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EDITORIAL

Gut–brain axis and neuropsychiatric health: recent advances

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The gut–brain axis, a bidirectional communication pathway, permits the central nervous system (CNS) to exert influence over gastrointestinal function in response to stress, while the gut microbiota regulates the CNS via immune, neuroendocrine, and vagal pathways. Current research highlights the importance of the gut microbiota in stress-related disorders and the need for further research into the mechanisms of gut–brain communication, with potential therapeutic implications for a wide range of health conditions. This is a challenge taken on in this *Scientific Reports* Collection on the Gut-Brain Axis. The gut–brain axis has significant implications for neurodegenerative, psychiatric, and metabolic disorders. Recent studies have underscored the role of the gut microbiome in conditions such as Parkinson's disease (PD), with evidence indicating that gut dysfunction and pathological features can precede motor symptoms by decades. The use of in vivo animal models has demonstrated that preformed α-synuclein fibrils (PFFs) can travel from the gut to the brain in a dosage-dependent manner, thereby supporting the "gut-first" theory in the context of PD, a theory that is explored in this Collection using in vitro approaches. There is also evidence that the gut–brain axis plays a role in obesity and machine learning algorithms may assist in differentiating between obese and overweight individuals based on their microbiota data. There is also growing interest in the role of the gut at the interface between post-traumatic stress disorder (PTSD), sleep disturbances, and irritable bowel syndrome (IBS). The studies described in this Collection support and expand on the observations from previous preclinical and clinical investigations, while also providing essential novel insights that can drive discovery into previously unexplored avenues of brain-gut-microbiome interactions in health and disease.

The bi-directional communication pathway between the gastrointestinal system and the brain, the gut–brain axis, originally dates back to the 1840s when Beaumont suggested the brain and the gut communicate after showing that different emotional states influenced the rate of digestion[1]. The gut–brain axis enables the central nervous system (CNS) to modulate gastrointestinal activity in response to psychological and physiological stress and thereby affect immune and secretory activities, while also enabling the enteric microbiota to regulate the CNS via immune, neuroendocrine, and vagal pathways and to produce behavioral and neurological changes[2].

The past decade or more has seen significant advances in our understanding of the role of the gut microbiome as a key node in this axis and with important implications for the neurobiology and treatment of CNS, neurodegenerative, neurodevelopmental, and psychiatric disorders. Notably, a recent genome-wide association study based on the data of 450,000 individuals found extensive genetic overlap and genetic correlations between gastrointestinal tract disorders and psychiatric disorders, showing a shared genetic basis that supports the gut–brain connection[3]. Another recent implication of the gut–brain axis was in relation to the COVID-19 pandemic. The alterations in the gut microbiome after the SARS-CoV-2 infection was suggested as one explanation for long COVID symptoms or "brain fog", which refer to the persistent neurological and psychiatric symptoms, whereupon therapeutic approaches based on the gut–brain axis such as a plant-based diet and probiotics and prebiotics were proposed to potentially be beneficial for long COVID symptoms[4].

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The recently emerging evidence seems to further support the conceptualization of the gut as the "second brain"[5], as more and more empirical evidence is accumulating around microbial regulation of brain function and behaviour via the gut–brain axis. Vagus nerve signaling from the gut is heavily implicated in the regulation of higher-order cognition such as anxiety, depression, learning, memory, and motivation, supporting the involvement of the gut in the control of neurocognitive processes that in turn guide adaptive behavioral responses[6,7]. Social cognition was also shown to be regulated by the gut–brain axis in young binge drinkers, where associations emerged between certain microbiome species and emotional processing and impulsivity[8].

The scope of the involvement and effects of the gut–brain axis seem to be very broad yet remain to be fully elucidated, with critical gaps in knowledge regarding the precise mechanisms of information transmission, which was an important focus of the Gut-Brain Axis Collection of *Scientific Reports*.

The aetiology and the underlying pathogenesis of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS) remain poorly understood and multidisciplinary rehabilitative approaches seem to be an urgent global medical care priority[2]. In addressing these issues, it has been suggested that the intestinal microbial ecosystem that is the human body's second genome can be connected with the initiation and/or progression of neurodegenerative diseases[2]. Meta-analyses have shown that both symptomatic gut dysfunction[9] and pathological features[10] can appear in PD patients decades before motor symptoms. Research using disease models, including the delivery of preformed α-synuclein fibrils (PFFs), supports the idea that these fibrils can travel from the gut to the central nervous system via vagal and non-vagal pathways. In their previous paper, Bindas et al.[11] have shown that PFFs propagate PD-like motor dysfunction in animal models, further supporting the gut–brain connection in PD. In the present Collection, Bindas et al.[12] elucidate the "gut-first" aetiology of PD and investigate the enteric and cortical neurons in a preformed fibril (PFF) PD model, employing this concept in a less frequently utilised in vitro cell culture model. In this study, the PFF PD model is used in conjunction with co-administered groups of butyrate and lipopolysaccharide (LPS) to elucidate the impact of the local gut microbiome. The findings indicate that an increase in LPS dosage is associated with a rise in the average intensity of aggregated a-Syn, suggesting that the enteric nervous system (ENS) and cortical neurons uptake PFFs dose-dependently. It thus would be beneficial for future studies to include aged, human, and chronically PFF-dosed neural populations in order to gain insight into the enteric formation of and response to PD pathology.

Another major public health concern involves obesity, which in this Collection authors Osadchiy et al.[13] conceptualize as an epidemic with national and international significance and present important evidence supporting gut–brain interactions as an important factor distinguishing obese from overweight individuals. They have found that brain regions involved in the emotional regulation (inferior frontal gyrus, cingulate gyrus, and straight gyrus) and somatosensory network (postcentral gyrus, posterior insula, and paracentral lobule) can differentiate obese from overweight individuals. Interestingly, the default mode network also plays a significant role, suggesting that obesity may represent a unique and distinct neuroimaging phenotype, rather than an extreme version of the overweight phenotype. Their machine learning model successfully made this differentiation using fecal metabolites and neuroimaging data. The application of machine learning approaches to understand the interface between the gut microbiota and the brain is an important feature of this study and represents an approach that has also recently yielded insights about other conditions, such as the successful use of virulence factor-related gut microbiota genes in a machine learning-based classification of autism spectrum disorder[14]. The application of machine learning in the field of diagnostic classification has the potential to enhance clinical decision-making by leveraging the comprehensive data sets derived from evidence-based diagnostic instruments, including neuroimaging and gut microbiome analysis. This approach may prove particularly advantageous in the context of early diagnosis, where symptoms may be less pronounced and the diagnostic decision-making process is often particularly challenging[15].

There is much interest at present in understanding a potential transdiagnostic role of the gut microbiota across traditional diagnostic boundaries[16]. The potential confounding role of host genetics in the associations reported between the gut microbiome and neuropsychiatric phenotype associations can be overcome using twin studies. Delanote and colleagues use this approach to demonstrate an association between the relative abundance of the genus Parabacteroides and diagnosis with a mental health disorder[17]. The grouping together of several different neuropsychiatric diagnoses in this study is an interesting feature, where they collectively consider depression, anxiety, or eating disorders, a choice they explain with the co-occurrence and some shared symptomatology of these conditions. Future studies focusing on higher resolution microbiota analysis methods, functional readouts, and the evaluation of sex-specific effects in longitudinal studies will be important to verify the broader importance of these interesting results.

Beside the gut-first approach, a number of key observations in this field highlighted the reciprocal nature of the relationship between stressed gut and the stressed brain[18]. A neglected focus in this regard has been post-traumatic stress disorder (PTSD). Howard and colleagues[19] take an important step in this regard by evaluating the interface between subclinical levels of post-traumatic stress, gastrointestinal issues (GI), and the central executive network (CEN). They found that stronger connectivity within the CEN exhibited a significantly reduced impact of PTS symptoms on the number of endorsed GI disorders in comparison to those with low connectivity of that network. These findings imply that synchronous activation of nodes within the CEN may facilitate neurological processes that modulate the established effect of traumatic stress on downstream signalling pathways. The gut microbiome plays a crucial role in influencing the brain's cognitive network, and emerging research suggests that imbalances in this microbial community may contribute to the development and severity of PTSD by affecting neural circuits involved in stress regulation and cognitive processes. The key observations from this study support a continued focus on this topic to gain deeper insights into the precise gut–brain axis mechanisms linking traumatic stress exposures to gastrointestinal symptoms and reinforce the concept of the bidirectional communication between CNS and the gut. In addition, this gut–brain link in PTSD involving CEN

may provide a biological mechanism for how cognitive elements play a role in the diagnosis and prognosis of PTSD, linking cognition with peripheral mechanisms, and may have implications for better understanding and improving cognitive therapies for PTSD.

It is increasingly appreciated that stress and circadian systems are interconnected[20,21], which highlights the necessity to understand how to maintain appropriate relationships between sleep, circadian rhythms and the gut microbiome[22]. Indeed, previous research noted that sleep indices during exam stress were improved due to consumption of a putative psychobiotic, a strain of *Bifidobacterium longum*[23]. Patterson and colleagues extend these observations to show particular benefits for sleep quality as well as improved social functioning and increased energy[24]. Targeting the gut microbiome to support sleep quality is an important objective and we anticipate further progress in this regard once the mechanisms are fully understood, which will be particularly important in moving this option into pathological populations with defined sleep disturbances.

Barrier function is an important feature of communication across the microbiota-gut–brain axis[25]. The mucus layer covering the epithelium is critical to gut homeostasis, including the regulation of barrier function, but requires more detailed scrutiny. While Coletto and colleagues[26] contribute new understanding in this regard by demonstrating an important association between impaired mucin glycosylation, barrier function, and memory, the precise role of microbial metabolites in producing such physiological and functional changes remains to be fully defined.

Irritable bowel syndrome (IBS) has been reframed as a disorder of gut–brain interaction[27]. There has been much focus on comorbid health conditions in IBS, particularly the high prevalence of anxiety and depression[28]. Purssell and colleagues instead focus on the overlap between IBS and non-alcoholic fatty liver disease (NAFLD)[29]. The high prevalence of IBS (35.2%) in this cohort of patients with NAFLD was also defined by impaired QoL and psychosocial distress[29], further reinforcing the importance of gut–brain connections in evaluating the multi-comorbid nature of stress-related disorders of gut brain interaction.

In conclusion, the growing body of research highlighting the intricate relationship between the microbiome and the gut–brain axis offers promising insights into the neuropsychological mechanisms underlying various health conditions and mental disorders, as well as for understanding the effects of certain viruses and illnesses. One example of this is the gut–brain axis being linked to long-haul COVID-19 syndrome, whereby alterations in the gut microbiome contribute to the development of neurological symptoms. The vagus nerve plays a regulatory role in cognitive and affective functions that are essential for our well-being and well-adjusted social behaviour. Understanding how the gut microbiota affects these brain functions could pave the way for early diagnosis and more targeted therapies for conditions such as depression, anxiety, and neurodegenerative diseases. Further studies are crucial to unravel the complex mechanisms at play and to translate this knowledge into clinical applications for mental health care. As the field progresses, exploring microbiome-based interventions may become an essential component of therapeutic strategies, and offer novel approaches to treatment in clinical and mental health settings.

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Declarations

Competing interests

The authors declare no competing interests.

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