Microbiome programming of brain development: implications for neurodevelopmental disorders

HANS FORSSBERG

Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden.

Correspondence to Hans Forssberg at Neuropediatric Unit, Astrid Lindgren Children's Hospital, Q2:07, 171 76 Stockholm, Sweden. E-mail: hans.forssberg@ki.se

PUBLICATION DATA
Accepted for publication 28th January 2019.
Published online 14th March 2019.

ABBREVIATION
ASD Autism spectrum disorder

During the last decade, research on germ-free mice has discovered that the gut microbiome (i.e. the normal bacteria colonizing the gastrointestinal tract) can programme brain function and behaviour during early development. At the same time a growing number of clinical studies have shown altered gut microflora in children with autism spectrum disorder (ASD), in combination with altered bacterial metabolites and inflammatory cytokines being part of the gut-brain axis. This review covers the concept of the microbiome; how it is established during childhood; how it is affected by malnutrition; how it can programme the development of the brain through epigenetic mechanisms; which pathways are used from the gut to the brain; and assesses findings that suggest the gut microbiome may be involved in ASD and other neurodevelopmental disorders. This is a new research field with a number of exciting, but so far fragmented, findings indicating the important role of the normal microbiome in shaping the brain. Research also suggests that disruptions of the microbiome may be involved in the aetiology of neurodevelopmental disorders.

The concept of a 'superorganism', including the genome of all microorganisms colonizing our body in addition to the 25 000 to 30 000 genes of the human genome, evolved in the beginning of this millennium in parallel with the exploration of the human genome.[1] The microbiome includes genes of an estimated trillion microbes (10^{14}), mainly bacteria located in the gastrointestinal tract. These genes, their protein products, and metabolites, play an important role in the development and homeostasis of a number of body functions.[2] For example, commensal microorganisms prevent invasion of other pathogenic microorganisms; contribute to the fermentation of non-digestible fibres; produce vitamins; are involved in metabolism of short-chain fatty acids and carbohydrates; promote absorption of minerals; and regulate inflammatory responses and the immune system. The interaction between microorganisms and their hosts has evolved during the entire mammalian evolution, resulting in a unique gastrointestinal microbial community in humans. It remains rather stable over time, but diet and other environmental factors can affect the microbial community with some components being more stable and others more replaceable. Failure to maintain the balance between the commensal microbiota and the host (dysbiosis) may disturb the complex homeostasis and cause a variety of disorders (e.g. intestinal, metabolic, and immune disorders).[2]

ESTABLISHMENT OF THE MICROBIOME

The fetus has been considered sterile and well protected in the womb, to be colonized first during delivery with the mother's vaginal and faecal microbiota. Recently, bacterial DNA was isolated in the placenta of term-born infants,[3] which suggests that the fetus might be colonized before birth. Infants born by caesarean section develop a partly different microbiota derived from the mother's skin and from the hospital environment.[4] After birth, bacteria adapted to extract energy from milk oligosaccharides successively take over and become dominating in breastfed infants. The introduction of solid food is accompanied by the development of a more diverse community of bacteria capable of digesting fibres, polysaccharides, and glycoproteins. The diversity of the microbiota continues to expand as new food products are introduced until an adult-like microbiome is established around 2 to 3 years of age.[5,6]

Studies of bacterial 16S ribosomal ribonucleic acid from faecal samples collected monthly from birth through the first 2 to 3 years have shown a pattern of age-discriminatory bacteria.[7] These age-dependent patterns are similar in children living in low-income countries and can be used to estimate the maturity of the microbiome in typically developing children. The microbiome of children in high-income countries is less diverse than in children living in low-income countries, who have bacteria adapted to digest a polysaccharide rich diet.[8] The decline in diversity in high-income countries has occurred in parallel with the introduction of antibiotics and sanitary processes. This has raised the question whether stricter hygiene and extended use of antibiotics can influence our health by affecting the commensal microbiome.[9] A growing number of studies on young children are showing that increased use of

 DOI: 10.1111/dmcn.14208 © 2019 Mac Keith Press

antibiotics is associated with increased risk of a variety of diseases including asthma and other allergies, inflammatory bowel disease, celiac disease, and diabetes.

MALNOURISHMENT AND EARLY CHILDHOOD DEVELOPMENT

Approximately 250 million children in low- and middle-income countries are at risk of not reaching their developmental potential because of stunting and poverty.[10] Undernutrition during the infant's first year is associated with adverse consequences later in life such as immune dysfunction and cognitive deficits. However, although poverty is a major cause of malnutrition, the aetiology seems to be more complex than a simple lack of food since the introduction of an adequate food supply has only modest effects in correcting the long-term effects. This has led to the hypothesis that development and growth are influenced by the gut microbiota, and that malnourishment may disrupt this development. Studies from Bangladesh and Malawi have shown that the development of the age-discriminatory bacteria in the gut during the first years of life was disrupted in malnourished children with kwashiorkor, that is their gut microbial community was less diverse and lacked more mature bacterial taxa compared with age matched typically developing children.[7]

In order to study whether the composition of the gut microbiota was causally related to childhood undernutrition, faecal transplants from undernourished Malawi infants were given to germ-free mice (i.e. mice bred and brought up in a sterile environment). The transplanted microbiota from the undernourished infants transmitted a reduced lean body mass gain compared to the transplantation of microbiota from well-nourished infants.[11] The transplants also transmitted alterations of bone morphometry and metabolism in muscle, liver, and brain. Analysis of bacterial genes of the faecal microbiota of the transplanted mice could identify groups of bacterial taxa that were discriminatory for some phenotypes. Some of these taxa were the same as the age-discriminatory taxa developing during the first years. These studies demonstrate that the development of the microbiota is associated with the development of several host functions, and that different composition of bacterial taxa from undernourished children can result in different phenotypes.

In another experimental study on mice, it was shown that pregnant mothers who were fed a high-fat diet became obese, and that the gut microbiome of their offspring was altered. Unexpectedly, the social behaviour of the offspring also changed in association with altered signalling in the mesolimbic reward system.[12] When these mice were given gut microbiota from control mice with an ordinary diet, the social behaviour reversed to the typical pattern. The transfer of one single bacterial taxa, Lactobacillus reuteri, was enough to restore the social behaviour. The correction of the behaviour was further associated with oxytocin levels in the hypothalamus and neural activity in the ventral tegmental area. These experiments demonstrate that the gut microbiome of the newborn mice can play an important role by influencing the development of social behaviour and by altering signalling in specific neural pathways.

What this paper adds

- The gut microbiome shapes the brain via the gut-brain axis.
- The microbiome may play a role in neurodevelopmental disorders.

EPIGENETIC PROGRAMMING OF THE BRAIN

The term epigenetics has historically been used to describe heritable traits that are not mediated by the DNA sequences. In the era of molecular genetics, it has become used to describe stable alterations in gene expression caused by environmental factors.[13] The genome contains two layers of information: first the DNA sequence inherited by the parents and conserved throughout life, and second, epigenetic information that can be altered by environmental signals. Environmental signals during prenatal and postnatal life can thus programme brain development resulting in life-long alteration of neural function and behaviour. At a molecular level the epigenetic mechanisms include DNA methylation, histone modification, and small non-coding ribonucleic acids, which control which genes are transcribed and which genes are silenced.

Barker hypothesized that early programming adapts the organism to the prenatal or postnatal environment expecting that similar conditions will persist later in life.[14] A mismatch between the fetal environment and later life conditions should thus result in reprogramming that increases the risk to develop disease. Barker based his hypothesis on associations between fetal growth retardation, and the metabolic syndrome and type 2 diabetes later in life.[14] The poor nutrition early in life programmed permanent changes in glucose-insulin metabolism that were harmful when there was enough with food. In addition to the nutritional condition, adverse conditions inducing stress in early life can programme the stress regulating pathways in the hypothalamo-pituitary-adrenal system.[13] This may lead to long lasting alterations of stress responsivity and increased vulnerability to develop mood disorders and depression later in life.

Infections and immune activation in early life are other conditions that can programme development of the brain and other organ systems with increased risk to develop neurodevelopmental disorders.[15] Cohort studies from the Danish Medical Birth Register have shown that maternal viral infections during the first trimester, and bacterial infections during the second trimester, causing hospitalization, increased the risk of the children developing autism spectrum disorder (ASD).[16] Elevated levels of cytokines in the amniotic fluid was associated with increased risk of ASD,[17] and the mothers of children with ASD had elevated serum cytokine levels when analysed in retrospect.[18] These results suggest that early activation of the immune system (e.g. in response to infections) may reprogramme the brain circuits in an unfavourable way contributing to the development of ASD symptoms.[19]

THE ROLE OF THE GUT MICROBIOME IN BRAIN DEVELOPMENT

Rearing animals in sterile environments without any microbes (e.g. germ-free mice) has been an important tool when studying the influence of the microbiome on the development of various body systems. Any difference compared with mice reared under normal conditions exposes functions and behaviour which are influenced by the microbiome. Germ-free mice display a behavioural phenotype that in several aspects differs from mice reared during ordinary conditions.[20] They exhibit increased locomotor activity and decreased anxiety-like behaviour in several tasks including the open field box, light-dark box, and elevated plus maze.[21,22] That means that a disruption of the microbiome during development seems to modulate the behaviour towards an attention-deficit/hyperactivity disorder-like phenotype. Lack of microbiota also induced higher expression of synaptic related proteins such as synaptophysin and PSD-95 in striatum.[21]

Germ-free mice also exhibit altered social behaviour. This has been investigated by studying the social preference of a mouse placed in the centre of a three-chamber box with another mouse placed in one neighbouring chamber and an object placed in the third chamber. The time germ-free mice spend with another mouse versus an object, or with an unfamiliar mouse versus a familiar mouse, was altered compared with ordinary mice.[23,24] The behavioural changes were associated with altered expression of brain derived nerve growth factor in the amygdala, which is a key hub of the social brain network.[24] The results suggest that normal microbiota is crucial for the programming of normal social behaviour. Since altered social communication is a functional hallmark of ASD, it also suggests that a disruption of the microbiome can affect the development of social and communication functions towards an ASD phenotype. This is supported by the previously mentioned study on the offspring of mothers with high-fat induced obesity and altered gut microbiome.[12] The offspring exhibited changed social behaviour that was linked to altered signalling in the mesolimbic reward system.

Although results from experimental studies in germ-free mice are currently fragmented and sometimes conflicting, and the germ-free phenotypes and underlying mechanisms are far from understood, the studies suggest that the gut microbiome can shape the brain during development by influencing gene transmission and synaptic signalling with life-long influence on motor and social behaviour. It seems that this epigenetic programming is limited to early stages of brain development, since germ-free mice that were exposed to gut microbiota as adults maintained their phenotype, while germ-free mice that were exposed to normal gut microbiota early developed similar behaviour and gene expression in the striatum as ordinary mice.[21]

THE GUT-BRAIN AXIS

The gut-brain axis is a bidirectional communication system involving neural and humoral mechanisms utilizing the enteric nervous system/vagus nerve and the circulatory system respectively.[25,26] Enteric and vagus nerve endings can be activated by metabolites and neuroactive substances produced by microbiota in the intestines and the signals are transmitted to various parts of the brain. Oral inoculation with pathogen bacteria or intraduodenal injection of probiotic bacteria in mice can induce neural activity in the vagus nerve and brainstem. When the vagus nerve was sectioned, the probiotic effects on anxiety, memory, and GABA receptor gene expression were reversed.[27] There is thus strong evidence from experimental studies that transmission through the vagus nerve plays an important role in modifying brain activity and behaviour. However, we do not know if these mechanisms are involved in the early brain programming by the gut microbiome.

The humoral gut-brain communication is dependent on translocation of signalling molecules produced in the intestinal lumen, passing the intestinal mucosal barrier to the blood stream, and the blood brain barrier to the brain. These semi-permeable barriers allow translocation of nutrients and smaller molecules, while limiting the passage of microorganisms, antigens, and larger molecules. The intestinal mucosa is permeable in the fetus and forms tight junctions reducing permeability after birth. There might thus be an excessive leakage of substances from the intestines early in life. Later in life the permeability of both the intestinal barrier and the blood brain barrier can be modified by microbiota and their products.[28,29] Therefore, microbiota seems to be able to modulate the amount and types of its bioactive substances that are translocated from the gut to the brain by controlling the permeability of the barriers. There also seem to be a window early in life with increased gut-brain translocation before the permeability of the barriers decreases. Interestingly, increased permeability has been reported in infants born preterm and children with ASD.[30]

The humoral bioactive substances translocated via the gut-brain axis are derived from several sources including bacterial metabolites, and endocrine and immune cells in the mucosa.[26] Several studies have demonstrated the influence of bacterial metabolites on brain development, while less information has been reported on the potential role of intestinal immune and endocrine cells. Short chain fatty acids (acetic, propionic, and butyric acid) are metabolic by-products of bacterial fermentation of non-digestible carbohydrates and proteins. They can pass the intestinal barrier, enter the systemic circulation, pass the blood brain barrier,[25] and influence hypothalamic appetite regulating circuits.[31] In experiments where short chain fatty acids were injected subcutaneously in pregnant or newborn mice, this had long-term effects on locomotor activity, anxiety, and startle responses depending on sex and time of injection.[32] These effects were associated with changes in lipid physiology and mitochondrial function. Short chain fatty acids are also known to exert epigenetic effects by histone modification of gene expression.

Another bacterial product that has attracted interest is peptidoglycan, which is a component of the bacterial cell

wall. It was first shown to be translocated into the circulation and influence the innate immune system by programming bone-marrow-derived neutrophils via specific pattern-recognition receptors.[33] Later, it was demonstrated that bacterial peptidoglycan could also be translocated over the blood brain barrier, and that neurons in the brain expressed early on the pattern recognition receptors and peptidoglycan transporter required to sense the peptidoglycan molecules.[34] The expression of these pattern recognition receptors also turned out to be sensitive to manipulations of the gut microbiota, that is they were reduced in germ-free mice and in mice treated with antibiotics. The potential role of peptidoglycans was further strengthened by studying the behaviour of pattern recognition receptor knockout mice (peptidoglycan recognition protein 2), finding sex-dependent changes in social behaviour, similar to mice with manipulated microbiota. Together, these findings support that activation of pattern recognition receptors in the brain by intestinal microbial products could be one of the signalling pathways between the gut microbiota and the developing brain.

Recent studies suggest that the microglia may be an important target for gut-brain communication, indirectly affecting the development and maintenance of the neural circuits. During brain development, microglia regulates neural cell numbers and synaptic refinements contributing to the development of neural circuits involved in cognitive function and social behaviour.[35] Microglial activity is regulated by cytokines, neurotransmitters, and other molecules produced within the brain. Recent studies show that the gut microbiota can affect the development of brain microglia, and that the maturation of microglia is blocked in germ-free mice in a sex- and time-dependent manner from prenatal stages.[25,36,37] The presence of a more complex and diverse bacterial community seems to be required for the transition to more adult forms of microglia. The same gut-brain pathways as previously described also influence the microglia (e.g. short chain fatty acids and vagal afferents).[25] A special gut-microglia pathway originates from the intestinal immune cells that produce inflammatory cytokines that via circulation are translocated to the brain and induce increased activity in the microglia expressing cytokine receptors. Interestingly, postmortem analysis of the brains of patients with ASD have shown disrupted microglial morphology and activity in combination with elevated levels of inflammatory cytokines.[25]

Emerging studies suggest that the microbiome may influence the myelination, but results are conflicting. In one study on 10-week-old germ-free mice, axons in the prefrontal cortex were hyper-myelinated and genes linked to myelination were upregulated,[38] while the opposite effect was reported in another study measuring the myelination with magnetic resonance imaging and myelin staining (Luxol fast blue) in 4- and 12-week-old germ-free mice.[39]

THE ROLE OF THE GUT MICROBIOME IN ASD AND OTHER NEURODEVELOPMENTAL DISORDERS

ASD is characterized by a wide range of cognitive and behavioural symptoms including impaired social and communicative skills and repetitive behaviour. The exact causes of ASD are unknown but family and twin studies have shown a heritability of 50% to 83%,[40] with no single gene having a major effect and many risk genes being associated with a slightly increased risk of developing ASD. That leaves 17% to 50% of the variation to environmental factors, and many studies have aimed to explore these risk factors. Gastrointestinal symptoms and immune dysregulation are of particular interest since numerous studies have reported abnormalities in the enteric nervous system and in the neuroimmune system (e.g. increased microglia activation in the brain and increased levels of proinflammatory cytokines in the cerebrospinal fluid).[41] Gastrointestinal symptoms such as constipation or diarrhoea, and irritable bowel syndrome are found in 23% to 70% of patients with ASD, and the gastrointestinal symptoms correlate strongly to the severity of the ASD symptoms.[42] A large number of studies, based on bacterial culture, gene sequencing, and metabolomics, comparing the gut microbiota composition between children with ASD and typically developing children show altered microbiota composition in children with ASD along with elevated levels of some short chain fatty acids.[32,43] Some studies suggest that there is a lower microbial diversity in ASD, while there is no consensus on which bacterial taxa are altered.[43] The cause of the altered microbiota is also unclear since children with ASD often exhibit altered diet and eating behaviour, which would influence the microbiota. Another gap is the lack of studies from early life (e.g. first months) when the programming of the brain occurs. To corroborate that a disrupted intestinal microflora contributes to development of the ASD symptoms, there is a need to analyse the longitudinal development of the composition of microbiota from birth. This is of course difficult, since the child will be diagnosed with ASD much later. Although we are still lacking evidence for the role of microbiota in the early programming of the brain in ASD, it seems that the microbiota can affect the current symptoms. A recent open-label study suggested that a faecal microbiota transplant that altered the gut microbiota and overall bacterial diversity reduced both the gastrointestinal and the behavioural ASD symptoms.[44]

The clinical association between early activation of the immune system (e.g. in response to maternal infections during pregnancy) and development of ASD symptoms has led to the development of a 'maternal immune activation' mouse model exhibiting some of the ASD symptoms.[19] In recent years, a large number of studies have explored the role of the microbiota in the development of molecular brain mechanisms and behaviour in this model and other environmental (valproic acid, maternal high-fat diet) and genetic (*Shank3B*, BTBR) ASD models. This is a rapidly emerging field which is not possible to summarize in this

brief review, but the development of animal models has laid the foundations for intervention studies that could be translated to humans. In a recent breakthrough study, Sgritta et al.[45] extended their findings that treatment with Lactobacillus reuteri, which reversed the social deficits in maternal high-fat diet mice,[12] also rescued the social deficits in several other environmental, genetic, and idiopathic mouse models of ASD. The experimental model allowed them to mechanically dissect that Lactobacillus reuteri was the sole source of the impact, and that the effect was mediated via the vagus nerve (the effect was abolished after lesion of the vagus nerve), and using the oxytocinergic and dopaminergic reward systems of the brain.

Most clinical studies have so far focused on ASD, probably because of the complex nature of ASD emerging as a multi-system disorder also affecting gastrointestinal and immune systems.[46] However, studies on germ-free mice suggest that other cognitive functions, such as anxiety and motor activity, can be modulated by the microbiome. These are symptoms more associated with attention-deficit/hyperactivity disorder. There are also reasons to believe that other functions, such as learning and memory, might be implicated. There is an emerging series of studies on the microbiome in other neurodevelopmental disorders. Recent intervention studies manipulating the microbiome in animal disease models also need to be translated into clinical research. For example, can treatment with Lactobacillus reuteri affect brain development in children with ASD? Based on the mechanisms, can a similar effect be achieved by stimulation of the vagus nerve, or intranasal oxytocin? We are just at the beginning of understanding how the microbiome can shape the brain during development, and far from evidence-based interventions, but the prospect is there.

ACKNOWLEDGEMENTS

This work was supported by Foundation Olle Engkvist Byggmästare. The author has stated that he had no interests that might be perceived as posing a conflict or bias.

REFERENCES

1. Hooper LV, Gordon JI. Commensal host-bacterial relationships in the gut. *Science* 2001; **292**: 1115–8.
2. Del Chierico F, Vernocchi P, Bonizzi L, et al. Early-life gut microbiota under physiological and pathological conditions: the central role of combined meta-omics-based approaches. *J Proteomics* 2012; **75**: 4580–7.
3. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. *Sci Transl Med* 2014; **6**: 237ra65.
4. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA* 2010; **107**: 11971–5.
5. Koenig JE, Spor A, Scalfone N, et al. Succession of microbial consortia in the developing infant gut microbiome. *Proc Natl Acad Sci USA* 2011; **108** (Suppl. 1): 4578–85.
6. Kane AV, Dinh DM, Ward HD. Childhood malnutrition and the intestinal microbiome. *Pediatr Res* 2015; **77**: 256–62.
7. Blanton LV, Barratt MJ, Charbonneau MR, Ahmed T, Gordon JI. Childhood undernutrition, the gut microbiota, and microbiota-directed therapeutics. *Science* 2016; **352**: 1533.
8. De Filippo C, Cavalieri D, Di Paola M, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. *Proc Natl Acad Sci USA* 2010; **107**: 14691–6.
9. Blaser MJ. Antibiotic use and its consequences for the normal microbiome. *Science* 2016; **352**: 544–5.
10. Lu C, Black MM, Richter LM. Risk of poor development in young children in low-income and middle-income countries: an estimation and analysis at the global, regional, and country level. *Lancet Glob Health* 2016; **4**: e916–22.
11. Blanton LV, Charbonneau MR, Salih T, et al. Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children. *Science* 2016; **351**: 830 pii: aad3311.
12. Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrosino JF, Costa-Mattioli M. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. *Cell* 2016; **165**: 1762–75.
13. Murgatroyd C, Spengler D. Epigenetics of early child development. *Front Psychiatry* 2011; **2**: 16.
14. Hales CN, Barker DJ. The thrifty phenotype hypothesis. *Br Med Bull* 2001; **60**: 5–20.
15. Brown AS. Epidemiologic studies of exposure to prenatal infection and risk of schizophrenia and autism. *Dev Neurobiol* 2012; **72**: 1272–6.
16. Atladóttir HO, Thorsen P, Østergaard L, et al. Maternal infection requiring hospitalization during pregnancy and autism spectrum disorders. *J Autism Dev Disord* 2010; **40**: 1423–30.
17. Abdallah MW, Larsen N, Grove J, et al. Amniotic fluid inflammatory cytokines: potential markers of immunologic dysfunction in autism spectrum disorders. *World J Biol Psychiatry* 2013; **14**: 528–38.
18. Goines PE, Croen LA, Braunschweig D, et al. Increased midgestational IFN-gamma, IL-4 and IL-5 in women bearing a child with autism: a case-control study. *Mol Autism* 2011; **2**: 13.
19. Bilbo SD, Block CL, Bolton JL, Hanamsagar R, Tran PK. Beyond infection – maternal immune activation by environmental factors, microglial development, and relevance for autism spectrum disorders. *Exp Neurol* 2018; **299** (Pt A): 241–51.
20. Sudo N, Chida Y, Aiba Y, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol* 2004; **558** (Pt 1): 263–75.
21. Diaz Heijtz R, Wang S, Anuar F, et al. Normal gut microbiota modulates brain development and behavior. *Proc Natl Acad Sci USA* 2011; **108**: 3047–52.
22. Neufeld KM, Kang N, Bienenstock J, Foster JA. Reduced anxiety-like behavior and central neurochemical change in germ-free mice. *Neurogastroenterol Motil* 2011; **23**: 255–64.
23. Desbonnet L, Clarke G, Shanahan F, Dinan TG, Cryan JF. Microbiota is essential for social development in the mouse. *Mol Psychiatry* 2014; **19**: 146–8.
24. Arentsen T, Raith H, Qian Y, Forssberg H, Diaz Heijtz R. Host microbiota modulates development of social preference in mice. *Microb Ecol Health Dis* 2015; **26**: 29719.
25. Abdel-Haq R, Schlachetzki JCM, Glass CK, Mazmanian SK. Microbiome-microglia connections via the gut-brain axis. *J Exp Med* 2018; **216**: 41–59.
26. Collins SM, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. *Nat Rev Microbiol* 2012; **10**: 735–42.
27. Hughes HK, Rose D, Ashwood P. The gut microbiota and dysbiosis in autism spectrum disorders. *Curr Neurol Neurosci Rep* 2018; **18**: 81.
28. Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice. *Sci Transl Med* 2014; **6**: 263ra158.
29. Kelly CJ, Zheng L, Campbell EL, et al. Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function. *Cell Host Microbe* 2015; **17**: 662–71.
30. Sajdel-Sulkowska EM, Makowska-Zubrycka M, Czarzasta K, et al. Common genetic variants link the abnormalities in the gut-brain axis in prematurity and autism. *Cerebellum* 2018. https://doi.org/10.1007/s12311-018-0970-1. [Epub ahead of print].
31. Frost G, Sleeth ML, Sahuri-Arisoylu M, et al. The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nat Commun* 2014; **5**: 3611.
32. MacFabe DF. Enteric short-chain fatty acids: microbial messengers of metabolism, mitochondria, and mind:

implications in autism spectrum disorders. *Microb Ecol Health Dis* 2015; **26**: 28177.

33. Clarke TB, Davis KM, Lysenko ES, Zhou AY, Yu Y, Weiser JN. Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. *Nat Med* 2010; **16**: 228–31.

34. Arentsen T, Qian Y, Gkotzis S, et al. The bacterial peptidoglycan-sensing molecule Pglyrp2 modulates brain development and behavior. *Mol Psychiatry* 2017; **22**: 257–66.

35. Paolicelli RC, Bolasco G, Pagani F, et al. Synaptic pruning by microglia is necessary for normal brain development. *Science* 2011; **333**: 1456–8.

36. Erny D, Hrabě de Angelis AL, Jaitin D, et al. Host microbiota constantly control maturation and function of microglia in the CNS. *Nat Neurosci* 2015; **18**: 965–77.

37. Thion MS, Low D, Silvin A, et al. Microbiome influences prenatal and adult microglia in a sex-specific manner. *Cell* 2018; **172**: 500–16.

38. Hoban AE, Stilling RM, Ryan FJ, et al. Regulation of prefrontal cortex myelination by the microbiota. *Transl Psychiatry* 2016; **6**: e774.

39. Lu J, Synowiec S, Lu L, et al. Microbiota influence the development of the brain and behaviors in C57BL/6J mice. *PLoS ONE* 2018; **13**: e0201829.

40. Sandin S, Lichtenstein P, Kuja-Halkola R, Hultman C, Larsson H, Reichenberg A. The heritability of autism spectrum disorder. *JAMA* 2017; **318**: 1182–4.

41. Vargas DL, Nascimbene C, Krishnan C, Zimmerman AW, Pardo CA. Neuroglial activation and neuroinflammation in the brain of patients with autism. *Ann Neurol* 2005; **57**: 67–81.

42. Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA. Gastrointestinal flora and gastrointestinal status in children with autism – comparisons to typical children and correlation with autism severity. *BMC Gastroenterol* 2011; **11**: 22.

43. Kang DW, Ilhan ZE, Isern NG, et al. Differences in fecal microbial metabolites and microbiota of children with autism spectrum disorders. *Anaerobe* 2018; **49**: 121–31.

44. Kang DW, Adams JB, Gregory AC, et al. Microbiota transfer therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. *Microbiome* 2017; **5**: 10.

45. Sgritta M, Dooling SW, Buffington SA, et al. Mechanisms underlying microbial-mediated changes in social behavior in mouse models of autism spectrum disorder. *Neuron* 2019; **101**: 246–59.

46. Vuong HE, Hsiao EY. Emerging roles for the gut microbiome in autism spectrum disorder. *Biol Psychiatry* 2017; **81**: 411–23.

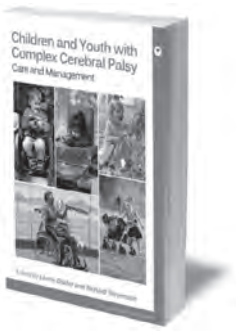
New from Mac Keith Press

Practical Guide

Children and Youth with Complex Cerebral Palsy

Care and Management

Edited by **Laurie Glader** and **Richard Stevenson**



- Provides useful summary points of key recommendations at the end of each chapter.
- Includes Clinical Care Tools to guide clinicians in evaluation, preventive care and crisis management.
- Care Tools include a Medical Review Supplement, Equipment and Services Checklist and an ICF-Based Care: Goals and Management Form.

Contact us at **admin@mackeith.co.uk** to receive full table of contents and further details.

Nov. 2018 / 240 x 170mm / 288 pp (approx.) / Softback / ISBN 978-1-909962-98-9 / £39.95

www.mackeith.co.uk/shop

RESUMEN

PROGRAMACIÓN MICROBIAMA DEL DESARROLLO CEREBRAL: IMPLICACIONES PARA LOS TRASTORNOS DEL DESARROLLO NEUROLÓGICO

Durante la última década, la investigación en ratones libres de gérmenes ha descubierto que el microbioma intestinal (es decir, las bacterias normales que colonizan el tracto gastrointestinal) pueden programar la función y el comportamiento cerebral durante el desarrollo temprano. Al mismo tiempo, un número creciente de estudios clínicos ha demostrado una microflora intestinal alterada en niños con trastorno del espectro autista (TEA), en combinación con metabolitos bacterianos alterados y citoquinas inflamatorias que forman parte del eje cerebro-intestino. Esta revisión cubre el concepto de microbioma, incluye; cómo se establece durante la infancia; cómo se ve afectado por la desnutrición; cómo puede programar el desarrollo del cerebro a través de mecanismos epigenéticos; qué vías se utilizan desde el intestino hasta el cerebro; y evalúa los hallazgos que sugieren que el microbioma intestinal puede estar involucrado en el TEA y otros trastornos del desarrollo neurológico. Este es un nuevo campo de investigación con una serie de resultados interesantes, pero hasta ahora fragmentados, que indican el importante papel que desempeña el microbioma normal en la configuración del cerebro. La investigación también sugiere que las alteraciones del microbioma pueden estar involucradas en la etiología de los trastornos del desarrollo neurológico.

RESUMO

PROGRAMAÇÃO DO MICROBIOMA PARA O DESENVOLVIMENTO CEREBRAL: IMPLICAÇÕES PARA TRANSTORNOS DESENVOLVIMENTAIS

Durante a última década, pesquisas em camundongos livres de germes descobriram que o microbioma do sistema gastrointestinal (ou seja, as bactérias que normalmente colonizam o trato gastrointestinal) podem programar a função cerebral e o comportamento no desenvolvimento preococe. Ao mesom tempo, um número crescent de estudos clínicos tem mostrado uma microflora gastrointestinal alterada em crianças com transtorno do espectro autista (TEA), em combinação com metabólitos bacterianos alterados e citocinas inflamatórias sendo parte do eixo gastrointestinal-cérebro. Esta revisão cobre o conceito de microbioma; como ele se estabelece na infância; como é afetado pela malnutrição; como pode programar o desenvolvimento do cérebro por meio de mecanismos epigenéticos; quais vias são usadas do sistema gastrointestinal para o cérebro; e avalia achados que sugerem que o microbioma gastrointestinal pode estar envolvido no TEA e outras desordens neurodesenvolvimentais. Este é um novo campos de pesquisas, porém até o momento, com achados fragmentados indicando o importante papel do miocrobioma normal na formação do cérebro. Pesquisas também sugerem que rupturas no microbioma podem estar envolvidas na etiologia de transtornos neurodesenvolvimentais.