OXFORD

THE GERONTOLOGICAL SOCIETY OF AMERICA®

Special Issue: The Gut Microbiome and Aging

Adolescence and Aging: Impact of Adolescence Inflammatory Stress and Microbiota Alterations on Brain Development, Aging, and Neurodegeneration

Nour Yahfoufi, PharmD,[1] Chantal Matar, PhD,[1,2] and Nafissa Ismail, PhD[3,*]

[1]Cellular and Molecular Medicine Department, Faculty of Medicine, University of Ottawa, Ontario, Canada. [2]School of Nutrition, Faculty of Health Sciences, University of Ottawa, Ontario, Canada. [3]School of Psychology, Faculty of Social Sciences, University of Ottawa, Ontario, Canada.

*Address correspondence to: Nafissa Ismail, PhD, Associate Professor, School of Psychology, University of Ottawa, 136 Jean-Jacques Lussier, Vanier 2076B, Ottawa, ON, Canada, K1N 6N5. E-mail: nafissa.ismail@uottawa.ca

Abstract

Puberty/adolescence is a critical phase during neurodevelopment with numerous structural, neurochemical, and molecular changes occurring in response to genetic and environmental signals. A consequence of this major neuronal reorganizing and remodeling is a heightened level of vulnerability to stressors and immune challenges. The gut microbiota is a fundamental modulator of stress and immune responses and has been found to play a role in mental health conditions and neurodegenerative disorders. Environmental insults (stress, infection, neuroinflammation, and use of antibiotics) during adolescence can result in dysbiosis subsidizing the development of brain disorders later in life. Also, pubertal neuroinflammatory insults can alter neurodevelopment, impact brain functioning in an enduring manner, and contribute to neurological disorders related to brain aging, such as Alzheimer's disease, Parkinson's disease, and depression. Exposure to probiotics during puberty can mitigate inflammation, reverse dysbiosis, and decrease vulnerabilities to brain disorders later in life. The goal of this review is to reveal the consequences of pubertal exposure to stress and immune challenges on the gut microbiota, immune reactivity within the brain, and the risk or resilience to stress-induced mental illnesses and neurodegenerative disorders. We propose that the consumption of probiotics during adolescence contribute to the prevention of brain pathologies in adulthood.

Keywords: Puberty, Adolescence, Neurodegeneration, Neuroinflammation, Microbiota

The gut microbiota is composed of nearly 100 trillion bacteria that are essential for health. These commensal microorganisms are important for the development of the immune system, protection of the host against pathogens, and metabolism of dietary nutrients and drugs (1). The gut microbiota is dynamic and changes throughout the life span. Maturation of the gut microbiota occurs in parallel with neurodevelopment and they both have similar critical developmental periods. In this review, we aim to reveal the impact of the gut microbiota on the pubertal brain. We highlight the enduring consequences of pubertal exposure to stress and immune challenges (bacterial, viral and parasitic infections, inflammatory conditions) on the gut microbiota, neuroinflammation, and stress-induced neurodegenerative disorders as well as suggest new directions for the development of effective therapeutic interventions.

The Pubertal/Adolescent Critical Period of Development

Puberty/Adolescence and hypothalamic–pituitary–adrenal axis

In humans and animals, puberty/adolescence is a critical period of development during which secondary sexual characteristics and reproductive capability are attained (2). This period is accompanied by numerous hormonal, behavioral, and social changes that impact behavior later in life (2,3). One of the critical systems that develop and mature during puberty/adolescence is the hypothalamic–pituitary–adrenal (HPA) axis (4). In rats, basal levels of stress hormones remain constant throughout pubertal/adolescent development (5). While exposure to physical and psychological stressors

increases corticosterone concentration in pubertal and adult rats, the increase in corticosterone concentration is significantly greater in pubertal rats compared with adults (6). Moreover, upon the termination of an acute stressor, the hormonal stress response (adreno-corticotropic hormone [ACTH] and corticosterone) takes longer to return to baseline in prepubertal male and female rats (28 days of age) compared with adults (77 days of age) (4) The heightened stress response in pubertal rats could be explained by the fact that the negative feedback process in the HPA axis is not fully developed and could slow the recovery of the HPA axis following stress exposure. Conversely, following chronic stress, peri-pubertal male rats (28 days of age) display greater HPA axis reactivity and faster return to baseline compared with adults (77 days of age) (6,7). This age difference in HPA axis activity following acute and chronic stress and different types of stressors is associated with greater production of corticotropin-releasing hormone (CRH) in the para-ventricular nucleus (PVN) in peri-pubertal compared with adult rodents. Therefore, vulnerability to stress increases during puberty/adolescence, and individuals are affected differently by different types of stressors during this critical period of development.

Neurodevelopment During Puberty and Adolescence

During puberty/adolescence, the brain undergoes significant reorganizing and remodeling leading to neurogenesis, synaptogenesis, and axonal and dendritic growth. This structural reshaping of neural circuits is important for brain function and behavior later in life (8). The first major change during adolescence is neuronal reorganization which is associated with the refinement of social and cognitive abilities, reward sensitivity, and stress responsivity (8,9). Multiple brain areas undergo morphological changes. For example, the frontal cortex, which is implicated in executive function, cognition, and memory, undergoes changes in synaptic connectivity and axonal myelination (10,11). The synapse number, as well, is modified during puberty and adult synapse quantity is attained by mid-adolescence (10,12). Synapse refinement continues throughout adolescence and into adulthood; it involves synaptic remodeling without any important loss of neurons with the establishment and consolidation of newly formed neural circuits. However, exposure to certain environmental factors during puberty can disrupt this neurodevelopmental process and lead to enduring, or even permanent, changes in brain function and behavior (13,14).

The second major change during adolescence is related to the process of myelination. Myelin is produced by glial cells and forms an insulating sheet around axons, leading to an increased speed of neural communication. Although in humans, axons are fully myelinated in the sensory and motor cortices during the first few years of life, the process of myelination continues in the frontal cortex throughout adolescence (15). In rats, myelin basic protein emerges 6–8 days after birth, peaks at about 15 days postnatal, and decreases thereafter (16). Thus, an increase in the speed of neural communication is observed in the frontal cortex during adolescence when compared with early childhood (17,18). In addition, gray matter volume increases in the frontal and parietal lobes throughout childhood and puberty, and then it decreases progressively (19,20). Brain areas subject to myelination show an increase in white matter volume (21). It is important to note that pruning and myelination modifications are directly associated with changes in gray and white matter volumes in addition to alterations in synaptic connectivity (19,22). These structural changes are related to

changes in brain function during adolescence. For example, adolescents show some performance deficiencies in cognitive performance when task loads increase. This performance deficit is related to reduced frontal brain activity and a greater involvement of emotional and motivational subcortical regions (23). Teens may display altered striatal responses to rewards. For example, there is an increase in reward-seeking behavior during mid-adolescence, which then decreases progressively into adulthood (24,25). In addition, social interactions increase during adolescence. Rodents and nonhuman primates show more social interactions as well as greater novelty-seeking behavior during adolescence (26,27). These behavioral changes are linked to dendritic pruning in the amygdala, nucleus accumbens, and prefrontal cortex and continued to increase in fiber density between the amygdala and prefrontal cortex into early adulthood (22,26,28,29). A consequence of this important neuronal rewiring during adolescence is high vulnerability to certain environmental factors, such as stress, drugs, infections, dietary deficiencies, inflammation, and more (26).

Enduring Effects of Pubertal Immune Challenge on Brain Function

Pubertal Immune Signals and Maturation of Microglia

The immune system and its cytokine signaling molecules play a key role in neurodevelopment and contribute to synapse formation, refinement, neurogenesis, neuronal differentiation, and response to injury (30,31). For example, both IL-1β and TNFα can inhibit excitatory synaptic transmission (32,33) and are implicated in synapse refinement and plasticity in the cerebellum, hippocampus, and cortex (30). Microglia, immune cells residing in the brain, play a major role in the elimination of certain synapses and in the maintenance of others (34). During synaptic pruning, frequently used synapses are strengthened, whereas scarcely used ones are eliminated (35). In sensory brain regions, synaptic density attains adult levels around adolescence (35,36). The prefrontal cortex, as well, undergoes synapse proliferation during childhood and puberty, followed by stability in synaptic density, and a subsequent postpubertal elimination and reorganization of synaptic connections (10,37,38). During adolescence, activated microglia have ameboid shape and this status is associated with elevated levels of cytokines. The degree of microglial colonization is affected by certain environmental factors (ie, stressors) (39). In response to a stressor, there is activation of the hypothalamic–pituitary–adrenal axis and the sympathetic–adrenal–medullary axis, resulting in the production of glucocorticoids and catecholamines. A wide variety of immune cells express glucocorticoid receptors which bind cortisol and interfere with the function of NF-kB, regulating the production of cytokines (40).

Microglial cells have a long life span and can be activated for a long period of time which often links them to the underlying mechanism of the enduring effects of early-life stress exposure (41). Although activated microglia do not chronically produce cytokines or pro-inflammatory mediators, they overproduce cytokines once triggered by an immune insult leading to the development of neural disorders later in life (42,43). Compared with male rats, females show more activated microglia in the hippocampus, parietal cortex, and amygdala, which makes them more vulnerable to neuroinflammation during puberty (44) and perhaps more susceptible to certain brain disorders later in life.

Enduring Effect of Pubertal Neuroinflammation

Neuroinflammation is characterized by an amplified production of pro-inflammatory cytokines in the brain. When microglia and astrocytes are continuously activated, they can cause neural damage (45,46). Neuroinflammation underlies the development of various neurodegenerative diseases such as Alzheimer's and Parkinson's diseases (47). It also contributes to the development of mental disorders, such as anxiety, major depression, and post-traumatic stress disorder (48). Hence, adolescent exposure to environmental insults such as stress and inflammation can trigger the activation of microglia, leading to short- or long-term changes in immune function and increase in inflammatory cytokines and C-reactive proteins later in life (49,50). For example, in Wistar rats, repeated exposure to a viral mimetic immune challenge during puberty resulted in continued cognitive deficits at postnatal day 80 (51). In addition, long-term anxiety and depression-like behavior are observed in adult male and female mice respectively after pubertal/adolescent exposure to an immune challenge (52). However, the mechanism underlying these enduring effects remains unclear, one possibility could be due to lipopolysaccharide-induced injury to the hippocampus (53). These findings show that pubertal neuroinflammation whether it is acute (lasting for days), chronic (lasting for several weeks), subclinical (asymptomatic), or clinical (symptomatic) may cause permanent impairments in cognitive performance and behaviors. Thus, pubertal exposure to an immune challenge may lead to permanent injuries in specific areas of the brain and to long-term neurological disorders.

Microbiota Development With Emphasis on Puberty/Adolescence

Recent progress in next-generation microbial sequencing technology has allowed us to better understand the composition of the microbiota in the human gut and to investigate its structural changes across the life span (54).

Normal Gut Microbiota

The bacterial composition of infant microbiota is simple and unstable when compared with the adult microbiota which is highly diverse and fairly stable (55,56). Although the gut is not germ-free while in utero, colonization of the infant gut occurs primarily during birth and the early postnatal period. Multiple factors contribute to gut colonization such as the mode of delivery, the place of birth, breastfeeding, and exposure to medication early in life (56). Recent findings show that adolescents have more diverse microbiota compared with adults (57). Adolescents have a higher abundance of *Bifidobacterium* and *Clostridium* compared with adults (57). Interestingly, gonadal steroid hormones cause sex differences in gut microbial composition. The gut microbiome is important for maintaining homeostasis; it is subject to significant shifts in composition and genetic content during critical periods of development and maturation. These changes occur during periods of dynamic brain development and are characterized by sex-specific shifts.

Males and females have distinct nutritional and energetic needs of growth, development, and reproduction which can explain the sex-specific shifts in the composition of the gut microbiome to meet these demands (58). For example, Actinobacteria and Tenericutes phyla and *Allobaculum, Anaeroplasma*, and *Erwinia* genera are more abundant in male than in female mice, whereas *SMB 53* from the *Clostridiaceae* family and three members of family Lachnospiraceae are more abundant in female than in male mice (58,59). However,

castration eliminates sex differences in intestinal microbiota of adult mice (60). It is unclear whether hormonal fluctuations during adolescence and their consequences on the microbiota of females and males contribute to the sex differences in the vulnerability to various disorders between males and females. It is known that autism and schizophrenia are more prevalent in males (61), whereas mood disorders and inflammatory bowel syndrome are more frequent in females (61,62). The immaturity of gut microbiota during adolescence could be vulnerable to environmental stressors. Hence, stress, infection, the use of antibiotics, poor diet, and inflammation can result in dysbiosis of the gut microbiota and may predispose the subject to brain disorders and psychiatric illnesses later in life (63,64). While the gut microbiome remains stable through adulthood, further changes in the microbiota occur in elderly individuals. Inadequate age-related changes in the microbiota may lead to a reduction in microbial diversity leading to inflammation ("inflammaging") and neurodegenerative diseases (65,66). Consequently, adolescence could be a time for crucial intervention to prevent microbial dysbiosis and optimize brain development and mental health later in life.

Microbiota and Neurodevelopment

The intestinal microbiota can influence the shaping of neural networks during neurodevelopment. For example, remodeling of synaptic connections and of neuronal brain circuits can be attributed to bacterial-derived molecules and impact neuronal function and behaviors (67). Work by Sudo and coworkers revealed an exaggerated stress response in germ-free mice or completely sterile mice when compared with specific pathogen-free counterparts (68) that have a normal gut flora. Remarkably, anxiety-like behavior in germ-free mice (sterile gut) can be reverted by conventionalization with specific pathogen-free microbiota. This effect is observed only in young mice but not at adult age (67,69) which highlights the key role of microbiota during neurodevelopment. Additionally, several proteins implicated in neuronal survival, differentiation, growth, synaptic plasticity, synaptic vesicles endocytosis, and synaptogenesis are expressed differently in germ-free mice. Although whole brain volume is not different in germ-free mice, they display larger amygdala and hippocampus volumes when compared with mice with conventional gut microbiota. These structural differences may be due to alterations in dendritic density and dendritic extensions and could be associated with neuropsychiatric disorders ranging from autism spectrum to anxiety disorders. Consequently, microbial alteration early in life can be associated with a number of neurodevelopmental disorders.

Microbiota and Stress

Stress can alter the gut microbial composition along the gastrointestinal tract. It favors the colonization by pathogenic bacterial species such as *Citrobacter rodentium* and increases cytokine concentration. Stress-induced gut dysbiosis may be due to alterations in the intestinal secretory IgA (70), leading to a dysfunctional gut–brain axis. Stress-induced activation of the HPA axis can affect thegut motility (71) and disrupt colonic homeostasis. The integrity of the intestinal barrier can also be compromised during stressful periods (72). However, exposure to probiotics can mitigate stress-induced activation of the HPA axis and intestinal permeability. For example, the probiotic *Lactobacillus helveticus R0052* and *Bifidobacterium longum R0175* can improve tight junction integrity in the colon of adult stressed mice and reduce bacterial translocation (73). These findings show that stress can cause a dysbiotic microbiota, which in

turn can modulate brain biochemistry and mental health (74,75). Gut dysbiosis and age-related disorders with focus on neurodegeneration Because many neurodegenerative diseases start with enteric symptoms, gut dysbiosis is thought to be an important factor contributing to the initiation of these diseases with robust implication of the gut–brain axis (76).

Neurodegenerative diseases include disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and amyloid lateral sclerosis (ALS). Older patients with neurodegenerative diseases show remarkable changes in their microbiota structure. For example, PD patients display less *Prevotellaceae* and anti-inflammatory butyrate-producing bacteria such as *Roseburia* and *Faecalibacterium* spp. and an increase in *Enterobacteriaceae* and pro-inflammatory *Proteobacteria* spp. In comparison to healthy aged subjects, *Prevotellaceae* are known to play a role in the protection of the intestinal barrier by producing mucin, whereas *Enterobacteriaceae* are associated with unstable posture (77,78). Moreover, PD patients display less short-chain fatty acids (SCFAs) as well as reduced concentration of butyrate involved in the protection of dopaminergic neurons (79). Interestingly, fecal microbiota transplant or transplantation of fecal bacteria from healthy donors into the intestine of a diseased recipient may help in the recovery and reduces PD symptoms in human patients as found per a single study case (80). However, transplantation of fecal samples from human PD patients into germ-free mice intensifies alpha-synuclein expression and leads to motor dysfunctions, while mice humanized with microbiota from matched healthy controls did not develop motor impairment (81). These findings suggest that the gut microbiota is directly related to the physiological symptoms of PD. Similarly, AD patients also display gut dysbiosis. AD patients have more gram-negative bacteria, which causes a disruption of the mucosal barrier. In addition, bacteria-producing amyloid β such as *Bacillus subtilis*, *Klebsiella pneumonia*, *Mycobacterium* spp., and *Streptococcus* spp. are further encountered in AD subjects (82). In AD patients, anti-inflammatory taxa (ie, *Eubacterium rectale*) are less abundant in the feces of participants, whereas pro-inflammatory taxa (ie, *Escherichia* and *Shigella*) that are linked to pro-inflammatory cytokines and amyloid deposition in the brain are more common (83). Together, these findings emphasize the important association between gut dysbiosis and neurodegenerative diseases and show the potential of targeting the gut microbiota as a therapeutic or preventative option.

Targeting Gut Microbiota in Neurodegenerative Disease and Potential Use of Probiotics

Modulating gut microbiome composition can improve the gastrointestinal barrier and reduce the development of inflammation and microglial activation, revealing a great therapeutic potential for the use of probiotics against neurodegeneration (84). In addition, targeting the microbiota composition can change the integrity of the blood–brain barrier (BBB) via producing different bacterial metabolites such as SCFAs. SCFAs are the main metabolites produced by bacterial fermentation of partially and nondigestible polysaccharides in the gastrointestinal tract; they are a major player in the maintenance of gut and immune homeostasis with anti-inflammatory, antitumorigenic, and antimicrobial effects properties (85). These molecules can be targeted by modifying the microbiome composition by using probiotics (86).

Another molecule that can be modified by probiotics is ferulic acid (FA). FA is a phenolic compound found in seeds of plants, vegetables, and fruits. It can be plentifully synthesized by some gut microbiota species such as *L. fermentum NCIMB 5221* (87). It is a reactive oxygen species (ROS) scavenger and has anti-inflammatory properties (88). FA also has curative (able to cure) characteristics in neurodegeneration and cellular aging (89). FA stimulates neural stem cells proliferation by inducing neurogenesis and upregulating BDNF, a nerve growth factor (90). FA prevents Aβ aggregation and reduces Aβ fibril formation leading to a better AD behavioral phenotypes with improvement in memory formation (91). Histamine can as well be targeted by modulating gut microbiota. Different species such as *Lactobacillus*, *Lactococcus*, *Streptococcus*, *Pediococcus*, and *Enterococcus* (92) can secrete histamine. Certain probiotics, such as *L. reuteri*, exert their immunomodulatory activity and suppress TNFα via histamine production which decrease TLR signaling (93,94). Gut histamine is known to have a potential therapeutic effect in neurodegenerative diseases such as AD and multiple sclerosis (95). It acts as a neurotransmitter in the brain in addition to its role in immunomodulation, cell proliferation, and allergic reactions (96). It may induce either pro-inflammatory reactions by inducing allergy or anti-inflammatory responses by acting
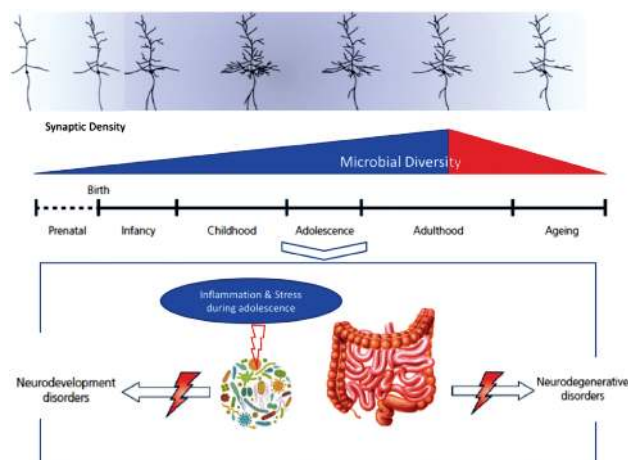
Figure 1. Microbiota diversity and neuronal complexity throughout life span with emphasis on the critical adolescence window. The core microbiota undergoes a dynamic shift across the life span. After initial colonization during infancy and birth, the gut microbiota continues to develop throughout childhood and adolescence. A less diverse microbiota is found in adolescent children in comparison with adults. As adulthood approaches, the gut microbiota stabilizes and becomes more diverse. With aging, microbiota diversity and stability decline. Shaping of the microbiota happens in parallel with neurodevelopment and they have similar critical developmental windows. Synaptogenesis begins at post-birth and synaptic density increases; the maximum density is attained at approximately 2 years of age. Then synaptic refinement and elimination occur in the human brain leading to reach the adult levels by mid-adolescence. During the critical developmental window (adolescence), there is an increased vulnerability to external stressors. Early adolescence is a key phase of neurodevelopment when major neuronal rewiring synaptic pruning or elimination of extra synapses occurs. A consequence of this important neuronal rewiring during adolescence is a high degree of vulnerability to different pathological stressors (inflammation, stress ....). The pubertal vulnerability of the brain to environmental stressors coincides with instability and immaturity of gut microbiota exacerbating the susceptibility of the brain to aberrant changes that may lead to the onset of brain disorders later in life (neurodegenerative or neurodevelopment disorders).

on H4R receptors; distinct responses depend on the type of receptors involved (95,96).

Ghrelin is another biomolecule that impacts neurological function and can be modulated by targeting the microbiota. It acts as a satiety hormone and a neuropeptide in the CNS. It is produced when the stomach is empty to ease the hunger sensation. Ghrelin can regulate inflammation, neuromodulation, and energy homeostasis (97). Gut microbiota dynamics influence ghrelin production; its levels are decreased when the gut microbiota composition is altered (ie, alteration in populations such as *Bifidobacterium* spp.) (98). Ghrelin has some neuroprotective effects and plays a protective role in AD and PD, as it inhibits apoptosis, lessens ROS accumulation, improves synaptic plasticity, decreases the accumulation of Aβ, and reduces inflammation. Exposure to *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium bifidum,* and *Lactobacillus fermentum* for 12 weeks improves the performance on the mini-mental state examination (MMSE), a cognitive test used to assess learning and memory (99).

Concluding Remarks and Future Directions

Puberty/adolescence is a fundamental and critical period of brain and microbiota development. During this period, the brain is extremely vulnerable to certain environmental factors such as stress and immune challenges and can result in enduring stress-induced mental illnesses and neurodegenerative disorders. Given the plasticity of the adolescent brain, the enduring effects of pubertal immune challenge on brain function, the role of the gut microbiota in neurodevelopment, and the important association between gut dysbiosis and neurodegenerative diseases, many preventive measures could be used to improve the resiliency of the teenage brain. For example, we could use a screening procedure to identify individuals at high risk for developing neurodegenerative diseases and expose them to prebiotics (health-promoting nondigestible food ingredients) and probiotics (health-promoting microbial food supplements) early in life to prevent the enduring effects of stress and inflammation. The gut–brain axis is an appealing target for the development of potential therapeutics for neurological diseases. However, further studies are needed to fully elucidate the impact of probiotics during adolescence in the prevention of debilitating diseases.

Funding

Conflict of Interest

None declared.

References

1. Cho I, Blaser MJ. The human microbiome: at the interface of health and disease. *Nat Rev Genet*. 2012;13:260–270. doi:10.1038/nrg3182
2. Cai KC, van Mil S, Murray E, Mallet JF, Matar C, Ismail N. Age and sex differences in immune response following LPS treatment in mice. *Brain Behav Immun*. 2016;58:327–337. doi:10.1016/j.bbi.2016.08.002
3. Schulz KM, Sisk CL. Pubertal hormones, the adolescent brain, and the maturation of social behaviors : lessons from the Syrian hamster. *Mol Cell Endocrinol*. 2006;254–255:120–126. doi:10.1016/j.mce.2006.04.025
4. Romeo RD. Adolescence: a central event in shaping stress reactivity. *Dev Psychobiol*. 2010;52:244–253. doi:10.1002/dev.20437
5. Pignatelli D, Xiao F, Gouveia AM, Ferreira JG, Vinson GP. Adrenarche in the rat. *J Endocrinol*. 2006;191:301–308. doi:10.1677/joe.1.06972
6. Romeo RD, Lee SJ, Chhua N, McPherson CR, McEwen BS. Testosterone cannot activate an adult-like stress response in prepubertal male rats. *Neuroendocrinology*. 2004;79:125–132. doi:10.1159/000077270
7. Romeo RD, Bellani R, Karatsoreos IN, et al. Stress history and pubertal development interact to shape hypothalamic-pituitary-adrenal axis plasticity. *Endocrinology*. 2006;147:1664–1674. doi:10.1210/en.2005-1432
8. Spear LP. Adolescent neurodevelopment. *J Adolesc Health*. 2013;52(2 suppl 2):S7–13. doi:10.1016/j.jadohealth.2012.05.006
9. Burnett S, Sebastian C, Cohen Kadosh K, Blakemore SJ. The social brain in adolescence: evidence from functional magnetic resonance imaging and behavioural studies. *Neurosci Biobehav Rev*. 2011;35:1654–1664. doi:10.1016/j.neubiorev.2010.10.011
10. Huttenlocher PR. Synaptic density in human frontal cortex – developmental changes and effects of aging. *Brain Res*. 1979;163:195–205. doi:10.1016/0006-8993(79)90349-4
11. Miller EK, Cohen JD. An integrative theory of prefrontal cortex function. *Annu Nev Neurosc*. 2001;24:167–202. doi:10.1146/annurev.neuro.24.1.167.
12. Glantz LA, Gilmore JH, Hamer RM, Lieberman JA, Jarskog LF. Synaptophysin and postsynaptic density protein 95 in the human prefrontal cortex from mid-gestation into early adulthood. *Neurosci*. 2007;149:582–591. doi:10.1016/j.neuroscience.2007.06.036
13. Ben-Ari Y. Neuropaediatric and neuroarchaeology: understanding development to correct brain disorders. *Acta Paediatr*. 2013;102(4):331–334. doi:10.1111/apa.12161
14. Thompson BL, Levitt P, Stanwood GD. Prenatal exposure to drugs: effects on brain development and implications for policy and education. *Nat Rev Neurosci*. 2009;10:303–312. doi:10.1038/nrn2598
15. Benes FM. Myelination of cortical-hippocampal relays during late adolescence. *Schizophr Bull*. 1989;15:585–593. doi:10.1093/schbul/15.4.585
16. Zeller NK, Behar TN, Dubois-Dalcq ME, Lazzarini RA. The timely expression of myelin basic protein gene in cultured rat brain oligodendrocytes is independent of continuous neuronal influences. *J Neurosci*. 1985;5:2955–2962.
17. Markham JA, Greenough WT. Experience-driven brain plasticity: beyond the synapse. *Neuron Glia Biol*. 2004;1:351–363. doi:10.1017/s1740925x05000219
18. Fair DA, Cohen AL, Dosenbach NUF, et al. The maturing architecture of the brain's default network. *Proc Natl Acad Sci U S A*. 2008;105:4028–4032.
19. Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW. Mapping cortical change across the human life span. *Nat Neurosci*. 2003;6:309–315. doi:10.1038/nn1008
20. Giorgio A, Watkins KE, Chadwick M, et al. Longitudinal changes in grey and white matter during adolescence. *Neuroimage*. 2010;49:94–103. doi:10.1016/j.neuroimage.2009.08.003
21. Barnea-Goraly N, Menon V, Eckert M, et al. White matter development during childhood and adolescence: a cross-sectional diffusion tensor imaging study. *Cereb Cortex*. 2005;15:1848–1854. doi:10.1093/cercor/bhi062
22. Tau GZ, Peterson BS. Normal development of brain circuits. *Neuropsychopharmacology*. 2010;35:147–168. doi:10.1038/npp.2009.115
23. Liston C, McEwen BS, Casey BJ. Psychosocial stress reversibly disrupts prefrontal processing and attentional control. *Proc Natl Acad Sci U S A*. 2009;106:912–917. doi:10.1073/pnas.0807041106
24. Cohen JR, Asarnow RF, Sabb FW, et al. A unique adolescent response to reward prediction errors. *Nat Neurosci*. 2010;13:669–671. doi:10.1038/nn.2558
25. Van Leijenhorst L, Gunther Moor B, Op de Macks ZA, Rombouts SA, Westenberg PM, Crone EA. Adolescent risky decision-making: neurocognitive development of reward and control regions. *Neuroimage*. 2010;51:345–355. doi:10.1016/j.neuroimage.2010.02.038
26. Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? *Nat Rev Neurosci*. 2008;9:947–957. doi:10.1038/nrn2513

27. Blakemore SJ, Choudhury S. Development of the adolescent brain: implications for executive function and social cognition. *J Child Psychol Psychiatry*. 2006;47:296–312. doi:10.1111/j.1469-7610.2006.01611.x

28. Blakemore SJ. The social brain in adolescence. *Nat Rev Neurosci*. 2008;9:267–277. doi:10.1038/nrn2353

29. Kilford EJ, Garrett E, Blakemore SJ. The development of social cognition in adolescence: an integrated perspective. *Neurosci Biobehav Rev*. 2016;70:106–120. doi:10.1016/j.neubiorev.2016.08.016

30. Boulanger LM. Immune proteins in brain development and synaptic plasticity. *Neuron*. 2009;64:93–109. doi:10.1016/j.neuron.2009.09.001

31. Deverman BE, Patterson PH. Cytokines and CNS development. *Neuron*. 2009;64:61–78. doi:10.1016/j.neuron.2009.09.002

32. Yang S, Liu ZW, Wen L, Qiao HF, Zhou WX, Zhang YX. Interleukin-1beta enhances NMDA receptor-mediated current but inhibits excitatory synaptic transmission. *Brain Res*. 2005;1034:172–179. doi:10.1016/j.brainres.2004.11.018

33. Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF-alpha. *Nature*. 2006;440:1054–1059. doi:10.1038/nature04671

34. Schafer DP, Lehrman EK, Kautzman AG, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. *Neuron*. 2012;74:691–705. doi:10.1016/j.neuron.2012.03.026

35. Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. *Nat Rev Neurosci*. 2009;10:647–658. doi:10.1038/nrn2699

36. Bourgeois JP, Rakic P. Changes of synaptic density in the primary visual cortex of the macaque monkey from fetal to adult stage. *J Neurosci*. 1993;13:2801–2820.

37. Bourgeois JP, Goldman-Rakic PS, Rakic P. Synaptogenesis in the prefrontal cortex of rhesus monkeys. *Cereb Cortex*. 1994;4:78–96. doi:10.1093/cercor/4.1.78

38. Woo TU, Pucak ML, Kye CH, Matus CV, Lewis DA. Peripubertal refinement of the intrinsic and associational circuitry in monkey prefrontal cortex. *Neuroscience*. 1997;80:1149–1158. doi:10.1016/s0306-4522(97)00059-6

39. Gómez-González B, Escobar A. Prenatal stress alters microglial development and distribution in postnatal rat brain. *Acta Neuropathol*. 2010;119:303–315. doi:10.1007/s00401-009-0590-4

40. Padgett DA, Glaser R. How stress influences the immune response. *Trends Immunol*. 2003;24:444–448. doi:10.1016/s1471-4906(03)00173-x

41. Town T, Nikolic V, Tan J. The microglial ""activation"" continuum: from innate to adaptive responses. *J Neuroinflamm*. 2005;2(24). doi:10.1186/1742-2094-2-24

42. Perry VH, Newman TA, Cunningham C. The impact of systemic infection on the progression of neurodegenerative disease. *Nat Rev Neurosci*. 2003;4:103–112. doi:10.1038/nrn1032

43. Bilbo SD, Smith SH, Schwarz JM. A lifespan approach to neuroinflammatory and cognitive disorders: a critical role for glia. *J Neuroimmune Pharmacol*. 2012;7:24–41. doi:10.1007/s11481-011-9299-y

44. Holder MK, Blaustein JD. Puberty and adolescence as a time of vulnerability to stressors that alter neurobehavioral processes. *Front Neuroendocrinol*. 2014;35:89–110. doi:10.1016/j.yfrne.2013.10.004

45. Kettenmann H, Hanisch UK, Noda M, Verkhratsky A. Physiology of microglia. *Physiol Rev*. 2011;91:461–553. doi:10.1152/physrev.00011.2010

46. Streit WJ. Microglial activation and neuroinflammation in Alzheimer's disease: a critical examination of recent history. *Front Aging Neurosci*. 2010;2:22. doi:10.3389/fnagi.2010.00022

47. Streit WJ, Mrak RE, Griffin WST. Microglia and neuroinflammation : a pathological perspective. *J Neuroinflamm*. 2004;1(14):1–4. doi:10.1186/1742-2094-1-14

48. Jones KA, Thomsen C. The role of the innate immune system in psychiatric disorders. *Mol Cell Neurosci*. 2013;53:52–62. doi:10.1016/j.mcn.2012.10.002

49. Bilbo SD, Schwarz JM. Early-life programming of later-life brain and behavior: a critical role for the immune system. *Front Behav Neurosci*. 2009;3:14. doi:10.3389/neuro.08.014.2009

50. Danese A, Moffitt TE, Harrington H, et al. Adverse childhood experiences and adult risk factors for age-related disease:depression, inflammation, and clustering of metabolic risk markers. *Pediatr Adolesc Med*. 2009;163(12):1135–1143.

51. Lukasz B, O'Sullivan NC, Loscher JS, Pickering M, Regan CM, Murphy KJ. Peripubertal viral-like challenge and social isolation mediate overlapping but distinct effects on behaviour and brain interferon regulatory factor 7 expression in the adult Wistar rat. *Brain Behav Immun*. 2013;27:71–79. doi:10.1016/j.bbi.2012.09.011

52. Traslaviña GAA, Oliveira FL De, Franci CR. Early adolescent stress alters behavior and the HPA axis response in male and female adult rats : the relevance of the nature and duration of the stressor. *Physiol Behav*. 2014;133:178. doi:10.1016/j.physbeh.2014.05.031

53. Bannerman DM, Rawlins JN, McHugh SB, et al. Regional dissociations within the hippocampus–memory and anxiety. *Neurosci Biobehav Rev*. 2004;28:273–283. doi:10.1016/j.neubiorev.2004.03.004

54. Forde BM, O'Toole PW. Next-generation sequencing technologies and their impact on microbial genomics. *Brief Funct Genomics*. 2013;12(5):440–453. doi:10.1093/bfgp/els062

55. Fouhy F, Ross RP, Fitzgerald GF, Stanton C, Cotter PD. Composition of the early intestinal microbiota: knowledge, knowledge gaps and the use of high-throughput sequencing to address these gaps. *Gut Microbes*. 2012;3:203–220. doi:10.4161/gmic.20169

56. Borre YE, O'Keeffe GW, Clarke G, Stanton C, Dinan TG, Cryan JF. Microbiota and neurodevelopmental windows: implications for brain disorders. *Trends Mol Med*. 2014;20:509–518. doi:10.1016/j.molmed.2014.05.002

57. Agans R, Rigsbee L, Kenche H, Michail S, Khamis HJ, Paliy O. Distal gut microbiota of adolescent children is different from that of adults. *FEMS Microbiol Ecol*. 2011;77:404–412. doi:10.1111/j.1574-6941.2011.01120.x

58. Jašarević E, Morrison KE, Bale TL. 2016 Sex differences in the gut microbiome - brain axis across the lifespan. *Phil Trans R Soc B*. 371:20150122. doi:10.1098/rstb.2015.0122

59. Org E, Mehrabian M, Parks BW, et al. Sex differences and hormonal effects on gut microbiota composition in mice. *Gut Microbes*. 2016;7:313–322. doi:10.1080/19490976.2016.1203502

60. Yurkovetskiy L, Burrows M, Khan AA, et al. Gender bias in autoimmunity is influenced by microbiota. *Immunity*. 2013;39:400–412. doi:10.1016/j.immuni.2013.08.013

61. Jacquemont S, Coe BP, Hersch M, et al. A higher mutational burden in females supports a "female protective model" in neurodevelopmental disorders. *Am J Hum Genet*. 2014;94:415–425. doi:10.1016/j.ajhg.2014.02.001

62. McHenry J, Carrier N, Hull E, Kabbaj M. Sex differences in anxiety and depression: role of testosterone. *Front Neuroendocrinol*. 2014;35:42–57. doi:10.1016/j.yfrne.2013.09.001

63. Golubeva AV, Crampton S, Desbonnet L, et al. Prenatal stress-induced alterations in major physiological systems correlate with gut microbiota composition in adulthood. *Psychoneuroendocrinology*. 2015;60:58–74. doi:10.1016/j.psyneuen.2015.06.002

64. Desbonnet L, Clarke G, Traplin A, et al. Gut microbiota depletion from early adolescence in mice : implications for brain and behaviour. *Brain, Behav, Immun*. 2015;48(April):1–9. doi:10.1016/j.bbi.2015.07.011

65. Claesson M, Cusack S, O'Sullivan O, et al. Composition, variability, and temporal stability of the intestinal microbiota of the elderly. *Proc Natl Acad Sci U S A*. 2011;108:(suppl 1):4586–4591. doi:10.1073/pnas.1000097107

66. Kumar M, Babaei P, Ji B, Nielsen J. Human gut microbiota and healthy aging : recent developments and future prospective. *Nutr Heal Aging*. 2016;4(1):3–16. doi:10.3233/NHA-150002

67. Tognini P. Gut Microbiota: a potential regulator of neurodevelopment. *Front Cell Neurosci*. 2017;11:25. doi:10.3389/fncel.2017.00025

68. 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(1):263–275. doi: 10.1113/jphysiol.2004.063388

69. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci*. 2012;13:701–712. doi:10.1038/nrn3346

70. Campos-Rodríguez R, Godínez-Victoria M, Abarca-Rojano E, et al. Stress modulates intestinal secretory immunoglobulin A. *Front Integr Neurosci.* 2013;7(86). doi:10.3389/fnint.2013.00086

71. Park A, Collins J, Blennerhassett P, et al. Altered colonic function and microbiota profile in a mouse model of chronic depression. *Neurogastroenterol Motil.* 2013;25(9):733-e575. doi:10.1111/nmo.12153

72. Smith F, Clark JE, Overman BL, et al. Early weaning stress impairs development of mucosal barrier function in the porcine intestine. *Am J Physiol Gastrointest Liver Physiol.* 2010;298:G352–G363. doi:10.1152/ajpgi.00081.2009

73. Ait-Belgnaoui A, Colom A, Braniste V, et al. Probiotic gut effect prevents the chronic psychological stress-induced brain activity abnormality in mice. *Neurogastroenterol Motil.* 2014;26:510–520. doi:10.1111/nmo.12295

74. Lyte M, Vulchanova L, Brown DR. Stress at the intestinal surface: catecholamines and mucosa-bacteria interactions. *Cell Tissue Res.* 2011;343:23–32. doi:10.1007/s00441-010-1050-0

75. Hsiao EY, McBride SW, Hsien S, et al. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell.* 2013;155:1451–1463. doi:10.1016/j.cell.2013.11.024

76. Rao M, Gershon MD. The bowel and beyond: the enteric nervous system in neurological disorders. *Nat Rev Gastroenterol Hepatol.* 2016;13:517–528. doi:10.1038/nrgastro.2016.107

77. Scheperjans F, Aho V, Pereira PA, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. *Mov Disord.* 2015;30:350–358. doi:10.1002/mds.26069

78. Keshavarzian A, Green SJ, Engen PA, et al. Colonic bacterial composition in Parkinson's disease. *Mov Disord.* 2015;30:1351–1360. doi:10.1002/mds.26307

79. Unger M, Spiegel J, Dillmann K, et al. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. *Park Relat Disord.* 2016;32:66–72. doi:10.1016/j.parkreldis.2016.08.019

80. Huang H, Xu H, Luo Q, et al. Fecal microbiota transplantation to treat Parkinson's disease with constipation. *Medicine (Baltimore).* 2019;98(26):e16163. doi:10.1097/md.0000000000016163

81. Sampson TR, Debelius JW, Thron T, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. *Cell.* 2016;167:1469–1480.e12. doi:10.1016/j.cell.2016.11.018

82. Friedland RP. Mechanisms of molecular mimicry involving the microbiota in neurodegeneration. *J Alzheimers Dis.* 2015;45:349–362. doi:10.3233/JAD-142841

83. Cattaneo A, Cattane N, Galluzzi S, et al.; INDIA-FBP Group. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiol Aging.* 2017;49:60–68. doi:10.1016/j.neurobiolaging.2016.08.019

84. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Front Cell Neurosci.* 2015;9:392. doi:10.3389/fncel.2015.00392

85. 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. doi:10.1126/scitranslmed.3009759

86. Westfall S, Lomis N, Kahouli I, Dia SY, Singh SP, Prakash S. Microbiome, probiotics and neurodegenerative diseases: deciphering the gut brain axis. *Cell Mol Life Sci.* 2017;74:3769–3787. doi:10.1007/s00018-017-2550-9

87. Tomaro-Duchesneau C, Saha S, Malhotra M, et al. Probiotic ferulic acid esterase active *Lactobacillus fermentum* NCIMB 5221 APA microcapsules for oral delivery: preparation and in vitro characterization. *Pharmaceuticals (Basel).* 2012;5:236–248. doi:10.3390/ph5020236

88. Trombino S, Cassano R, Ferrarelli T, Barone E, Picci N, Mancuso C. Trans-ferulic acid-based solid lipid nanoparticles and their antioxidant effect in rat brain microsomes. *Colloids Surf B Biointerfaces.* 2013;109:273–279. doi:10.1016/j.colsurfb.2013.04.005

89. Hu CT, Wu JR, Cheng CC, et al. Reactive oxygen species-mediated PKC and integrin signaling promotes tumor progression of human hepatoma HepG2. *Clin Exp Metastasis.* 2011;28:851–863. doi:10.1007/s10585-011-9416-6

90. Yu L, Zhang Y, Liao M, et al. Neurogenesis-enhancing effect of sodium ferulate and its role in repair following stress-induced neuronal damage. *World J Neurosci.* 2011;1(2):9–18. doi:10.4236/wjns.2011.12002

91. Yan JJ, Jung JS, Kim TK, et al. Protective effects of ferulic acid in amyloid precursor protein plus presenilin-1 transgenic mouse model of Alzheimer disease. *Biol Pharm Bull.* 2013;36:140–143. doi:10.1248/bpb.b12-00798

92. Landete JM, De las Rivas B, Marcobal A, Muñoz R. Updated molecular knowledge about histamine biosynthesis by bacteria. *Crit Rev Food Sci Nutr.* 2008;48:697–714. doi:10.1080/10408390701639041

93. Thomas C, Hong T, Pijkeren J van, Et A. Histamine derived from probiotic Lactobacillus reuteri suppresses TNF via modulation of PKA and ERK signaling. *PLoS One.* 2012;7(2):e31951. doi:10.1371/journal.pone.0031951

94. Yahfoufi N, Mallet JF, Graham E, Matar C. Role of probiotics and prebiotics in immunomodulation. *Curr Opin Food Sci.* 2018;20. doi:10.1016/j.cofs.2018.04.006

95. del Rio R, Noubade R, Saligrama N, et al. Histamine H4 receptor optimizes T regulatory cell frequency and facilitates anti-inflammatory responses within the central nervous system. *J Immunol.* 2012;188:541–547. doi:10.4049/jimmunol.1101498

96. Naddafi F, Mirshafiey A. The neglected role of histamine in Alzheimer's disease. *Am J Alzheimers Dis Other Demen.* 2013;28:327–336. doi:10.1177/1533317513488925

97. Gahete MD, Córdoba-Chacón J, Kineman RD, Luque RM, Castaño JP. Role of ghrelin system in neuroprotection and cognitive functions: implications in Alzheimer's disease. *Peptides.* 2011;32:2225–2228. doi:10.1016/j.peptides.2011.09.019

98. Queipo-ortuño M, Seoane L, Murri M, et al. Gut microbiota composition in male rat models under different nutritional status and physical activity and its association with serum leptin and ghrelin levels. *PLoS One.* 2013;8(5):e65465. doi:10.1371/journal.pone.0065465

99. Akbari E, Asemi Z, Daneshvar Kakhaki R, et al. Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: a randomized, double-blind and controlled trial. *Front Aging Neurosci.* 2016;8:256. doi:10.3389/fnagi.2016.00256