebrun, L.J., Lenaerts, K., Kiers, D., Pais de Barros, J.P., Le Guern, N., Plesnik, J., Thomas, C., Bourgeois, T., Dejong, C.H.C., Kox, M., et al. (2017). Enteroendocrine L Cells Sense LPS after Gut Barrier Injury to Enhance GLP-1 Secretion. Cell Rep. *21*, 1160–1168. https://doi.org/10.1016/J.CELREP.2017.10.008.

Maljaars, P.W.J., Peters, H.P.F., Mela, D.J., and Masclee, A.A.M. (2008). Ileal brake: A sensible food target for appetite control. A review. Physiol. Behav. *95*, 271–281. https://doi.org/10.1016/J.PHYSBEH.2008.07.018.

Zhang, T., Perkins, M.H., Chang, H., Han, W., and de Araujo, I.E. (2022). An Inter-Organ Neural Circuit for Appetite Suppression. Cell *185*, 2478–2494. https://doi.org/10.1016/j.cell.2022.05.007.

Flaviviruses hijack the host microbiota to facilitate their transmission

Lejla Gul,[1,2] Tamas Korcsmaros,[1,2,3] and Neil Hall[1,4,5,*]
[1]Earlham Institute, Norwich, UK
[2]Imperial College London, Department of Metabolism, Reproduction and Development, London, UK
[3]Quadram Institute Bioscience, Norwich, UK
[4]Department of Biological Sciences, King Abdulaziz University, Jeddah 21589, Saudi Arabia
[5]School of Biological Sciences, University of East Anglia, Norwich, UK
*Correspondence: neil.hall@earlham.ac.uk
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Flaviviruses, such as Dengue and Zika viruses, infect millions of people worldwide using mosquitos as vectors. In this issue of *Cell*, Zhang et al. reveal how these viruses manipulate the skin microbiome of infected hosts in a way that increases vector recruitment and viral spread. They propose vitamin A as a way to counteract the virus and decrease transmission.

Flaviviruses are a group of vector-borne pathogens that cause several important human diseases including Zika and dengue. Because climate change is increasing the distribution of their mosquito hosts, many of these viruses pose an increasing global health threat, and consequently there is an urgent need to control their spread. Both dengue and Zika viruses use *Aedes* mosquitoes to spread between hosts, including humans. These insects transmit viruses by feeding on an infected vertebrate host, followed by an uninfected host, allowing the virus to enter the host's bloodstream and