Published in final edited form as:

Nat Rev Gastroenterol Hepatol. 2017 March ; 14(3): 135–136. doi:10.1038/nrgastro.2016.199.

XIVth Little Brain Big Brain: next-generation enteric neuroscience

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Abstract

Little Brain Big Brain has been a biannual meeting organized and attended exclusively by young investigators in neurogastroenterology since 1989. The XIVth meeting featured cutting-edge work advancing several novel hypotheses in the main themes of motility, inflammation and metabolism.

Since 1989, the Little Brain Big Brain (LBBB) meeting has been organized and attended by young investigators. LBBB has a simple model — select some of the brightest young minds in neurogastroenterology and lock them in a room. At LBBB, everyone presents, and discussion is unlimited. The results are inarguable; most LBBB attendees have launched life-long friendships and collaborations, and have also become the scientific and thought leaders of our field. The XIVth LBBB was held in Santa Cruz, USA, immediately preceding the Federation of Neurogastroenterology and Motility (FNM) 2016 meeting. Of >60 applicants, 30 promising junior investigators were selected by a panel of previous LBBB attendees and leading scientists. Attendees came from all over the world: ten from North America, 14 from Europe and six from Australia; 17 of 30 attendees were women.

Meeting highlights

The XIVth LBBB lived up to the standards of past meetings in terms of high-quality work and lively discussion. Herein, we discuss highlights of the three main themes (FIG. 1).

All authors contributed equally to this work.

Competing interests statement

The authors declare no competing interests.

Neurogastroenterology & motility

The issues that plague study of functional gastrointestinal diseases (FGIDs) relate to the disconnect between symptoms and identifiable organic pathologies. To address these knowledge gaps, presenters used innovative techniques to ask several questions. What molecular abnormalities lead to functional disruptions? How can treatments shift from symptom support to molecular targeting? And what novel approaches can aid diagnosis?

The gastrointestinal tract is composed of multiple cell types with diverse functions¹. It is critical to study these cells in their native environment. Several LBBB attendees used transgenic mice with innovative reporter systems that show stunning improvements in signal-to-noise ratio *in vitro* and *in vivo*; not only were individual cells 'crystal clear', but they allowed for visualization of subcellular signalling!

Reports have pointed out the difficulties of translating studies from animal models to human disease². FGIDs are no exception. The value of preclinical models for understanding basic pathophysiological mechanisms is indisputable. However, parallel studies on humans and human tissues are required. To that end, several LBBB investigators pursued translational and clinical studies. Interestingly, one study using human tissues generated a novel hypothesis suggesting further mechanistic testing in rodents, opposite to the more traditional paradigm of hypothesis generation using animal models and confirmation in humans.

The lack of specific diagnostic techniques remains a major handicap in FGIDs. The advent of high-resolution manometry has revolutionized the understanding of gastrointestinal, oesophageal and colonic motility³. LBBB investigators explored high-resolution manometry for diagnosis of both upper and lower gastrointestinal function and found novel physiological parameters altered in patients with FGIDs.

ENS inflammation & development

The ENS has key roles in gut physiology^{1,4}. Functional and developmental ENS abnormalities lead to disease, stress and inflammatory influences can, in turn, affect the ENS. Neuroimmune mediators have important roles in the manifestation of stress and inflammatory responses of the gut, both locally within the ENS and via extrinsic afferent nerve signalling. These complex signalling pathways are critical to our understanding of gastrointestinal function. LBBB attendees discussed the involvement of intrinsic and extrinsic nerve activity in a wide range of gastrointestinal disorders and symptoms (such as IBS, gastroparesis and colitis), as well as exciting new possibilities for ENS-targeted gene therapies using viral vector gene delivery. Over the past 30 years, ENS structure and function have garnered substantial interest, but factors and mechanisms affecting ENS development are still poorly understood. LBBB participants leveraged the latest technology to answer important outstanding questions. They used high-resolution *in vivo* fate mapping to understand the diversity of ENS lineages and to examine the connectivity of clonally related enteric neurons by calcium imaging. This approach combined with a variety of genetic recombinations, immunohistochemistry and functional analysis highlighted the role of ENS progenitors. Some attendees used optogenetics, in which neural progenitors express

light-sensitive ion channels, to examine whether the transplanted enteric neural progenitors can generate functional neurons.

Recent studies have shown that postnatal maturation of immune regulation is largely driven by exposure to microorganisms, and evidence suggests that ENS development is also affected. LBBB participants explored several factors responsible for the establishment of gut microbiota in infants during prenatal, delivery and postnatal periods. Early adverse exposures of the gut microbiota were associated with the development of several childhood diseases that might persist into adulthood.

Nutrition & metabolism

Metabolic diseases range from undernutrition, accounting for nearly half of all global deaths in young children⁵, to overnutrition, whereby excess energy stored as fat leads to obesity⁶. LBBB participants demonstrated that metabolic diseases can result in long-term physiological disturbances, from the gut to the brain, perpetuating malnourished states.

Prior work linked gut microbiota with metabolic diseases and their comorbidities⁷. To address causality, LBBB presenters manipulated gut bacteria using germ-free animals, faecal microbiota transplants, antibiotics, dietary changes and pathogenic infections, as well as microbiome profiling and metabolomics to identify putative bacteria and their products that might mediate pathophysiology. Dysbiosis in early life had many potential physiological and behavioural effects: impaired memory; a link to autism spectrum disorder; dysmotility; weight gain. Thoughtful discussions ensued about the value of each technique, concluding that each approach for microbial manipulation is crucial to understanding the influence of the gut microbiota on health and disease, but the data should be interpreted with caution.

The vagus nerve is a key component of the nutrient-sensing machinery intersecting the ‘little brain’ and ‘big brain’⁸. LBBB presenters used immunohistochemistry and electrophysiology to identify mechanisms disrupting vagally mediated satiation in diet-induced obesity. A novel approach combining confocal and electron microscopy provided 3D ultrastructure of vagal afferent terminal contact with enteroendocrine cells in the gut. Clinically, vagal activity was negatively correlated with rebounding after weight loss in obesity. Neural circuits responsive to gastrointestinal signals that control energy homeostasis were identified in animals and humans. Viral-mediated knockdown, rescued with targeted pharmacology, highlighted the role of a circuit that controls energy expenditure in rats. In humans, dynamic PET scanning of dopamine in response to visual food cues provided *in vivo* functional imaging of reward circuits over time.

Three LBBB winners were selected by their peers on the basis of presentation quality and engagement in discussions: Geoffrey Preidis, Roeland Buckinx and the overall winner Meenakshi Rao. Each winner received *Nature Reviews Gastroenterology & Hepatology* subscriptions and Dr Rao received a cash prize sponsored by the journal.

LBBB: the path forward

For almost 30 years, LBBB has provided a unique forum for young scientists in neurogastroenterology, and the work of 'LBBB-ers' is illuminating many novel and fundamentally important areas, advancing the field in exciting new ways. The next LBBB will be held before the 3rd FNM meeting in Amsterdam, Netherlands, and will be organized by Roeland Buckinx, John Broad, Barbara Vossen and Nazar Mazurak. The XVth LBBB is again poised to provide a top-notch platform for young neurogastroenterology investigators worldwide.

Acknowledgments

The XIVth LBBB was supported by *Nature Reviews Gastroenterology & Hepatology*, a National Institute of Diabetes and Digestive and Kidney Disease R13 Award, the American Neurogastroenterology and Motility Society, the European Society of Neurogastroenterology & Motility, the Australasian Neurogastroenterology & Motility Association, Takeda, Ironwood Pharmaceuticals, Allergan, Biocodex and Bio-Techne. We would also like to acknowledge the mentorship of D. Linden and S. Gibbons (Mayo Clinic, Rochester).

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Figure 1.
Key themes for the XIVth LBBB meeting.