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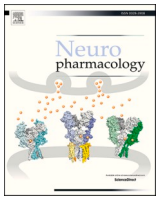

The gut-brain connection: Exploring the influence of the gut microbiota on neuroplasticity and neurodevelopmental disorders

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ABSTRACT

Neuroplasticity refers to the ability of brain circuits to reorganize and change the properties of the network, resulting in alterations in brain function and behavior. It is traditionally believed that neuroplasticity is influenced by external stimuli, learning, and experience. Intriguingly, there is new evidence suggesting that endogenous signals from the body's periphery may play a role. The gut microbiota, a diverse community of microorganisms living in harmony with their host, may be able to influence plasticity through its modulation of the gut-brain axis. Interestingly, the maturation of the gut microbiota coincides with critical periods of neurodevelopment, during which neural circuits are highly plastic and potentially vulnerable. As such, dysbiosis (an imbalance in the gut microbiota composition) during early life may contribute to the disruption of normal developmental trajectories, leading to neurodevelopmental disorders. This review aims to examine the ways in which the gut microbiota can affect neuroplasticity. It will also discuss recent research linking gastrointestinal issues and bacterial dysbiosis to various neurodevelopmental disorders and their potential impact on neurological outcomes.

This article is part of the Special Issue on "Microbiome & the Brain: Mechanisms & Maladies".

1. Introduction

The brain evolves and matures following trajectories which are only partially encoded by genes (Boyce et al., 2020; Desbonnet et al., 2015; Halperin and Healey, 2011; Kelly et al., 2017; Miguel et al., 2019; Wang et al., 2018). Neuronal circuits have the incredible talent of reorganizing their structure to adapt to the changing environment, in a process called neuroplasticity (Box 1) (Fuchs and Flügge, 2014; Ganguly and Poo, 2013; Voss et al., 2017; Zilles, 1992).

There has been a long-standing focus on identifying the mechanisms that control and drive neuroplasticity within the brain itself, but growing evidence suggests that brain function cannot be considered independent from peripheral influences. The gut microbiota - an ecosystem of fungi, archaea, bacteria, and viruses that live in the gastrointestinal (GI) tract - is one such influence that has been shown to affect various aspects of human physiology, including metabolism and immune system function (Nicholson et al., 2012; Rooks and Garrett, 2016). In addition, the relationship between the gut microbiota and its host appears to be complex and multifaceted, extending beyond its impact on metabolism and immunity to the regulation of central nervous system (CNS) functions (Murakami and Tognini, 2019).

The gut microbiota play a relevant role in converting the food we eat into nutrients and bioactive compounds with activities within the intestine and systemically. Thus, the microbiota could act as a "filter" and a "sensor" for exogenous compounds that enter the body (Clarke et al., 2014). It is not only a forgotten organ (O'Hara and Shanahan, 2006; Szajewska, 2021) but could work as a "sixth sense," providing a "gut feeling" (Holzer, 2017, 2022). As with the other senses, information must be transmitted between the microbiota and the brain, requiring a system of bidirectional communication with a shared language. The term "*microbiota-gut-brain axis*" refers precisely to the complex network of direct and indirect signaling via chemical transmitters, neuronal pathways and the immune system that creates such communication (Bercik et al., 2011; Borre et al., 2014; Cryan et al., 2019, 2019de Theije et al., 2014).The first evidence that commensal microbes could affect the CNS comes from research performed in germ-free (GF) mice, which are rodents completely devoid of microbes and living in a sterile environment (Arvidsson et al., 2012). In the pioneer work from 2004, Sudo and

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colleagues showed that the absence of the gut microbiota affected the hypothalamic–pituitary–adrenal (HPA) axis with subsequent altered endocrine responses to stress (Sudo et al., 2004). The novel idea of a gut microbiota impact on the brain has been strengthened in 2011 with the discovery that GF mice display alteration in motor activity and reduced anxiety-like behavior (Heijtz et al., 2011), and the revelation of the anxiolytic and antidepressant effects of the probiotic *Lactobacillus rhamnosus* (JB-1) (Bravo et al., 2011). Also, GF animals exhibited altered spatial working memory and reference memory (Gareau et al., 2011), defective adult hippocampal neurogenesis (Ogbonnaya et al., 2015) and reduced long-term potentiation (LTP) in the CA1 region of the hippocampus (Darch et al., 2021). From those early works, taking advantage of different strategies to interfere with the gut bacterial communities, such as the use of antibiotics, probiotics and the transplantation of fecal microbes, the field has expanded exponentially (Cryan and Dinan, 2012; Fan and Pedersen, 2021; Lupori et al., 2022). For instance, treating mice living in an enriched environment with an antibiotic cocktail completely prevented the enrichment-driven enhancement in cortical plasticity. On the other hand, the fecal microbiota transfer from enriched donors to standard recipient mice reactivated cortical plasticity (Lupori et al., 2022). Long-term antibiotic administration in adult mice significantly decreased hippocampal neurogenesis, which could be restored by probiotics or exercise (Möhle et al., 2016). In another set of experiments, altering the gut microbiome through antibiotic treatment from weaning induced behavioral impairment by decreasing adult hippocampal neurogenesis and LTP of synaptic transmission (G. Liu et al., 2022). Interestingly, transplanting the microbiota from young donors reversed aging-associated impairment of cognitive functions (Boehme et al., 2021). The reversed experiment induced deficits in cognitive behavior, and a decrease in dendritic spines in the hippocampus and prefrontal cortex of young rats (Li et al., 2020); while in mice, led to a decrease in memory performance and altered expression of hippocampal proteins involved in synaptic transmission and plasticity (D'Amato et al., 2020). Finally, a *Bifidobacteria* mix enhanced LTP in hippocampus CA1, increased brain-derived neurotrophic factor (BDNF) and dendritic spines density in rats (Talani et al., 2020). Also, probiotic (*Lactobacillus acidophilus*, *Bifidobacterium bifidum* and *Bifidobacterium longum)* treatment restored hippocampal LTP in a rat model of Alzheimer Disease (Rezaei Asl et al., 2019).

The studies mentioned previously only provide a small sampling of the research on the microbiota-gut-brain-axis. This axis appears to have a central role in modulating numerous brain related processes, including myelination (Gacias et al., 2016; Hoban et al., 2016), microglia maturation (Erny et al., 2015), neural plasticity (Buffington et al., 2016; Chu et al., 2019; Darch et al., 2021; Lupori et al., 2022), and eventually influencing complex behaviors (Boehme et al., 2021; Buffington et al., 2021; Chu et al., 2019; Hsiao et al., 2013).

The purpose of this review is to examine the current literature on how signals from the intestinal microbiota may influence neuroplasticity and behavior. Potential mechanisms through which the gut microorganisms may affect brain function will be described, with a focus on microglia activity modulation. Additionally, the potential link between neurodevelopmental disorders and alterations in plasticity processes as well as changes in the composition of gut microbes will be discussed. In this manuscript, the term "microbiota" refers to bacteria since most of the investigation performed so far has been focusing on those microorganisms.

2. Mechanisms of communication

There are various ways in which changes in the microbiota could influence brain plasticity. Some of the mechanisms include the regulation of gene expression, the production of neuroactive molecules, and the modulation of microglial activity (Fig. 1).

2.1. Potential regulation of gene expression by gut microbiota signals

How can the gut microbiota affect gene expression in a far-away land, such as the CNS? One answer lies in the ability of the intestinal microbiota to produce a great number of metabolites that could reach distal tissues after being released into the bloodstream. Intriguingly, several of those metabolites have the potential to shape the epigenetic footprint (Collins et al., 2012; O'Riordan et al., 2022; Rooks and Garrett, 2016; Tomasova et al., 2021).

In the brain, epigenetic marks are best known for their involvement in cell fate determination during neurodevelopment (Salinas et al., 2020). In the fully formed nervous system, epigenetics can still play a role in the acute regulation of gene expression, particularly in response to environmental signals and experience (Sweatt, 2009). Neuroepigenetics, as it is often referred to, plays a central role in plasticity

Box 1
NEUROPLASTICITY

Neuroplasticity refers to the brain's ability to adapt and change in response to external stimuli and experiences. This complex process involves a variety of mechanisms, including synaptic plasticity, neurogenesis, and changes in glial cell function, which enable neurons to form new connections, strengthen existing ones, and weaken others. Neuroplasticity can occur at the molecular, cellular and functional levels. Indeed, it may involve changes in the activity of single synapses, individual neurons, or entire patterns of activity across the neuronal network (Forrest et al., 2018). Specifically, at the cellular level, neuroplasticity involves changes in the strength and number of synapses between neurons, in a process called synaptic plasticity.

There are two main forms of synaptic plasticity: Hebbian and homeostatic plasticity (Abbott and Nelson, 2000; Cooper et al., 2004; Turrigiano, 2017; Zenke et al., 2017). Hebbian plasticity is a mechanism by which the correlated activity between neurons leads to long-lasting changes in the efficacy of synapses. The main forms of Hebbian plasticity are long-term potentiation (LTP) and Long-term depression (LTD) which can increase or decrease respectively the strength of synaptic connections influencing neuronal spine number, size and stability (Bliss and Collingridge, 1993; Bliss and Lomo, 1973; Bosch and Hayashi, 2012; Kemp et al., 2000; Linden, 1999). Those mechanisms represent the basis for learning and memory processes (Elphick, 2009; Martin et al., 2000; Nabavi et al., 2014). Homeostatic plasticity, in the form of synaptic scaling (Turrigiano, 2008) and homeostatic metaplasticity (Abraham and Bear, 1996), controls neuron and circuit excitability allowing network stabilization (Turrigiano, 2012; Wefelmeyer et al., 2016).

In addition to synaptic plasticity, there are other mechanisms that contribute to neuroplasticity, including changes in gene expression, protein synthesis, neurotrophine signaling, the growth of new neurons, and the rewiring of neural circuits (Berardi et al., 2003; Gómez-Palacio-Schjetnan and Escobar, 2013; Guzman-Karlsson et al., 2014; Lledo et al., 2006; Sweatt, 2016). Taken together, these mechanisms enable the brain to reorganize itself in response to changing environments, experience and learning opportunities, and are crucial for normal brain development and function throughout lifespan.

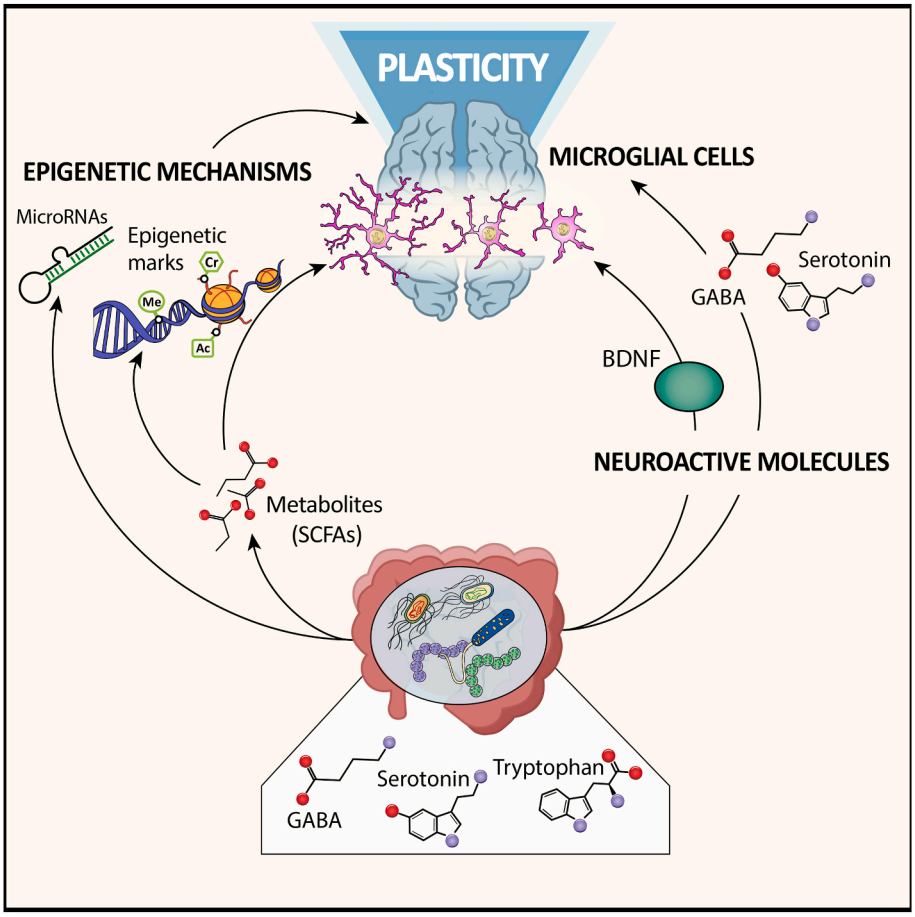

Fig. 1. General overview of the mechanisms through which the gut microbiota may influence neuroplasticity. Gut bacteria synthesize a variety of neuroactive molecules, including GABA, tryptophan and serotonin, which potentially influence neurotransmitter production and/or concentration in the brain. The gut microbiota may also affect neuronal plasticity by regulating microglia maturation and function, in a mechanism involving SCFA action and/or modulation of neuroactive molecules. SCFA, a product of microbial fermentation of non-digestible dietary fibers, might participate in epigenetics chromatin remodeling in a variety of brain cells, as demonstrated for microglia. Brain microRNA expression was recently proposed to be regulated by the gut microbiota.
Ac = histone lysine acetylation; Cr = histone lysine crotonylation; Me = DNA methylation; GABA = γ-Aminobutyric acid; SCFA = short chain fatty acids; BDNF = brain derived neurotrophic factor.

mechanisms in the CNS, serving as a bridge between experience and long-term behavioral changes, and allowing experience to shape future gene expression (Day and Sweatt, 2011; Guzman-Karlsson et al., 2014; Koshibu et al., 2009; McClung and Nestler, 2008; Miller and Sweatt, 2007; Sharma, 2010; Sweatt, 2016; Tognini et al., 2015a). Several epigenetic modifications – occurring on either histone proteins or DNA - have been associated with plasticity phenomena. Examples include histone acetylation (Sharma, 2010), DNA methylation (Duke et al., 2017; Tognini et al., 2015b), micro-RNA transcriptional silencing (Bredy et al., 2011; Hu and Li, 2017; Mellios et al., 2011; Napoli et al., 2020; Tognini et al., 2011) and long non-coding RNA regulation (Briggs et al., 2015; Wang et al., 2017). For instance, histone acetylation is known to increase as a result of neuronal activity to promote synaptic plasticity, memory formation and consolidation (Gräff and Tsai, 2013; Kandel, 2004; Monsey et al., 2011; Putignano et al., 2007; Sharma, 2010).

Epigenetic regulation is dynamically controlled by specific modifying enzymes whose activity requires metabolites that either serve as co-substrates or act as activators/inhibitors (Etchegaray and Mostoslavsky, 2016). Therefore, the activity of these enzymes is a function of the availability of endogenous metabolites (Fan et al., 2015). The gut microbiota might represent a source of such metabolites, ultimately affecting gene expression in the whole body, impinging on metabolic, immune, and neuronal function.

Short Chain Fatty Acids (SCFA), primarily butyrate, acetate, and propionate, are a class of metabolites mainly produced by the microbial fermentation of non-digestible dietary fibers in the colon (Morrison and Preston, 2016). Intriguingly, these metabolites, particularly butyrate and, to a lesser extent, propionate and acetate, have been shown to act as histone deacetylase (HDAC) inhibitors (Davie, 2003; Stilling et al., 2016; Waldecker et al., 2008). SCFA could promote the acetylation of histone proteins allowing the binding of transcription factors to DNA and eventually activating gene transcription (Thomas and Denu, 2021). A study comparing the pattern of histone acetylation in the liver and the proximal colon of GF mice and their conventionalized littermates has demonstrated that the acetylation process is affected by the gut bacterial community and that the administration of SCFA to GF mice was able to recapitulate the microbiota-driven epigenetic reprogramming (Krautkramer et al., 2016).

But how can SCFA cross the blood-brain barrier (BBB) to affect epigenetic processes in the brain? These molecules are transported across cell membranes via monocarboxylate transporters (MCT and SMCT) (Felmlee et al., 2020; Kim et al., 2014). In the brain, the presence of these transporters has been demonstrated in the cell membrane of neurons, astrocytes, oligodendrocytes and microglia (Lee et al., 2012; Moreira et al., 2009; Pierre and Pellerin, 2009; Zhang et al., 2022). Thus, a direct effect of SCFA on the transcriptional landscape of neural cells is conceivable. Indeed, in a study from 2021, it has been found that physiological doses of SCFA could impact gene expression on primary cortical astrocytes (Spichak et al., 2021). The authors showed a SCFA-mediated modulation of the transcriptional program, which involved immunomodulatory and histone deacetylase inhibition pathways. Interestingly BDNF and Peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, genes well-known to be involved in neuroplasticity mechanisms (Miranda et al., 2019; J. Wang et al., 2020; Wrann et al., 2013), were among the transcripts upregulated in this study (Spichak et al., 2021). The action of SCFA has been found to be relevant taking into account another post-translational modification (PTM) of histones: crotonylation, a type of short-chain lysine acylation marking active promoters and potential enhancers (Ntorla and Burgoyne, 2021; Tan et al., 2011). Fellows and colleagues (Fellows et al.,

2018) observed that the depletion of the microbiota led to a wide-ranging decrease in histone crotonylation in the colon. They suggested a mechanism through which microbial-derived SCFA, in particular butyrate, influenced the level of this epigenetic mark via the inhibition of class I HDAC activity, the major enzyme for histone de-crotonylation. The exceptional abundance of this PTM in the brain (Fellows et al., 2018) and the evidence showing its importance in neuronal differentiation (Dai et al., 2022), neurodevelopment (M. Wang et al., 2019), and stress-induced depression (Liu et al., 2019; M. Wang et al., 2019) make crotonylation one of the ways through which the microbiota could impinge on brain plasticity phenomena. Further research is needed to explore this possibility.

We recently demonstrated that SCFA could promote visual cortex plasticity in adult mice, an effect associated with changes in microglia morphology (Lupori et al., 2022). The specific molecular mechanisms have not been discovered yet, however, the possibility of SCFA influence on the brain epigenetic landscape is tempting, since experience-dependent plasticity in the visual cortex is enhanced by HDAC inhibitor administration (Putignano et al., 2007; Silingardi et al., 2010).

Another epigenetic mark extensively studied for its involvement in neuronal plasticity, and linked to the microbiota, is DNA methylation. Methylation of cytosine nucleotides is a covalent epigenetic modification typically connected to transcriptional silencing (Portela and Esteller, 2010). Changes in DNA methylation occur during learning and memory formation (Moore et al., 2013) and its involvement has been proven in experience-dependent plasticity (Tognini et al., 2015b) and regulation of synaptic function (Feng et al., 2010). DNA methylation depends on the one-carbon metabolism pathway which is limited by the availability of specific vitamins as cofactors for DNA methyltransferases (DNMT) (Anderson et al., 2012; Pizzorusso and Tognini, 2020). Those cofactors include bacterial metabolites, such as folate, riboflavin, pyridoxine and cobalamin, that can reach the cells of the host organism (Bhat and Kapila, 2017; Mischke and Plösch, 2016). While in the intestine it has been demonstrated that commensal bacteria were able to induce DNA methylation changes in epithelial cells (Ansari et al., 2020), so far, there is no demonstration of a direct microbiota-driven action on DNA methylation and transcription in the brain, nor a link to changes in network plasticity. Nonetheless, in a mouse model of Alzheimer's disease it has been reported a correlation between microbiota composition and both cognitive performance and level of DNA methylation in the hippocampus (Kundu et al., 2021). Moreover, the administration of probiotics in Zebrafish led to alterations in the methylation level of BDNF and tryptophan 5-monooxygenase (Tph1A) gene loci (Cuomo et al., 2021), both well-known for being involved in behavior, mood and cognition (Höglund et al., 2019; Miranda et al., 2019).

Further investigation is necessary to discover how and if vitamins or cofactors produced by intestinal microbes could reach the brain and influence the epigenetic landscape of neural cells with functional consequences on neuroplasticity and behavior.

Finally, novel evidence has shown that the gut microbiota could modulate microRNA (miRNA) expression. MiRNA are a class of endogenous small non-coding RNA that act as post-transcriptional gene silencers interfering with target mRNA and inhibiting their function virtually in every apparatus including the CNS (Bartel, 2004; Guo et al., 2010).

Several CNS miRNA display dendritic localization, which, coupled with their ability to simultaneously regulate the expression of different transcripts and to respond to neuronal activity, makes brain-specific miRNA excellent candidates for the fine-tuning of gene expression underlying neural plasticity and memory formation (Schratt, 2009). For instance, miR-132 regulates dendritic morphology and spine density in hippocampal neurons (Impey et al., 2010; Magill et al., 2010), and controls visual cortical plasticity, possibly interfering with spine remodeling (Mellios et al., 2011; Tognini et al., 2011; Tognini and Pizzorusso, 2012). Similarly, miR-29 has been demonstrated to act as a cortical age-dependent regulator of plasticity through the control of several epigenetic remodelers (i.e. DNMT3a) (Napoli et al., 2020).

The first evidence that the gut microbiota may influence the pool of miRNA in the brain came from a study in GF mice (Hoban et al., 2017). The absence of the gut microbiota was associated with changes in the expression of several miRNA, particularly in the amygdala and prefrontal cortex. These brain regions are known to play a central role in controlling anxiety and fear responses, behaviors that have been shown to be impaired in GF mice (Hoban et al., 2018; Luczynski et al., 2016a; Neufeld et al., 2011). In GF mice, the expression of some miRNA (e.g., miR-182, miR-219a) was restored upon post-weaning microbial colonization, while the expression of others (e.g., miR-206–3p, miR-1a) remained altered (Hoban et al., 2017). This may suggest the existence of a developmental time window in which the gut microbiota can influence specific miRNA levels. To further confirm the link between brain miRNA expression and the gut microbiota, two separate studies reported dysregulation in the expression of several miRNA in the hippocampus of GF mice, demonstrating that signals from the intestine may fine-tune gene expression in different brain regions (Chen et al., 2017; Moloney et al., 2017).

The microbiota capability of modulating brain miRNA levels, although fascinating, is still not entirely clear. As the intestinal microbes might indirectly remodel the neural epigenetic marks by restricting the availability of key metabolites, the miRNA expression pattern might be affected by changes in the chromatin landscape. Importantly, the ability of a single miRNA to regulate the expression of multiple transcripts makes miRNA ideal players in implementing the crosstalk between neuronal plasticity, gut and environmental cues.

2.2. Potential regulation of neuroactive molecules

The intestinal microbes have the capability of providing an incredible number of different metabolites which could act as essential neuroactive molecules for the nervous system. Gut bacteria can synthesize a variety of neurotransmitters, including gamma-aminobutyric acid (GABA), tryptophan, serotonin (5-HT), histamine, and dopamine, or their precursors, like tyrosine, tryptophan, choline and acetate (Chen et al., 2021; Williams et al., 2014; Yano et al., 2015). The BBB forms a physical blockade that prevents the passage of large molecules from the bloodstream into the brain. Neurotransmitters such as dopamine and serotonin cannot cross the BBB and must be synthesized within the brain from their precursors. The ability of the gut microbiota to produce precursor molecules that may reach the brain and influence neurotransmitter production and/or concentration, suggests a potential role in shaping cognitive function and behavior through impacting neuronal plasticity (Chen et al., 2021).

The production of 5-HT is an emblematic example. 5-HT regulates the most disparate neuronal functions, including mood, appetite, sleep, learning, memory, and social behaviors (Lv and Liu, 2017). Additionally, serotonergic signaling is involved in synaptic plasticity, with the regulation of long-term potentiation (LTP) and depression (LTD), two key aspects of learning and memory formation (Bear and Malenka, 1994; Bosch and Hayashi, 2012). The insertion or internalization of AMPA receptors on synapses from extrasynaptic sites is a central mechanism in LTP/LTD induction (Collingridge et al., 2004; Malinow and Malenka, 2002), and the serotonergic signaling can modulate the intracellular pathways involved in those processes, such as ERK1/2 activation (Lesch and Waider, 2012; Zhong et al., 2008). The activation of the 5-HT7 receptor in the hippocampus has been shown to regulate LTP and LTD, as well as dendritic arborization and spine formation (Canese et al., 2015; Costa et al., 2012; Kobe et al., 2012). There is also evidence suggesting that 5-HT plays a role in the regulation of prefrontal cortex synaptic plasticity during postnatal development (Higa et al., 2022).

Despite its reputation as a key neuromodulator in the CNS, only 10% of the body's total serotonin is produced in the brain (Bakshi and Tadi,

2021). The majority of serotonin (around 95%) is synthesized in the enterochromaffin cells of the GI tract starting from the amino acid tryptophan (Gershon and Tack, 2007). While variations in intestinal serotonin production are unlikely to directly affect the CNS, some evidence suggests that the gut microbiota may play a role in influencing brain serotonin (Hata et al., 2017; Yano et al., 2015). Although this remains controversial. Some studies demonstrated GF mice displayed increased levels of hippocampal 5-HT and plasma tryptophan (Clarke et al., 2013), while other groups found that the absence of microbiota caused a decrease in plasma and colonic concentration of 5-HT, an effect associated with a deficient expression of TPH1 and an increase in tryptophan concentration (Reigstad et al., 2015; Wikoff et al., 2009). Furthermore, L-lactate, which is the major product of lactic acid intestinal bacteria (i.e. Lactobacilli, Bifidobacteria, Enterococci, Streptococci) (Macfarlane and Gibson, 1997), might regulate the expression of genes involved in 5-HT receptor trafficking in the hippocampus (Carrard et al., 2018). Finally, evidence of a more direct effect of the microbiota on brain 5-HT levels came from studies on probiotics. The administration of *Akkermansia muciniphila* increased the concentration of 5-HT in the hippocampus and affected the expression of Tph2 gene, a TPH isoform, involved in 5-HT biosynthesis in the brain. The observed increase in hippocampal 5-HT was even greater with the administration of *A. muciniphila*-derived extracellular vesicles (Yaghoubfar et al., 2020). Since extracellular vesicles released by bacteria can enter the blood circulation and pass across the BBB, they could directly influence the regulation of various pathways in the CNS, including 5-HT synthesis (Haas-Neill and Forsythe, 2020; Han et al., 2019; Yaghoubfar et al., 2020). Therefore, an effect of the intestinal microbes on brain 5-HT level and its influence on neuroplasticity, although not fully demonstrated yet, is plausible.

GABA is the major inhibitory neurotransmitter in the CNS, with GABAergic transmission representing around 20–50% of all synapses widely distributed throughout the areas of the mammalian brain (Lee et al., 2019; Shrivastava et al., 2011). GABAergic transmission is deeply involved in the regulation of plasticity levels in brain sensory areas controlling both developmental and adult cortical plasticity (Castillo et al., 2011; Chen et al., 2022; Fagiolini and Hensch, 2000; Griffen and Maffei, 2014; Hensch et al., 1998; Sale et al., 2007; Tognini et al., 2012).

There is no straight demonstration of microbiota-dependent modulation of brain plasticity through GABA changes. The existence of GABA-producing bacteria has been demonstrated (Barrett et al., 2012; Strandwitz et al., 2019), with Bacteroides being the major producers of GABA in the human gut (Strandwitz et al., 2019). Indeed, stool GABA levels have been reported to be significantly decreased in GF rodents (Matsumoto et al., 2017, van Berlo et al., 1987) and to be affected by different antibiotic treatments (Fujisaka et al., 2018). Nevertheless, how bacterial-derived GABA can reach the brain remains an open question. While some evidence showed that GABA cannot cross the BBB (Knudsen et al., 1988; Kuriyama and Sze, 1971; Van Gelder and Elliott, 1958), others suggested that GABA can pass through, albeit in small amounts (Al-Sarraf, 2002; Shyamaladevi et al., 2002; Takanaga et al., 2001). Nonetheless, bacterial-derived GABA might affect brain function indirectly, acting locally on the enteric nervous system or through the vagus nerve (Cryan and Dinan, 2012).

The probiotic *Lactobacillus rhamnosus* administration increased the level of various CNS neuro-metabolites, including GABA (Janik et al., 2016) and affected the expression levels of GABA receptors in different subcortical (hippocampus, amygdala, locus coeruleus) and cortical (cingulate, prelimbic cortex) brain regions (Bravo et al., 2011). These alterations were coupled with a decrease in anxiety and depressive-like behavior and an enhancement in memory formation during a fear conditioning test (Bravo et al., 2011), cognitive processes modulated by GABAergic transmission (Kalueff and Nutt, 2007; Makkar et al., 2010; Slattery and Cryan, 2006).

Furthermore, gut microbiota-derived acetate could modulate GABA levels in the hypothalamus (Frost et al., 2014; Olson et al., 2018). Finally, the Hsiao group investigated the mechanisms by which a ketogenic diet (KD) can improve seizures in epilepsy (Olson et al., 2018), a disorder that has been associated with abnormalities in GABAergic transmission (Cossart et al., 2001; Sperk et al., 2004; Yu et al., 2006). KD led to changes in the composition of the gut microbiota, which in turn modulates GABA concentrations in the hippocampus. The authors found a significant increase in the hippocampal GABA/glutamate ratios in KD-fed mice suggesting a modulation of seizure susceptibility via alterations in the excitatory/inhibitory (E/I) balance. Notably, the modulation of the E/I balance within neuronal circuits is essential for maintaining the stability of cortical networks (van Vreeswijk and Sompolinsky, 1996), and appeared to play a pivotal role in sensory pathway plasticity during development (D'amour and Froemke, 2015; Froemke, 2015; Hensch and Fagiolini, 2005; Vogels et al., 2011). The beneficial effect of KD on epileptic seizures was mediated by the gut microbiota, as the transfer of KD-related intestinal bacteria alone produced a similar effect. Importantly, mice treated with antibiotics or raised in a GF environment were not protected from seizures by the KD (Olson et al., 2018), suggesting that the relationship between nutrition, brain function and plasticity may be influenced by signals from gut microbes.

2.3. Influence on microglia

The brain is highly heterogeneous, and so far, little information is available regarding the cell-specific action of the gut microbes on neural tissue function and plasticity. Emerging evidence has indicated microglial cells as special targets of signals coming from the intestinal microbiota (Abdel-Haq et al., 2019; Zhou et al., 2022).

In the brain, the only tissue-resident immune cells are microglial cells. Their constant monitoring and sensing of the microenvironment ensure prompt responses to a variety of different stimuli (Soares and Vieira, 2022). Traditionally thought to act only in response to immune-related stimuli, microglia are nowadays known to be important in influencing the proper establishment of the brain circuitry (Cornell et al., 2022; Schafer et al., 2013; Sierra et al., 2019).

In the developing brain, microglia aid in synapse elimination and formation by physically interacting with synaptic elements (Miyamoto et al., 2016; Paolicelli et al., 2011; Schafer et al., 2012; Weinhard et al., 2018) or through diffusible factors (Lim et al., 2013; Parkhurst et al., 2013). During adulthood, microglia can regulate experience-dependent synaptic plasticity (Sipe et al., 2016) and learning and memory processes (Parkhurst et al., 2013; C. Wang et al., 2020). In 2015, Marco Prinz's team provided the first evidence that the gut microbiota is essential for shaping the microglial phenotype (Erny et al., 2015). By analyzing microglial cells isolated from GF mice, the authors found that, in the absence of the gut microbiota, microglia displayed an immature transcriptomic signature and altered morphology that could be rescued by SCFA administration. Moreover, microglia cells from antibiotic-treated mice mostly mirrored the results obtained in GF animals confirming that inputs coming from the intestinal bacterial community are essential for the proper maturation of these cells (Erny et al., 2015).

The crucial role of the gut microbiota in modulating microglial phenotype starts even before birth. Indeed, the long-term absence of maternal microbiome induced microglial transcriptomic and chromatin accessibility alterations during prenatal stages (Matcovitch-Natan et al., 2016; Thion et al., 2018). These perturbations lasted into adulthood, with microglia characterized by an underdeveloped phenotype and displaying a downregulation of genes associated with inflammation and defense responses (Matcovitch-Natan et al., 2016). Notably, acetate was identified as an essential SCFA affecting microglia maturation and regulating their homeostatic metabolic state through epigenetic mechanisms. The immature microglia phenotype found in GF mice was demonstrated to be epigenetically imprinted by the presence of H3K4me3 and H3K9ac marks on metabolic genes, with consequent alterations in mitochondrial functionality, and respiratory chain

dysfunctions (Erny et al., 2021). This data shed light on a novel link between microbiota-derived metabolites-driven epigenetic remodeling and microglia function, reinforcing the possibility of microglial cells as effectors/translators of microbiota-dependent signals on neural circuits.

Despite the lack of clear evidence, the interaction between the gut microbiota and microglia may be relevant for neural plasticity and the reorganization of synapses. Interestingly, the gut microbiota has been shown to affect the shape and density of dendritic spines, but the mechanisms behind this effect remain unclear. GF mice displayed abnormalities in dendritic and spine structure in the ventral hippocampus and basolateral amygdala (Luczynski et al., 2016b). Additionally, during postnatal development, GF mice showed an increase in the expression of genes involved in activity-dependent synapse formation and an increase in spine density in the cerebellum, which was accompanied by a lack of microglial reactivity. This aberrant density of synapses led to a deficit in the transmission of signals through the Purkinje cell circuit which may affect brain connectivity in these mice (Luck et al., 2020). This suggests that an impairment in microglial phagocytic activity may cause abnormal pruning and an excess of synapses, leading to functional consequences that may contribute to the observed deficits in mouse behavior.

A recent study in GF zebrafish found that impairment in social behavior was accompanied by a reduction in neurite complexity and less precise targeting of forebrain neurons. This phenotype was associated with changes in the number of microglial cells and in the expression of the complement cascade, particularly C1q, by microglia (Bruckner et al., 2022). C1q is known to tag axons and synapses, initiating synaptic pruning (Chu et al., 2010; Gomez-Arboledas et al., 2021; Stevens et al., 2007). These findings suggest that the gut microbiota may modulate structural plasticity processes and ultimately behavior by influencing the actions of microglia on synapses. Furthermore, it is possible that adult neuronal circuits, which are constantly undergoing remodeling in response to learning and experience (Wu et al., 2015), could be affected by the microbiota through microglia. For example, in a fear extinction learning paradigm, the ability to forget fear-related memories has been linked to the microbiome. Using two-photon imaging, a deficit in the learning-related rate of spine formation and elimination was observed in mice with depleted gut microbiota, along with dysregulation in the gene expression profile of excitatory neurons and microglia. Microglia from GF and antibiotic-treated mice showed an immature transcriptomic signature that could lead to defective dendritic spine remodeling and contribute to the deficit in extinction learning (Chu et al., 2019). Consistent with this evidence, Lupori et al. found that experience-dependent changes in gut microbiota composition could enhance cortical plasticity in adult mice (Lupori et al., 2022). Depletion of intestinal microbes through the use of antibiotics prevented environmental enrichment-dependent functional plasticity and dendritic spine dynamics, processes that are known to be influenced by an enriched environment (Baroncelli et al., 2010; Nguyen et al., 2020; Nithianantharajah and Hannan, 2006). These findings support the idea that structural plasticity may be the cellular underpinning through which signals from the gut influence the brain. Intriguingly, changes in spine density and plasticity levels were accompanied by changes in the shape of microglia (Lupori et al., 2022).

In summary, microglia, which are sensitive to signals produced by the gut microorganisms (Cook and Prinz, 2022), may act as a link between the microbiota and various forms of plasticity, including experience-dependent plasticity. It is possible that environmental factors such as diet, exercise, and antibiotic use, which alter the composition of the intestinal microbiota, could influence the reorganization of neuronal networks through their effects on microglial cells.

3. Development: a time-window for the action of microbiota on Neuroplasticity

According to a number of sequencing studies reporting the potential existence of microbial communities in the placenta and amniotic fluid of the mother, microbial colonization of the human intestinal tract might start during gestation (Aagaard et al., 2014; Collado et al., 2016; Younge et al., 2019). Nevertheless, the massive exposure to microbes in humans occurs during birth and in the first months of life, when different factors like birth mode and breastfeeding concur in increasing the complexity of the infant intestinal microbiome (Dominguez-Bello et al., 2019).

Since the microbial colonization and rearrangement coincide with the maturation of the CNS (Borre et al., 2014; Chu et al., 2017), the postnatal period may represent a window of opportunity for the gut microbiome to shape the development of the brain (Tognini, 2017). In fact, during this specific period neuronal circuits are exquisitely plastic and susceptible to the outside world influences. Studies in young GF mice demonstrated how their exaggerated response to stress could be normalized via fecal transplantation from young Specific Pathogen Free (SPF) donors, but only when the microbes inoculation was performed at an early developmental stage (Sudo et al., 2004). Moreover, microbial depletion of SPF mice from weaning onwards was proven to have a strong impact on brain chemistry, resulting in cognitive, social and emotional behavior impairment in a manner that is similar to that reported in GF mice (Desbonnet et al., 2015). Notably, the conventionalization of GF mice at a young age rescued locomotor and anxiety-like behavior deficits in their adult offspring, while the conventionalization of GF mice during adulthood did not normalize their behavioral impairment (Heijtz et al., 2011). The data suggests that the gut microbiome may have an impact on brain function and behavior later in life, potentially acting during a postnatal sensitive period.

It is worth noting that the postnatal maturation of the intestinal microbiota also co-occurs with the development of the immune system, in a process of reciprocal engagement in which bacteria guide and coordinate immune function refinement (Belkaid and Hand, 2014; Kamada and Núñez, 2014). The establishment of a microbiota-immune system alliance during early postnatal periods, might set the basis for a proper development of host physiology, including brain physiology (Arentsen et al., 2017; Gonzalez-Santana and Diaz Heijtz, 2020). The immune system, indeed, has been identified as one of the most important communication routes between intestinal microbes and the CNS (Sampson and Mazmanian, 2015). As commensal microbes directly and indirectly shape neurochemical and immunologic responses, those alterations might influence the crosstalk between the immune system and the brain subsequently affecting neuroplasticity and behavior, during neurodevelopment and beyond (Arentsen et al., 2017; Gonzalez-Santana and Diaz Heijtz, 2020). Notably, the gut microbiota could influence the function of immune system cells in the CNS, as demonstrated by the action on microglia (see section “Influence on microglia”). Early-life microglial dysfunction may contribute to the development of neurological diseases later in life (Desplats et al., 2020). This may indicate that the relationship between gut bacteria, the immune system, and brain development could affect brain health not only in the short term, but also at older ages.

The growing understanding that gut microbes can influence the gut-immune-brain axis and potentially affect neuroplasticity has opened new avenues for investigating the underlying causes of various diseases. Subclinical immune dysregulation and chronic inflammation are common features in patients affected by neurological disorders (major depression, Alzheimer’s, Parkinson’s diseases), pathological conditions that have been associated with changes in neuroplasticity (Frank-Cannon et al., 2009; Hayley, 2011). Intriguingly, several studies proposed the involvement of the gut microbiota in igniting these alterations (Colombo et al., 2021; Dash et al., 2022; Marin et al., 2017; Minter et al., 2016; Morais et al., 2021; Sampson et al., 2020). Inflammation may function as a common denominator in the crosstalk between microbes, immune system and the brain, as further demonstrated by the fact that gut microbiota itself is able to induce inflammation (Dash et al., 2022). As a consequence, perturbations occurring in the gut microbiota composition during critical periods might alter the host’s “immune

status" leading to atypical brain development and ultimately to neurological disorders. In support of this hypothesis, recent findings highlighted how, along with GI discomfort, several patients affected by neurological disorders commonly present conditions of subclinical immune dysregulation associated with alterations in the intestinal microbiota composition (Grochowska et al., 2018). All together, those results indicate that maintaining a balanced microbiota might be important for preserving physiological neurodevelopmental trajectories.

4. A focus on neurodevelopmental disorders

Neurodevelopmental disorders (NDD) are a group of heterogeneous conditions characterized by impaired brain development and function, resulting in cognitive, emotional, and motor deficits (Dash et al., 2022; Morris-Rosendahl and Crocq, 2020). Although their etiology is still not fully comprehended in most of the cases, what is clear is that both genetic and environmental factors concur in altering the normal neurodevelopmental trajectories. A common feature of NDD is defective synaptic plasticity, a key aspect of neuroplasticity (Johnston, 2004; Lesch and Waider, 2012; Penna et al., 2020; Zoghbi and Bear, 2012). In fact, the core symptoms of NDD may not be caused by issues with the formation of synapses in the brain during prenatal development, but instead by problems with the brain's ability to reorganize and strengthen its circuit connections during postnatal maturation (Lesch and Waider, 2012).

NDD include a variety of conditions, such as autism spectrum disorder (ASD), schizophrenia, attention deficit hyperactivity disorder, intellectual disability disorder, Rett syndrome (RTT), and childhood epilepsy disorders, comprising CDKL5 deficiency disorder (CDD) (Lukens and Eyo, 2022; Olson et al., 2019). For the purposes of this article, focus will be limited to ASD, RTT and CDD.

The co-occurrence of gut bacterial dysbiosis in many NDD patients has boosted the clinical and pre-clinical research focus on the gut microbiota as a new potential etiological factor in the onset and progression of NDD. In this regard, an increasing number of studies have been exploring the mechanisms underlying the influence of the intestinal microbiota-brain axis to physiological and pathological CNS development (Adams et al., 2011; Bojović et al., 2020; Dash et al., 2022; Hsiao et al., 2013; O'Mahony et al., 2017; Rogers et al., 2016). Intriguingly, alterations in microglial phenotype have been reported in different NDD, including ASD, Rett syndrome and CDD (Cronk et al., 2015; Horiuchi et al., 2017; Lukens and Eyo, 2022; Morgan et al., 2010; Tetreault et al., 2012; Velmeshev et al., 2019; Zhao et al., 2017)(Galvani et al., 2021). Microglial cells could be active players in the onset and progression of NDD symptomatology, being implicated in many aspects of neurodevelopment, from synaptic plasticity to the refinement of neuronal connectivity (Cowan and Petri, 2018). Microglia seem also to be involved in social behavior dysfunction, even though the underlying mechanisms remain an open question (Barcik et al., 2021). Based on the relationship between microglial cells and microbiota, recent research has focused on identifying the communication route linking gut metabolites, microglia, and NDD (Cronk et al., 2015; Horiuchi et al., 2017; Lukens and Eyo, 2022; Morgan et al., 2010; Tetreault et al., 2012; Velmeshev et al., 2019; Zhao et al., 2017). Understanding this connection might aid in developing targeted therapies to alleviate NDD symptoms.

4.1. Autism spectrum disorder

ASD is a developmental condition characterized by a variety of early-appearing deficits involving two main domains: social interaction/communication, and stereotypical sensory/motor behaviors (Lord et al., 2018; Zeidan et al., 2022). Nowadays, it is the most common neurodevelopmental disorder worldwide. The median prevalence of ASD has been estimated to range from 1.09 per 10,000 to 436.0 per 10,000 by 2022, and it is still on the rise since 2012 (Zeidan et al., 2022). Accepted theories suggest that symptoms of ASD may originate from an imbalance in the ratio between excitation and inhibition, which leads to hyper-excitability of cortical circuits (Canitano and Palumbi, 2021; Rubenstein and Merzenich, 2003). Among the mechanisms that may contribute to this imbalance, synaptic plasticity is believed to play a critical role (Froemke, 2015; Zhou and Yu, 2018). Accordingly, growing evidence highlighted a condition of aberrant synaptogenesis and atypical synaptic plasticity in the ASD brain (Desarkar et al., 2022). Moreover, many ASD-risk associated genes are regulated by neuronal activity and are involved in synaptic plasticity (Arons et al., 2012; Boccuto et al., 2013; Bourgeron, 2015; Durand et al., 2007; Kim et al., 2008; Lai et al., 2021; Moessner et al., 2007; Pfeiffer et al., 2010; Sato et al., 2012).

In addition to neuropsychiatric conditions, autistic individuals have a significantly higher risk of developing comorbidities, including GI dysfunctions, immune abnormalities, pro-inflammatory responses, impaired intestinal permeability, diabetes and obesity (Croen et al., 2015; Rose et al., 2018). Despite the ASD's large incidence worldwide, genetic or environmental causes underlying the major symptoms and the related comorbidities are still unknown. The prenatal immune environment could participate in ASD etiology, as shown in several reports (Jash and Sharma, 2021; Kim et al., 2022; Manjeese et al., 2021; Ozaki et al., 2020; Sato et al., 2022; Shuid et al., 2021; Tioleco et al., 2021). As a consequence to maternal infections, metabolic disorders, and even gut bacterial dysbiosis, the aberrant activation of the maternal immune system could ignite pro-inflammatory responses proven to significantly increase the risk of developing ASD (Malkova et al., 2012; Ravaccia and Ghafourian, 2020; Wong and Hoeffer, 2018). An increased number of monocytes, plasma concentration of pro-inflammatory cytokines such as IL-8, TNF-alpha and IL-1β, and abnormal T-helper cell profile are some of the immune-related factors altered in ASD patients (Ashwood et al., 2011; Ferrante et al., 2003; Yonk et al., 1990; Zhao et al., 2021). Further dysregulation of the immune system has been identified in the brain of ASD individuals, where microglia have been shown to be aberrantly activated with changes in morphology, density and spatial localization (Lee et al., 2017; Morgan et al., 2010, 2012; Tetreault et al., 2012; Vargas et al., 2005; Voineagu et al., 2011). As microglia play a fundamental role in regulating synaptogenesis and synaptic plasticity, it seems plausible how an aberrant microglial activity may be involved in the disruption of such processes (Davoli-Ferreira et al., 2021).

GI problems, such as constipation, chronic diarrhea, bloating, abdominal pain, reflux, vomit and difficulties in bowel movement (Borghi and Vignoli, 2019; Holingue et al., 2018), have been demonstrated to be strongly correlated with the severity of the overall symptomatology in ASD patients (Adams et al., 2011; Chakraborty et al., 2021; Neuhaus et al., 2018; Restrepo et al., 2020). GI disturbances could be linked to bacterial dysbiosis, thus a potential role for the gut microbiota may be envisioned. Data from the literature revealed an enormous inter-individual heterogeneity in terms of microbial strains affected in ASD patients (Beopoulos et al., 2021). Nevertheless, the most consistent observation seems to be an increase in Clostridium bacteria together with other Firmicutes, and a reduction in the abundance of Bacteroidetes in ASD patients (De Angelis et al., 2013; Finegold et al., 2010; Kang et al., 2013; Parracho et al., 2005).

The possibility of a disrupted gut microbiome in individuals with ASD has shifted the interest toward new approaches for restoring balance in the gut bacteria, including probiotics, microbiota transfer therapy, prebiotics, antibiotics, and dietary changes (Kang et al., 2019; J. Liu et al., 2022; Mintál et al., 2022; Sanlier and Kocabas, 2021; Sivamaruthi et al., 2020; Tan et al., 2021; Yang et al., 2020). Studies in both mouse models and patients have consistently shown that these non-invasive strategies can improve ASD symptoms (Alfawaz et al., 2018; Buffington et al., 2016; Hsiao et al., 2013; Kang et al., 2019; Li et al., 2021; Sgritta et al., 2019; X. Wang et al., 2019). Research in preclinical models has provided insight into the potential neural plasticity mechanisms. For instance, the probiotic *Lactobacillus reuteri* supplementation has been demonstrated to rescue social interaction-dependent synaptic potentiation in the ventral tegmental area in several mouse model of autism

(Buffington et al., 2016; Sgritta et al., 2019). Despite some encouraging results in using the gut microbiome as a target for improving ASD symptoms, other reports have been inconclusive showing contradictory data (Beopoulos et al., 2021; Davies et al., 2021; Samonis et al., 1993). The inconsistency in findings and high inter-individual variability of the ASD microbiota suggest that the cause of ASD-associated gut bacterial dysbiosis is likely to be multifactorial, and it cannot be directly linked to neurological symptoms. The attenuation of autonomic nervous system function may be a contributing factor. This attenuation may result in dysregulation of the intestinal immune system and lead to dysbiosis (Beopoulos et al., 2021). The dysbiosis may perpetuate itself in a self-sustaining cycle that maintains changes in the microbiota over time. There is evidence to support this hypothesis, as ASD patients often demonstrate deficits in parasympathetic activity (Benevides and Lane, 2015; Kong et al., 2021; Kushki et al., 2014).

4.2. Rett syndrome

RTT is a severe neurodevelopmental disorder resulting from *de novo* mutations mainly occurring on the X-chromosomal methyl-CpG binding protein 2 (MECP2) gene. Individuals with RTT are typically characterized by an initial phase of apparent normal development that lasts 6–18 months, when the first signs of regression start to appear, and kids progressively lose the motor and communicative skills already acquired. It is during this period that the typical hand stereotypes appear (Gold et al., 2018; Neier et al., 2021).

MeCP2 has been implicated in several essential functions within the neuron and it is becoming increasingly evident how RTT pathogenetic mechanisms involve alterations in synaptic transmission and neuroplasticity (Della Sala and Pizzorusso, 2014). For instance, studies in RTT postmortem brains revealed a reduction in the number of dendritic spines and presynaptic markers, and studies in MeCP2 knockout rodents observed deficits in neurogenesis and synaptic plasticity (Boggio et al., 2010; Carstens et al., 2021; Chapleau et al., 2009; Colantuoni et al., 2001).

Although there has been progress in understanding the causes of RTT, the full range of symptoms and related conditions are not yet fully understood. The widespread expression of MeCP2 in all cell types may explain the presence of various comorbidities with neurological symptoms. Many RTT patients experience GI problems, which can greatly impact their quality of life (Motil et al., 2012). These issues are reported by over 50% of families of RTT children, including difficulty with bowel movements, constipation, and prolonged feeding or difficulty with chewing (Borghi and Vignoli, 2019). Interestingly, two clinical studies have shown a decrease in the diversity of gut bacteria in individuals with RTT (Borghi et al., 2017; Strati et al., 2016). RTT patients have been found to have altered levels of certain microbial byproducts in their feces, including SCFA (Borghi et al., 2017; Strati et al., 2016) and other metabolites such as GABA, tyrosine, and glutamate. Pre-clinical research in both rats and mouse models demonstrated the existence of bacterial dysbiosis in RTT (Gallucci et al., 2021; Thapa et al., 2021). Additionally, investigations in RTT rats revealed a specific shift in gut bacteria that occurs before the peaks of metabolic and motor symptoms (Gallucci et al., 2021). This result supports the possible role of host-microbiota interactions in disease progression and represents an important step in translational RTT research.

However, at present, it is not possible to infer a causal relationship linking RTT gut bacterial dysbiosis to GI dysfunction or to neurological outcomes in humans. The differences in gut microbiomes of RTT patients may be related to variations in their dietary habits and feeding behaviors compared to individuals without the disorder (Neier et al., 2021). Studies that have correlated demographic, clinical, and dietary information of RTT patients with their gut microbiome composition, have found that the type of diet can have a significant impact on the microorganismal taxa, even within the same cohort of RTT patients (Thapa et al., 2021).

If and how the gut microbiota "talk" to the RTT brain is still a matter of debate. We could speculate the involvement of a "gut microbiota-microglia axis", as dysfunctional microglia have been observed in RTT (Cronk et al., 2015; Horiuchi et al., 2017; Jeziorski, n.d.; Maezawa and Jin, 2010; Zhao et al., 2017). MeCP2 ablated microglial cells excessively engulfed presynaptic inputs at the end stages of disease, when synaptic loss typically occurs (Schafer et al., 2016). A transcriptomic analysis on MeCP2-deficient microglia revealed differences in the expression level of several genes involved in innate immunity and macrophage activation, further supporting a dysregulation of microglia functions. Such aberrant activation of microglial cells may contribute to the dendritic and synapses abnormalities observed in the RTT preclinical phenotype, ultimately contributing to the symptomatology (Zhao et al., 2017).

In summary, RTT may represent another small piece in the puzzle describing the interaction between gut microbiota and NDD, although the precise mechanisms by which gut bacteria affect the neurological symptoms of RTT are still enigmatic.

4.3. CDKL5 deficiency disorder

CDD is a rare X-linked developmental encephalopathy caused by a disruption of the CDKL5 gene (Fehr et al., 2013). Since CDKL5 disorder was recognized as a distinct medical condition, there has been increasing interest in understanding its underlying molecular and cellular mechanisms. This has led many research labs to focus on this disorder, resulting in significant advancements in our understanding of CDKL5 and CDD (Demarest et al., 2019; Hao et al., 2021; Jakimiec et al., 2020; Kilstrup-Nielsen et al., 2012; Van Bergen et al., 2022; Zhu and Xiong, 2019). Nonetheless, the full spectrum of CDD is unknown and no curative or targeted therapies are available. CDD shares some similarities with other developmental encephalopathies, such as intellectual delays and attention deficits. However, it sets itself apart with its early onset refractory epilepsy, which usually develops within the first six months of life, stereotypical behaviors, severe muscle weakness, and visual impairment (Lupori et al., 2019; Mazziotti et al., 2017; Olson et al., 2019). Increasing evidence supports a critical role for CDKL5 protein in regulating synaptic function and plasticity. Several known CDKL5 phosphorylation targets, putative substrates and CDKL5-interacting proteins are important for proper synaptic development and functioning (Van Bergen et al., 2022). Accordingly, in vivo studies revealed deficits in hippocampus-dependent learning and memory in CDKL5 mice (Tang et al., 2017; Wang et al., 2012). These deficits were accompanied by a decrease in dendritic complexity and a trend towards increased spine density in the hippocampal pyramidal neurons lacking CDKL5 (Tang et al., 2017).

In addition to the mentioned core symptoms, patients with CDKL5 mutations often exhibit a subclinical state of chronic inflammation, as evidenced by elevated levels of proinflammatory markers in peripheral blood (Cortelazzo et al., 2017; Mangatt et al., 2016; Takahashi et al., 2018). In line with this subclinical immune dysregulation, a similar inflammatory status has been recently characterized in the brain of CDKL5 knockout mice, which display an increase in microglial cell number and activation (Galvani et al., 2021). This aberrant microglial activation is present during the postnatal period and further progresses with aging (Galvani et al., 2021). The subclinical immune dysregulation and GI dysfunctions seen in individuals with CDKL5 mutations (Cortelazzo et al., 2017; Mangatt et al., 2016; Takahashi et al., 2018) may potentially be attributed to alterations in the gut microbiome, however a thorough characterization of the intestinal microbiota in CDKL5 patients or mouse models is yet to be performed.

As the connection between gut microbes and brain disorders becomes more widely accepted, it may be relevant to study the intestinal bacteria in people with CDD and how it relates to the development and progression of symptoms. This research could help in understanding the role of signals from the gut in CDD's pathogenesis and symptom progression, opening new avenues for future therapeutic strategies.

5. Conclusions and open questions

Traditionally, the human body has been viewed as a collection of separate and independent systems, however there is increasing recognition of the importance of a more holistic understanding of physiology. In this context, the gut microbiome has emerged as a key player in the complex interactions between different tissues in the body. There is a general consensus that the gut microbiota plays a role in metabolism and immune system function. However, it is more difficult to demonstrate a direct interaction between the intestine and the brain, as the CNS is physically distant from the intestine and there are many potential pathways of communication between the two. Nonetheless, there is evidence to support the existence of a crosstalk between the brain and the microbiome. For example, the microbiome's ability to produce a wide range of different metabolites may allow it to influence brain function or alter neurodevelopmental processes.

While there is some consensus on the influence of the gut microbiota on neuroplasticity and behavior, several questions are still enigmatic. Among them: which are the major brain cell-types affected by the gut microbiota signals? Are inhibitory circuits more sensitive than excitatory circuits? Are all the different brain areas affected in the same way? And if not, why are some areas affected more than others? Which are the specific mechanisms through which the gut microbiome promotes/impair neuroplasticity? When are the signals from intestinal microorganisms relevant in reshaping neural circuits and behavior during an individual's life? Do those signals contribute to fine-tuning neurodevelopmental trajectories?

Future research on neural function and plasticity will help to shed light on these issues and bring the gut microbiome - a previously overlooked aspect of brain complexity - into focus.

Author contribution

FD prepared the graphic abstract, SC prepared the figure. FD, SC and PT conceived and wrote the manuscript.

Data availability

No data was used for the research described in the article.

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