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Does the gut microbiota contribute to the oligodendrocyte progenitor niche?

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Abstract

The past decade has seen a growing number of studies on the relationship between the gut microbiota and the brain. This mini-review will focus on the unexpected findings linking the microbiome to myelination. We first address the temporal correlation between the acquisition of a gut microbiota in the developing organism and developmental myelination. We then review the factors impacting the composition of the child's gut microbiota, ranging from maternal stress to modality of delivery and from breastfeeding and diet composition to antibiotic treatment early in life. We discuss the topic of gut-brain communication with an emphasis on myelination, and propose the concept that gut microbes produce metabolites which may constitute a "metabolic" niche. Distinct bacterial communities may create very different "niches", some permissive and others inhibitory for myelin generation or maintenance. We speculate that this concept of "gut dysbiosis" may also in part explain the reduced myelin content detected in several neurological and psychiatric disorders. We conclude by envisioning intervention with probiotics and prebiotics to favor the formation of a microbial metabolic "niche" favoring myelin production to promote brain health.

Keywords

Microbiome; Oligodendrocyte; Development; Myelination; Brain

1. Introduction

"We are shared, rented, occupied." [1] Almost half a century ago, Lewis Thomas published observations on the prevalence of symbiotic relationships among life on Earth and within our cells. Thomas was keenly aware of the fantastic world of intra- and inter-organismal relationships. Humans harbor trillions of bacteria in their body, which if pooled would amount to an estimated mass of two kilograms in adults [2]. These microorganisms live in communities, which are collectively defined as "microbiota" and have the ability to modulate immune cell function, promote or counteract absorption of micro and

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macronutrients from the gut, affect neurotransmitter release in the enteric nervous system and shape the metabolic profile [3,4]. Herein, the word gut “microbiota” is used as a term defining the community of the organisms, while the word “microbiome” is used to refer to their genomes [5]. This review focuses on the perspective that intestinal microbiota may contribute to the “biochemical niche” modulating oligodendrocyte progenitor behavior.

1.1. Acquisition of the microbiota in the infant

Surging interest on the identification of the microbial genome (gut microbiome) in physiological and pathological conditions, has led to the development of key concepts related to the temporal acquisition and progressive maturation of tissue-resident microbiota [6]. One of these concepts suggests that brain development and gut microbiota may be influenced by the same external factors, although several steps still demand future experimental validation. It is unclear, for instance whether the first microorganisms are acquired after birth, with the exposure to the mother’s skin and opening of airways [7], or whether colonization may start even earlier, from the amniotic fluid, umbilical cord and/or placenta [8]. The ability to isolate certain microbial species from umbilical cord would suggest the existence of a prenatal microbiota [9,10] which could be of high relevance when considering the importance of maternal diet and stress levels during pregnancy. The first microbes to take residence in the baby’s gut are largely uniform communities, which are shaped by the method of childbirth [7,11]. Delivering mothers harbor a diversity of microbial communities in different tissues (i.e. oral, vaginal, or epidermal) [12,13], and their newborn children acquire the microbes with which they come in contact during delivery. Babies delivered vaginally, for instance, acquire species which are abundant in the maternal vaginal microbiota (such as *Prevotella* or *Lactobacillus*), while babies delivered by C-section are colonized with bacteria residing on the mother’s skin (such as *Staphylococcus*, or *Corynebacterium*) [7]. Additional factors shaping the gut microbiota in children are related to the modality of breast- versus bottle-feeding [11,14], antibiotic treatment and other environmental factors (reviewed in [4]), which continue to alter microbial species in infants and then in adolescents [15]. This concept may explain why factors creating a gut dysbiosis during the first 24 months from birth may result in consequences later in life [16]. Antibiotic use in infants, for instance, has been associated with overgrowth of facultative species and long-lasting metabolic alterations and possibly disease states, including diabetes and obesity [11]. Of interest to the topic of this review, is the consideration that similar concepts apply also to demyelinating disorders, such as Multiple Sclerosis (MS) [17,18]. While this disease has been traditionally diagnosed in young adults, recent reports have highlighted a rise in the pediatric population [17,18], which was associated with a microbiome “signature” distinct from that of healthy children. In addition, retrospective studies analyzing modality of delivery, duration of breast-feeding and other indicators in over 2000 MS patients revealed a correlation between earlier age of disease onset and C-section and short duration of breast-feeding [19]. Based on the previously discussed importance of mode of delivery and length of breast-feeding on the microbiota, these studies further support the concept that onset of MS in children could be linked to the composition of gut microbiota [19].

1.2. Shaping of the gut microbiome coincides with the critical period of developmental myelination

The co-occurrence of specific aspects of brain development with the gradual acquisition of a complex microbiota led to the concept that these two events may be functionally related. The concept that the placenta and amniotic fluid shape the microbiota led to the hypothesis that its altered composition due to preterm birth [20] could be causally linked to delayed developmental myelination and possibly long-term neurodevelopmental disabilities [20-22]. The comparative analysis of the fecal microbiome of neonates born either preterm or full-term revealed lower overall diversity in the premature babies compared to full term [23], although these initial differences eventually normalized [23,24]. While these were just association studies, causality was suggested by experiments of colonization in gnotobiotic mice. Briefly, germ-free (GF) dams were colonized with the human microbiota isolated from infants with either slow or fast growth rate and the effects on the offspring were analyzed and revealed long term effects on myelination in the pups as the MBP content was higher in mice colonized with stools from the fast growth babies [25].

Comparative transcriptomic studies in the brain of GF mice and those kept in standard pathogen free conditions (SPF) further supported the hypothesis that gut microbes may functionally affect the developing brain, although the precise mechanism remains unclear [26]. For instance, genes regulating synaptic plasticity and metabolic pathways were differentially expressed in the two groups [27]. Importantly, however, while some groups reported higher levels of Brain Derived Neurotrophic Factor (*Bdnf*) in GF mice [28], opposite results were obtained by others [27,29,30]. In addition, while some reported increased hippocampal neurogenesis in GF mice [31], others reported decreased branching of hippocampal pyramidal or dentate granule cells [32]. A potential explanation for these discrepancies could be the effect of the mouse genetic background and the distinct SPF conditions in different centers, both impacting the variety of the microbial species and therefore the complexity of the metabolic niche.

The relationship between gut microbiota and psychiatric disorders associated with white matter alterations [33,34], was also suggested by a recent 10-year longitudinal study on babies exposed to chronic antibiotic treatment (either *in utero* or during early childhood), which correlated higher incidence of hyperactivity disorders and depression to altered microbiota composition [35]. Also in this case, causality was suggested by intriguing studies conducted in mice, which nicely provided a link between bacterially-derived metabolites (such as p-cresol) and autistic-like behavior [36].

Together, these data may reinforce the concept of microbially derived metabolites as contributing to the developmental myelination niche.

1.3. Adult microbiota and disease relevance

While we have emphasized the importance of early life events in the establishment of the microbiota, its unique and resilient composition can also be slowly affected over time [37], due to changes in dietary habits [38], co-habitation with pets [39], antibiotic treatment [40] and disease states [41,42]. The importance of diet and gut microbiota composition appears

intuitive due to its essential role in regulating metabolism and extraction of nutrients from diverse dietary sources [43]. Even short-term dietary interventions in human subjects with either animal or plant-based diets have shown differences in microbial composition and related metabolic output [44]. The differences in microbiota composition induced by dietary changes in human subjects were reminiscent of those detected between carnivores (mostly relying on animal-based diets) and herbivores (mostly relying on a plant-based diet), thereby highlighting an important degree of conservation across species [44,45]. The relationship between diet and microbiota also highlights the importance of dietary changes in disease states [46], and underscore the importance of evaluating chronic antibiotic treatment as enhancing or decreasing the effectiveness of disease-modifying drugs [47-49].

The causal link between gut microbiota and the onset of MS was suggested by seminal studies on GF “humanized” mice with the propensity to develop spontaneous autoimmune demyelination, which were colonized with stools from homozygotic twins, who were discordant for the disease [50]. Despite the fact that twins had an identical genetic risk (since twins shared the same genotype), the GF mice colonized with fecal samples from MS-affected twins showed a higher incidence of autoimmune demyelination than mice colonized with the stools of the healthy twins [50]. Besides the previously described role of microbiota in pediatric MS [17], these studies and others highlighted differences in the microbiome of adult MS patients versus matched controls [42,51,52]. The overall consensus from several groups was that gut dysbiosis drives a pro-inflammatory response, while reducing the number of regulatory T-cells. For example, abundant *Akkermansia* had been reported in MS stool samples [50,52] and co-cultures of human T-lymphocytes with these bacteria resulted in high levels of IFN γ and of the master transcription factor TBET [50,52]. The concept that microbiota alteration led to immune dysregulation also suggested that drugs used as immunomodulators could impact microbiota composition. The relationship between immunomodulatory therapy and the gut microbiota was explored in a recent study from our laboratory in MS patients on dimethyl fumarate (DMF) or glatiramer acetate (GA), as disease modifying treatments [53]. The microbiome of patients on DMF treatment was characterized by increased abundance of *Bacteroides*, which were related to anti-inflammatory activity [53,54] and had been previously reported to be decreased in MS patients [18]. Treatment with either DMF or GA was also found to decrease the abundance of *Clostridiales*, which have been previously reported to be present at higher abundance in MS patients [18,53,55].

Additional support for a causal relation between adult myelination and the gut microbiota was provided by mouse studies. One study, for instance, focused on the characterization of the mechanistic relationship between specific microbial species, metabolites, myelination and social behavior [56], while others identified myelin gene transcript differences in GF mice [57] compared to those reared in SPF conditions. Validation of these findings identified a region-specific elevation of myelin gene transcripts confined to the prefrontal cortex of male Swiss Webster mice which was not observed in females or in other brain areas such as hippocampus and cerebellum [57]. These transcriptomic differences were age-dependent as exposure of GF mice to normal SPF conditions at weaning was sufficient to prevent differences in adult myelination [57]. However, very different conclusions were reached by others [58], using macromolecular proton fraction (MPF) mapping and *ex vivo* magnetic

resonance imaging (MRI) followed by histopathological assessment of myelin in C57BL/6 mice. The study reported significantly lower fractional anisotropy and reduced white matter volume in male GF mice compared to SPF controls [58]. The difference in white matter tracts was validated by histopathology and confirmed to be region specific and confined to the anterior commissure and internal capsule [58]. These structural differences in white matter were associated with several altered behavioral outcomes including spatial and learning memory, fear conditioning and anxiety in GF male mice, while females did not show any alteration [58]. Overall, these experiments underscore the importance of gut microbial signals for regulating the plasticity of white matter tracts and their functional output in the young adult brain.

1.4. Potential mechanisms of regulation of the “oligodendrocyte progenitor niche” by the gut microbiota

Insights on potential mechanisms on how the microbiota may condition the “biochemical niche” responsible for modulating oligodendrocyte progenitor differentiation and myelination, have been suggested by a number of recent studies. Proposed mechanisms range from modulations of the levels of promyelinating factors, such as Insulin-like Growth Factor 1 (IGF-1), to potential effects on the hypothalamic pituitary axis (HPA) and from microbe-derived metabolites, such as p-cresol or indoxyl-3-sulfate, to the production of short chain fatty acids (SCFA) or neurotransmitters.

We have previously mentioned that prenatal colonization of gnotobiotic pregnant mice affected myelin content in the offspring, depending on whether the stool samples were derived from preterm babies with different growth rate [25]. The potential mechanisms responsible for these long-lasting effects of early gut colonization on myelinated tracts were further investigated and attributed to microbial-release of Insulin-like Growth Factor 1 (IGF-1), since its levels were lower in blood and brain of mice with lower myelin content [25]. While the causal link between IGF-1 and oligodendrocyte development was not directly tested in that study, previous studies in *Igf1^{-/-}* mice [59] support the concept that disruption of IGF-1 signaling consequent to gut dysbiosis [60] might be responsible for the long-term detrimental effects on myelin.

The potential impact of microbiota on the hypothalamic pituitary axis (HPA) and myelination was suggested by studies, including unpublished data from our laboratory, reporting impaired developmental myelination (either hypomyelination or delayed myelination) in pups that experienced early separation from their mother during the first two weeks of life [61,62]. It has recently been acknowledged that a healthy response of the HPA axis requires an intact microbiota, as GF mice displayed exaggerated response to early life stress, which could be mitigated by colonization [63] and other groups further validated this concept and discerned between the impact of the microbiota on the development of anxiety and the activation of the HPA axis by external stressors [64].

Additional modalities of microbiota-mediated regulation of the oligodendrocyte niche include production of metabolites which can modulate the ability of progenitors to differentiate, either directly (such as p-cresol or SCFA) or indirectly (e.g. indoxyl-3-sulfate, 4-ethylphenylsulfate or SCFA), possibly by modulating function of astrocytes or microglia.

There is a general agreement on the contribution of gut microbes to the overall levels of metabolites in the tryptophan pathway including: indoxyl-3-sulfate [65] and 5-hydroxytryptamine [66], with the former being a ligand for the arylhydrocarbon receptor on astrocytes, potentially playing a role in neuroinflammation [67]. Specifically, the presence of certain phyla involved in commensal gut metabolism of tryptophan was negatively correlated with astrocyte-driven inflammatory CNS responses in an EAE model [63]. Moreover, the ablation of tryptophanase expressing microbiota through specific antibiotic treatment was shown to reduce circulating indoxyl-3-sulfate and worsen disease course in a mouse model of MS [63]. The metabolite 4-ethylphenylsulphate was identified in a study on a mouse model for autism and shown to be sufficient to induce autism-like symptoms in mice [36]. As white matter disturbance have been reported in children with autism [34,68], it will be important to determine whether this metabolite can exert direct or indirect effects on the oligodendrocyte progenitors.

Studies from our group in non-obese diabetic (NOD) and C57BL/6 mice reported that social avoidance behavior in adult mice, and associated deficits in adult myelination in the prefrontal cortex, could be transferred to C57BL/6 adult recipients, which had received long-term antibiotic treatment [56]. We further demonstrated that the behavioral phenotype was detected only in mice which were successfully colonized with a microbiota harboring *Clostridiales*, *Lachnospirace* and *Ruminococcaceae* after engrafting and that the aberrant behavior was associated with high levels of the p-cresol metabolite, which, in vitro, was capable of halting the differentiation of progenitors into mature oligodendrocytes [56]. Remarkably, the same bacterial species were detected as abundant in the microbiome of MS patients compared to controls [42,52,69] and their abundance was decreased by disease modifying treatment [53].

Additional studies in a non-immune model of demyelination in mice suggested that gut dysbiosis led to a worsened disease course which could be partially ameliorated with supplementation of animals with SCFA propionate or acetate [70]. An even stronger effect was detected with butyrate supplementation, which resulted in a significant myelin regeneration in the corpus callosum. A similar pro-regenerative effect of butyrate on myelin was detected in organotypic cerebellar slice cultures after lysolecithin induced demyelination [70], as treatment with this SCFA increased the number of mature, Olig2⁺ CC-1⁺ oligodendrocytes. As butyrate was previously shown to be a potent inhibitor of histone deacetylase (HDAC) enzymes [71], comparative experiments showed similar enhancement of remyelination in lysolecithin using the HDAC pharmacological inhibitor Trichostatin A [70].

Recent studies also provide evidence of disrupted SCFA metabolism influencing disease course in MS patients. Zeng [72] and colleagues collected fecal samples from a cohort of Chinese MS patients and report a correlative depletion in the *Prevotella_9* genus of microorganisms with reduced circulating SCFA [72]. In these patients, circulating Th17 T-cells were increased, whereas CD25⁺ Treg cells were decreased [72], thereby suggesting a link between decreased SCFA and increased inflammatory Th17 T-cells, a concept which was further elaborated in a current review by Melbye et al. [73].

Overall these studies collectively support the concept of gut bacteria as contributors of circulating factors defining a “biochemical niche” which tends to favor or impair myelination directly or indirectly, depending on the composition of the microbial communities.

2. Concluding remarks

Novel concepts related to the effect of external factors in shaping the gut microbiome continue to emerge and a deeper understanding of its influence on brain physiology is truly needed, especially given the importance of the biomedical implications [74]. Here we reviewed the evidence suggesting potential mechanisms of gut-brain communication impacting the oligodendrocyte lineage. While it is becoming quite clear that dysbiosis occurs in several disorders characterized by white matter damage or disruption, more work is needed to define the precise relationship between microbial species, gut-derived metabolites and myelinating cells in pediatric and adult neurological and mental disorders. In addition, as dysbiosis is often concurrent with other pathologies in the aging population, it will be important to define and clarify cumulative effects of age, diet and distinct medications on gut bacteria [53]. It is exciting to speculate that probiotics [75] or food selection, such as the ketogenic diet [76], might positively influence the differentiation potential of oligodendrocyte progenitors and promote myelin regenerative strategies. However future studies are needed to better tailor specific treatment to the individual features of each subject and promoting personalized therapeutic approaches Fig.1.

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References

- [1]. Thomas L, The lives of a cell, N. Engl. J. Med 284 (1971) 1082–1083. [PubMed: 5553197]
- [2]. Stilling RM, Dinan TG, Cryan JF, Microbial genes, brain & behaviour - epigenetic regulation of the gut-brain axis, Genes Brain Behav. 13 (2014) 69–86. [PubMed: 24286462]
- [3]. Pronovost GN, Hsiao EY, Perinatal interactions between the microbiome, immunity, and neurodevelopment, Immunity 50 (2019) 18–36. [PubMed: 30650376]
- [4]. Diaz Heijtz R, Fetal, neonatal, and infant microbiome: perturbations and subsequent effects on brain development and behavior, Semin. Fetal Neonatal Med 21 (2016) 410–417. [PubMed: 27255860]
- [5]. Marches JR, Ravel J, The vocabulary of microbiome research: a proposal, Microbiome 3 (2015) 31. [PubMed: 26229597]
- [6]. Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, Knight R, Bacterial community variation in human body habitats across space and time, Science 326 (2009) 1694–1697. [PubMed: 19892944]
- [7]. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R, Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns, Proc. Natl. Acad. Sci. U.S.A 107 (2010) 11971–11975. [PubMed: 20566857]
- [8]. Jimenez E, Fernandez L, Marin ML, Martin R, Odriozola JM, Nueno-Palop C, Narbad A, Olivares M, Xaus J, Rodriguez JM, Isolation of commensal bacteria from umbilical cord blood of healthy neonates born by cesarean section, Curr. Microbiol 51 (2005) 270–274. [PubMed: 16187156]

- [9]. Prince AL, Chu DM, Seferovic MD, Antony KM, Ma J, Aagaard KM, The perinatal microbiome and pregnancy: moving beyond the vaginal microbiome, *Cold Spring Harb. Perspect. Med* 5 (2015).
- [10]. Mueller NT, Bakacs E, Combellick J, Grigoryan Z, Dominguez-Bello MG, The infant microbiome development: mom matters, *Trends Mol. Med* 21 (2015) 109–117. [PubMed: 25578246]
- [11]. Bokulich NA, Chung J, Battaglia T, Henderson N, Jay M, Li H, Lieber AD, Wu F, Perez-Perez GI, Chen Y, Schweizer W, Zheng X, Contreras M, Dominguez-Bello MG, Blaser MJ, Antibiotics, birth mode, and diet shape microbiome maturation during early life, *Sci. Transl. Med* 8 (2016) 343ra382.
- [12]. Lloyd-Price J, Mahurkar A, Rahnavard G, Crabtree J, Orvis J, Hall AB, Brady A, Creasy HH, McCracken C, Giglio MG, McDonald D, Franzosa EA, Knight R, White O, Huttenhower C, Strains, functions and dynamics in the expanded Human Microbiome Project, *Nature* 550 (2017) 61–66. [PubMed: 28953883]
- [13]. Cho I, Blaser MJ, The human microbiome: at the interface of health and disease, *Nature reviews, Genetics* 13 (2012) 260–270.
- [14]. Gregory KE, Samuel BS, Houghteling P, Shan G, Ausubel FM, Sadreyev RI, Walker WA, Influence of maternal breast milk ingestion on acquisition of the intestinal microbiome in preterm infants, *Microbiome* 4 (2016) 68. [PubMed: 28034306]
- [15]. Stewart CJ, Ajami NJ, O'Brien JL, Hutchinson DS, Smith DP, Wong MC, Ross MC, Lloyd RE, Doddapaneni H, Metcalf GA, Muzny D, Gibbs RA, Vatanen T, Huttenhower C, Xavier RJ, Rewers M, Hagopian W, Toppari J, Ziegler AG, She JX, Akolkar B, Lernmark A, Hyoty H, Vehik K, Krischer JP, Petrosino JF, Temporal development of the gut microbiome in early childhood from the TEDDY study, *Nature* 562 (2018) 583–588. [PubMed: 30356187]
- [16]. Yassour M, Vatanen T, Siljander H, Hamalainen AM, Harkonen T, Ryhanen SJ, Franzosa EA, Vlamakis H, Huttenhower C, Gevers D, Lander ES, Knip M, Xavier RJ, Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability, *Sci. Transl. Med* 8 (2016) 343ra381.
- [17]. Tremlett H, Fadrosch DW, Faruqi AA, Hart J, Roalstad S, Graves J, Lynch S, Waubant E, Gut microbiota composition and relapse risk in pediatric MS: a pilot study, *J. Neurol. Sci* 363 (2016) 153–157. [PubMed: 27000242]
- [18]. Tremlett H, Fadrosch DW, Faruqi AA, Zhu F, Hart J, Roalstad S, Graves J, Lynch S, Waubant E, Gut microbiota in early pediatric multiple sclerosis: a case-control study, *Eur. J. Neurol* 23 (2016) 1308–1321. [PubMed: 27176462]
- [19]. Dalla Costa G, Romeo M, Esposito F, Sangalli F, Colombo B, Radaelli M, Moiola L, Comi G, Martinelli V, Caesarean section and infant formula feeding are associated with an earlier age of onset of multiple sclerosis, *Mult. Scler. Relat. Disord* 33 (2019) 75–77. [PubMed: 31158806]
- [20]. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ, Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis, *Jama* 288 (2002) 728–737. [PubMed: 12169077]
- [21]. Larroque B, Ancel PY, Marret S, Marchand L, Andre M, Arnaud C, Pierrat V, Roze JC, Messer J, Thiriez G, Burguet A, Picaud JC, Breart G, Kaminski M, Neurodevelopmental disabilities and special care of 5-year-old children born before 33 weeks of gestation (the EPIPAGE study): a longitudinal cohort study, *Lancet (London, England)* 371 (2008) 813–820.
- [22]. Lu J, Claud EC, Connection between gut microbiome and brain development in preterm infants, *Dev. Psychobiol* 61 (2019) 739–751. [PubMed: 30460694]
- [23]. Dahl C, Stigum H, Valeur J, Iszatt N, Lenters V, Peddada S, Bjornholt JV, Midtvedt T, Mandal S, Eggesbo M, Preterm infants have distinct microbiomes not explained by mode of delivery, breastfeeding duration or antibiotic exposure, *Int. J. Epidemiol* 47 (2018) 1658–1669. [PubMed: 29688458]
- [24]. Claud EC, Keegan KP, Brulc JM, Lu L, Bartels D, Glass E, Chang EB, Meyer F, Antonopoulos DA, Bacterial community structure and functional contributions to emergence of health or necrotizing enterocolitis in preterm infants, *Microbiome* 1 (2013) 20. [PubMed: 24450928]

- [25]. Lu J, Lu L, Yu Y, Cluette-Brown J, Martin CR, Claud EC, Effects of intestinal microbiota on brain development in humanized gnotobiotic mice, *Sci. Rep* 8 (2018) 5443. [PubMed: 29615691]
- [26]. Sampson TR, Mazmanian SK, Control of brain development, function, and behavior by the microbiome, *Cell Host Microbe* 17 (2015) 565–576. [PubMed: 25974299]
- [27]. Diaz Heijtz R, Wang S, Anuar F, Qian Y, Bjorkholm B, Samuelsson A, Hibberd ML, Forssberg H, Pettersson S, Normal gut microbiota modulates brain development and behavior, *Proc. Natl. Acad. Sci. U.S.A* 108 (2011) 3047–3052. [PubMed: 21282636]
- [28]. Neufeld KM, Kang N, Bienenstock J, Foster JA, Reduced anxiety-like behavior and central neurochemical change in germ-free mice, *Neurogastroenterol. Motil* 23 (2011) 255–264 e119. [PubMed: 21054680]
- [29]. Gareau MG, Wine E, Rodrigues DM, Cho JH, Whary MT, Philpott DJ, MacQueen G, Sherman PM, Bacterial infection causes stress-induced memory dysfunction in mice, *Gut* 60 (2011) 307–317. [PubMed: 20966022]
- [30]. Clarke G, Grenham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, Dinan TG, Cryan JF, The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner, *Mol. Psychiatry* 18 (2012) 666. [PubMed: 22688187]
- [31]. Ogbonnaya ES, Clarke G, Shanahan F, Dinan TG, Cryan JF, O’Leary OF, Adult hippocampal neurogenesis is regulated by the microbiome, *Biol. Psychiatry* 78 (2015) e7–9. [PubMed: 25700599]
- [32]. Luczynski P, Whelan SO, O’Sullivan C, Clarke G, Shanahan F, Dinan TG, Cryan JF, Adult microbiota-deficient mice have distinct dendritic morphological changes: differential effects in the amygdala and hippocampus, *Eur. J. Neurosci* 44 (2016) 2654–2666. [PubMed: 27256072]
- [33]. Lange N, Travers BG, Bigler ED, Prigge MB, Froehlich AL, Nielsen JA, Cariello AN, Zielinski BA, Anderson JS, Fletcher PT, Alexander AA, Lainhart JE, Longitudinal volumetric brain changes in autism spectrum disorder ages 6–35 years, *Autism Res.* 8 (2015) 82–93. [PubMed: 25381736]
- [34]. Aoki Y, Yoncheva YN, Chen B, Nath T, Sharp D, Lazar M, Velasco P, Milham MP, Di Martino A, Association of white matter structure with autism Spectrum disorder and Attention-Deficit/Hyperactivity disorder, *JAMA Psychiatry* 74 (2017) 1120–1128. [PubMed: 28877317]
- [35]. Slykerman RF, Thompson J, Waldie KE, Murphy R, Wall C, Mitchell EA, Antibiotics in the first year of life and subsequent neurocognitive outcomes, *Acta Paediatr.* 106 (2017) 87–94 (Oslo, Norway : 1992). [PubMed: 27701771]
- [36]. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, Codelli JA, Chow J, Reisman SE, Petrosino JF, Patterson PH, Mazmanian SK, Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders, *Cell* 155 (2013) 1451–1463. [PubMed: 24315484]
- [37]. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, Sogin ML, Jones WJ, Roe BA, Affourtit JP, Egholm M, Henrissat B, Heath AC, Knight R, Gordon JI, A core gut microbiome in obese and lean twins, *Nature* 457 (2009) 480–484. [PubMed: 19043404]
- [38]. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P, Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa, *Proc. Natl. Acad. Sci. U.S.A* 107 (2010) 14691–14696. [PubMed: 20679230]
- [39]. Song SJ, Lauber C, Costello EK, Lozupone CA, Humphrey G, Berg-Lyons D, Caporaso JG, Knights D, Clemente JC, Nakielnny S, Gordon JI, Fierer N, Knight R, Cohabiting family members share microbiota with one another and with their dogs, *eLife* 2 (2013) e00458. [PubMed: 23599893]
- [40]. Palleja A, Mikkelsen KH, Forslund SK, Kashani A, Allin KH, Nielsen T, Hansen TH, Liang S, Feng Q, Zhang C, Pyl PT, Coelho LP, Yang H, Wang J, Typas A, Nielsen MF, Nielsen HB, Bork P, Wang J, Vilsbøll T, Hansen T, Knop FK, Arumugam M, Pedersen O, Recovery of gut microbiota of healthy adults following antibiotic exposure, *Nat. Microbiol* 3 (2018) 1255–1265. [PubMed: 30349083]
- [41]. Qin J, Li Y, Cai Z, Li S, Zhu J, Zhang F, Liang S, Zhang W, Guan Y, Shen D, Peng Y, Zhang D, Jie Z, Wu W, Qin Y, Xue W, Li J, Han L, Lu D, Wu P, Dai Y, Sun X, Li Z, Tang A, Zhong S, Li

- X, Chen W, Xu R, Wang M, Feng Q, Gong M, Yu J, Zhang Y, Zhang M, Hansen T, Sanchez G, Raes J, Falony G, Okuda S, Almeida M, LeChatelier E, Renault P, Pons N, Batto JM, Zhang Z, Chen H, Yang R, Zheng W, Li S, Yang H, Wang J, Ehrlich SD, Nielsen R, Pedersen O, Kristiansen K, Wang J, A metagenome-wide association study of gut microbiota in type 2 diabetes, *Nature* 490 (2012) 55–60. [PubMed: 23023125]
- [42]. Jangi S, Gandhi R, Cox LM, Li N, von Glehn F, Yan R, Patel B, Mazzola MA, Liu S, Glanz BL, Cook S, Tankou S, Stuart F, Melo K, Nejad P, Smith K, Topcuolu BD, Holden J, Kivisakk P, Chitnis T, De Jager PL, Quintana FJ, Gerber GK, Bry L, Weiner HL, Alterations of the human gut microbiome in multiple sclerosis, *Nat. Commun* 7 (2016) 12015. [PubMed: 27352007]
- [43]. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD, Linking long-term dietary patterns with gut microbial enterotypes, *Science* 334 (2011) 105–108 (New York, N.Y.). [PubMed: 21885731]
- [44]. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB, Dutton RJ, Turnbaugh PJ, Diet rapidly and reproducibly alters the human gut microbiome, *Nature* 505 (2014) 559–563. [PubMed: 24336217]
- [45]. Muegge BD, Kuczynski J, Knights D, Clemente JC, Gonzalez A, Fontana L, Henrissat B, Knight R, Gordon JI, Diet drives convergence in gut microbiome functions across mammalian phylogeny and within humans, *Science* 332 (2011) 970–974 (New York, N.Y.). [PubMed: 21596990]
- [46]. O’Keefe SJD, Li JV, Lahti L, Ou J, Carbonero F, Mohammed K, Posma JM, Kinross J, Wahl E, Ruder E, Vippera K, Naidoo V, Mtshali L, Tims S, Puylaert PGB, DeLany J, Krasinskas A, Benefiel AC, Kaseb HO, Newton K, Nicholson JK, de Vos WM, Gaskins HR, Zoetendal EG, Fat, fibre and cancer risk in African Americans and rural Africans, *Nat. Commun* 6 (2015) 6342. [PubMed: 25919227]
- [47]. Hibberd MC, Wu M, Rodionov DA, Li X, Cheng J, Griffin NW, Barratt MJ, Giannone RJ, Hettich RL, Osterman AL, Gordon JI, The effects of micronutrient deficiencies on bacterial species from the human gut microbiota, *Sci. Transl. Med* 9 (2017).
- [48]. Dethlefsen L, Relman DA, Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation, *Proc. Natl. Acad. Sci. U.S.A* 108 (Suppl 1) (2011) 4554–4561. [PubMed: 20847294]
- [49]. Namasivayam S, Maiga M, Yuan W, Thovarai V, Costa DL, Mittereder LR, Wiperman MF, Glickman MS, Dzutsev A, Trinchieri G, Sher A, Longitudinal profiling reveals a persistent intestinal dysbiosis triggered by conventional anti-tuberculosis therapy, *Microbiome* 5 (2017) 71. [PubMed: 28683818]
- [50]. Berer K, Gerdes LA, Cekanaviciute E, Jia X, Xiao L, Xia Z, Liu C, Klotz L, Stauffer U, Baranzini SE, Kumpfel T, Hohlfeld R, Krishnamoorthy G, Wekerle H, Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice, *Proc. Natl. Acad. Sci. U.S.A* 114 (2017) 10719–10724. [PubMed: 28893994]
- [51]. Chen J, Chia N, Kalari KR, Yao JZ, Novotna M, Paz Soldan MM, Luckey DH, Marietta EV, Jeraldo PR, Chen X, Weinshenker BG, Rodriguez M, Kantarci OH, Nelson H, Murray JA, Mangalam AK, Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls, *Sci. Rep* 6 (2016) 28484. [PubMed: 27346372]
- [52]. Cekanaviciute E, Yoo BB, Runia TF, Debelius JW, Singh S, Nelson CA, Kanner R, Bencosme Y, Lee YK, Hauser SL, Crabtree-Hartman E, Sand IK, Gacias M, Zhu Y, Casaccia P, Cree BAC, Knight R, Mazmanian SK, Baranzini SE, Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models, *Proc. Natl. Acad. Sci. U.S.A* 114 (2017) 10713–10718. [PubMed: 28893978]
- [53]. Katz Sand I, Zhu Y, Ntranos A, Clemente JC, Cekanaviciute E, Brandstadter R, Crabtree-Hartman E, Singh S, Bencosme Y, Debelius J, Knight R, Cree BAC, Baranzini SE, Casaccia P, Disease-modifying therapies alter gut microbial composition in MS, *Neurol. Neuroimmunol. Neuroinflamm* 6 (2019) e517. [PubMed: 30568995]
- [54]. Ochoa-Reparaz J, Mielcarz DW, Wang Y, Begum-Haque S, Dasgupta S, Kasper DL, Kasper LH, A polysaccharide from the human commensal *Bacteroides fragilis* protects against CNS demyelinating disease, *Mucosal Immunol.* 3 (2010) 487–495. [PubMed: 20531465]

- [55]. Rumah KR, Linden J, Fischetti VA, Vartanian T, Isolation of *Clostridium perfringens* type B in an individual at first clinical presentation of multiple sclerosis provides clues for environmental triggers of the disease, *PLoS One* 8 (2013) e76359. [PubMed: 24146858]
- [56]. Gacias M, Gaspari S, Santos PM, Tamburini S, Andrade M, Zhang F, Shen N, Tolstikov V, Kiebish MA, Dupree JL, Zachariou V, Clemente JC, Casaccia P, Microbiota-driven transcriptional changes in prefrontal cortex override genetic differences in social behavior, *Elife* 5 (2016).
- [57]. Hoban AE, Stilling RM, Ryan FJ, Shanahan F, Dinan TG, Claesson MJ, Clarke G, Cryan JF, Regulation of prefrontal cortex myelination by the microbiota, *Transl. Psychiatry* 6 (2016) e774. [PubMed: 27045844]
- [58]. Lu J, Synowiec S, Lu L, Yu Y, Bretherick T, Takada S, Yarnykh V, Caplan J, Caplan M, Claud EC, Drobyshevsky A, Microbiota influence the development of the brain and behaviors in C57BL/6J mice, *PLoS One* 13 (2018) e0201829. [PubMed: 30075011]
- [59]. Ye P, Li L, Richards RG, DiAugustine RP, D'Ercole AJ, Myelination is altered in insulin-like growth factor-I null mutant mice, *J. Neurosci* 22 (2002) 6041–6051. [PubMed: 12122065]
- [60]. Yan J, Herzog JW, Tsang K, Brennan CA, Bower MA, Garrett WS, Sartor BR, Aliprantis AO, Charles JF, Gut microbiota induce IGF-1 and promote bone formation and growth, *Proc. Natl. Acad. Sci. U.S.A* 113 (2016) E7554–e7563. [PubMed: 27821775]
- [61]. Yang Y, Cheng Z, Tang H, Jiao H, Sun X, Cui Q, Luo F, Pan H, Ma C, Li B, Neonatal maternal separation impairs prefrontal cortical myelination and cognitive functions in rats through activation of wnt signaling, *Cereb. Cortex* 27 (2017) 2871–2884 (New York, N.Y. : 1991). [PubMed: 27178192]
- [62]. Bordner KA, George ED, Carlyle BC, Duque A, Kitchen RR, Lam TT, Colangelo CM, Stone KL, Abbott TB, Mane SM, Nairn AC, Simen AA, Functional genomic and proteomic analysis reveals disruption of myelin-related genes and translation in a mouse model of early life neglect, *Front. Psychiatry* 2 (2011) 18. [PubMed: 21629843]
- [63]. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, Kubo C, Koga Y, Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice, *J. Physiol. (Lond.)* 558 (2004) 263–275. [PubMed: 15133062]
- [64]. De Palma G, Blennerhassett P, Lu J, Deng Y, Park AJ, Green W, Denou E, Silva MA, Santacruz A, Sanz Y, Surette MG, Verdu EF, Collins SM, Bercik P, Microbiota and host determinants of behavioural phenotype in maternally separated mice, *Nat. Commun* 6 (2015) 7735. [PubMed: 26218677]
- [65]. Donia MS, Fischbach MA, HUMAN MICROBIOTA. Small molecules from the human microbiota, *Science* 349 (2015) 1254766(New York, N.Y.). [PubMed: 26206939]
- [66]. Gershon MD, 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract, *Current opinion in endocrinology, diabetes, and obesity* 20 (2013) 14–21.
- [67]. Rothhammer V, Mancias ID, Bunse L, Takenaka MC, Kenison JE, Mayo L, Chao CC, Patel B, Yan R, Blain M, Alvarez JJ, Kebir H, Anandasabapathy N, Izquierdo G, Jung S, Obholzer N, Pochet N, Clish CB, Prinz M, Prat A, Antel J, Quintana FJ, Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor, *Nat. Med* 22 (2016) 586–597. [PubMed: 27158906]
- [68]. Ben Bashat D, Kronfeld-Duenias V, Zachor DA, Ekstein PM, Hendler T, Tarrasch R, Even A, Levy Y, Ben Sira L, Accelerated maturation of white matter in young children with autism: a high b value DWI study, *Neuroimage* 37 (2007) 40–47. [PubMed: 17566764]
- [69]. Cekanaviciute E, Pröbstel A-K, Thomann A, Runia TF, Casaccia P, Katz Sand I, Crabtree E, Singh S, Morrissey J, Barba P, Gomez R, Knight R, Mazmanian S, Graves J, Cree BAC, Zamvil SS, Baranzini SE, Multiple sclerosis-associated changes in the composition and immune functions of spore-forming Bacteria, *mSystems* 3 (2018) e00083–18. [PubMed: 30417113]
- [70]. Chen T, Noto D, Hoshino Y, Mizuno M, Miyake S, Butyrate suppresses demyelination and enhances remyelination, *J. Neuroinflammation* 16 (2019) 165. [PubMed: 31399117]
- [71]. Candido EP, Reeves R, Davie JR, Sodium butyrate inhibits histone deacetylation in cultured cells, *Cell* 14 (1978) 105–113. [PubMed: 667927]

- [72]. Zeng Q, Junli G, Liu X, Chen C, Sun X, Li H, Zhou Y, Cui C, Wang Y, Yang Y, Wu A, Shu Y, Hu X, Lu Z, Zheng SG, Qiu W, Lu Y, Gut dysbiosis and lack of short chain fatty acids in a Chinese cohort of patients with multiple sclerosis, *Neurochem. Int* 129 (2019) 104468. [PubMed: 31108132]
- [73]. Melbye P, Olsson A, Hansen TH, Sondergaard HB, Bang Oturai A, Short-chain fatty acids and gut microbiota in multiple sclerosis, *Acta Neurol. Scand* 139 (2019) 208–219. [PubMed: 30427062]
- [74]. Zmora N, Soffer E, Elinav E, Transforming medicine with the microbiome, *Sci. Transl. Med* 11 (2019) eaaw1815. [PubMed: 30700573]
- [75]. Tankou SK, Regev K, Healy BC, Cox LM, Tjon E, Kivisakk P, Vanande IP, Cook S, Gandhi R, Glanz B, Stankiewicz J, Weiner HL, Investigation of probiotics in multiple sclerosis, *Mult. Scler* 24 (2018) 58–63 (Houndmills, Basingstoke, England). [PubMed: 29307299]
- [76]. Stumpf SK, Berghoff SA, Trevisiol A, Spieth L, Duking T, Schneider LV, Schlaphoff L, Dreha-Kulaczewski S, Bley A, Burfeind D, Kusch K, Mitkovski M, Ruhwedel T, Guder P, Rohse H, Denecke J, Gartner J, Mobius W, Nave KA, Saher D, Ketogenic diet ameliorates axonal defects and promotes myelination in Pelizaeus-Merzbacher disease, *Acta Neuropathol.* 138 (2019) 147–161. [PubMed: 30919030]

Fig. 1.

The gut microbiome – brain axis: an unconventional “niche” for oligodendrocyte lineage cells. **A.** The panel depicts the positive influences of diet and life style on the intestinal microbiota. The inset shows the role of metabolites (e.g. short chain fatty acids, SCFA) and growth factors (e.g. IGF-1 and BDNF) supporting oligodendrocyte progenitor (OPC) differentiation into myelinating oligodendrocytes. Please see text for a description of the experimental evidence in support. **B.** The panel depicts perturbations of normal gut microbiota, due to disease states or negative environmental influences. The inset shows one of the metabolites (e.g. p-cresol), whose production and release to the circulation negatively

affects oligodendrocyte progenitor cell (OPC) differentiation. Figure generated with [Biorender.com](https://biorender.com).

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