

# Article • The Gut-Brain Axis and its Relationship to Attention, Cognition, and Visual Perception

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## ABSTRACT

In recent years, there has been a paradigm shift in conceptual thinking about health and disease, including disorders of the central nervous system. A growing body of literature has demonstrated bidirectional signalling between the brain and the gut microbiome involving the neural, endocrine, and immune pathways. This has become known as the gut-brain axis. Psychological and physical stressors can affect the composition and activity of the gut microbiome, which not only is implicated in disorders of the gut like irritable bowel syndrome, but also appears to play a role in the regulation of emotion, mood, behaviour, attention, and cognition. Studies on neurodevelopmental disorders have shown a relationship between gut dysbiosis and risk of developing disorders like ADHD and autism. As optometrists who understand that the eye is an organ that cannot be viewed in isolation, we are well placed to understand that any changes affecting the neural pathways will also have an impact on how we visually perceive the world.

**Keywords:** ADHD, autism, gut-brain axis, microbiome, visual perception

## Introduction

The worldview of neuroscience has dramatically changed with the discovery of the human microbiome, particularly the gut microbiome.<sup>1</sup> While gut-brain interactions have been studied for decades, the discovery of the gut microbiome has added a component to the complex bidirectional signalling between mind, brain, gut, and its microbiome. There has been a paradigm shift in the understanding of many psychiatric and neurological diseases. Although many of these new concepts are based on experimental findings in mice, initial human studies suggest that there is a relationship between the microbiota in our intestines and brain structure and function.<sup>2</sup>

As behavioural optometrists, we are well placed at the intersection of science and optics, cognitive neuroscience, psychology, and integrative medicine to understand that the eye as an organ cannot be viewed in isolation and that vision is infinitely more than sight. The eye is an extension of the brain as well as a window into the brain. Any changes affecting neural

pathways in the brain will have an impact not only on how we visually perceive the world, but also on how we project ourselves in space and time through visually guided movement. Vision, which is described by Harris<sup>3</sup> as the deriving of meaning and direction of action as triggered by light, emerges from a balanced interplay of neural processes affecting our understanding of where we are placed in space, where objects are located, the clarity of the object, and the ability to interpret through language the object at which we are looking. Accurate interpretation of the image we view requires balance, proprioception, attention, and cognition to derive meaning and to direct our action.

Vision is much more dependent on healthy brain function than on an optically correct set of eyes. No amount of seeing is actually accomplished by the eyes, but rather by the brain.<sup>4</sup> Visual perception is viewed as an information-processing task involving the reception, organization, and assimilation of visual information in the central nervous system

(CNS). Anything affecting the CNS is also by definition going to affect neural pathways, as well as perception and processing.

Patients present with vision problems as well as a conglomeration of physical and mental ailments. As behavioural optometrists, we are concerned with the general well-being of the patient, not just with what they can see. A holistic approach to patient management is essential and may require referral to other health practitioners who specialise in other fields. Neurodevelopmental disorders like autism and ADHD are on the rise, and children with these conditions are likely to present at our practices with visual efficiency and visual processing difficulties. Many of these children have comorbid physical and behavioural difficulties, and a model that incorporates a whole body integrative approach to diagnosis and management helps not only with our understanding of the disorders, but also allows for the best care for our patients.

The case history offers a rich source of information about medical, family, behavioural, and developmental histories that are vital for gathering information to develop a clinical hypothesis. Prenatal, birth, and early childhood histories provide essential information about early life experiences that may impact the development of the individual mentally and physically in later years. Early exposure to stress, environmental toxins, antibiotics, and poor diet may all contribute to developmental deficiencies.<sup>5</sup> It is also during this period that the gut-brain axis develops and establishes itself as the moderator of the immune, endocrine, neural, and metabolic systems in the body. As our food habits and diets change, and exposure to chemicals, antibiotics, and environmental toxins becomes more of a reality, our microbiome modifies too, exerting influence on the brain and, by extension, cognition, perception, attention, and behaviour. It is also of vital importance to glean information on the nutritional history and

diet patterns of the patient. We have become aware in recent years of the increase in food allergies and intolerances that have become part of our culture, from gluten and dairy intolerances to fructose and oligosaccharides; the list is becoming endless. The influence of sugar in our diet has become a focal topic recently, with the increased incidence of type 2 diabetes and other metabolic disorders, as well as the potential negative effect of highly refined foods, food colourants, and sugar on behaviour and cognition in children.<sup>6</sup> The relationship between diet and the microbiome has been established, along with its effect on attention and cognition in ADHD.<sup>7</sup>

There is minimal literature discussing visual perception and the microbiome. The aim of this review is to identify the potential role of the gut-brain-microbiota in the development of cognition, attention, and visual perception, as well as in neurodevelopmental disorders. This could open up new avenues for early and improved intervention, as well as providing an integrative approach to our management of those patients who present daily at our practices.

### **What is the Gut-Brain Axis?**

The gut and the brain communicate bidirectionally through anatomic, endocrine, and immune pathways, establishing what is known as the gut-brain axis. The CNS sends information to the gastrointestinal tract, while changes at the intestinal level can modulate CNS function using similar communication strategies.<sup>8,9</sup> Continuous bi-directional communication between the gut and brain regulates various physiological events and is important for maintaining homeostasis in the body. This axis can suffer alterations, especially in response to stress, and has been implicated in gastrointestinal diseases such as irritable bowel syndrome (IBS) and some CNS disorders such as Parkinson's or Alzheimer's disease, autism, or depression.<sup>10-12</sup>

Recent studies reveal how variations and changes in the composition of the gut microbiota influence normal physiology and contribute to disease. Studies show that the gut microbiota communicates with the CNS through neural (vagus nerve and enteric nervous system), endocrine (cortisol), metabolic (short-chain fatty acids), and immune (cytokines) pathways, thereby influencing brain development and function and behaviour.<sup>12-15</sup> Studies in germ-free animals and in animals exposed to pathogenic bacterial infections, probiotic bacteria, or antibiotic drugs suggest that there is a role for the gut microbiota in the regulation of anxiety, mood, motivation, attention, and cognition.<sup>12,15</sup>

In order to understand the mechanisms involved in the gut-brain axis fully, further explanation of the microbiome and its relationship to the enteric nervous system and the immune and endocrine pathways is necessary. The microbiome and its relationship to cognition, attention, and mood needs expounding, as well as the implications for both neurodevelopment and neurodevelopmental disorders.

## The Gut Microbiota – The Microbiome

The human gastrointestinal tract is inhabited by around 100 trillion microorganisms that contain 150 times as many genes as our genome.<sup>16</sup> A diverse microbial community is present in the gastrointestinal lumen and is in a delicate equilibrium with the host. This group of bacteria, fungi, and viruses is known as the intestinal microbiota.

The gut metagenome is the aggregate of all of the genomes of gut microbiota. In humans, the gut microbiota has the largest number of bacteria and the greatest number of species compared to other parts of the body. Its composition is dependent on age, nutritional state, and the overall health of the host.<sup>17</sup>

Colonization of bacteria begins at birth, when delivery exposes the infant to the

maternal microbiota. After one to two years of age, a complex adult-like microbiota is evident.<sup>18,19</sup> After establishment, the intestinal epithelium and the intestinal mucosal barrier that it secretes have co-developed in a way that is both tolerant and even supportive of the gut flora, and that also provides a barrier to pathogenic organisms.<sup>20,21</sup> Firmicutes and Bacteroidetes phyla constitute the vast majority of the dominant human gut microbiota, with Bacteroides the most abundant but also most variable genus. Bacterial communities tend to fall into three distinct eotypes, defined by their bacterial composition: Bacteroides spp, Prevotella spp, or Ruminococcus spp.<sup>22</sup>

Our relationship with the microbiome is now considered mutualistic.<sup>20</sup> Gut organisms benefit their host by collecting energy from the fermentation of undigested carbohydrates and the subsequent absorption of short-chain fatty acids (SCFAs), acetate, butyrate, and propionate. Intestinal bacteria also play a role in synthesizing vitamin B and vitamin K, as well as metabolizing bile acids, sterols, and xenobiotics.<sup>23</sup> The systemic importance of the SCFAs and other compounds produced by the gut flora allow the microbiome to act like an endocrine organ.<sup>23</sup> The gut flora can also produce a range of neuroactive molecules, such as acetylcholine, catecholamines, gamma-aminobutyric acid (GABA), histamine, melatonin, and serotonin, which is important for regulating peristalsis and sensation in the gut and also plays a role in neurodevelopment, mood, emotion, and attention.<sup>24</sup> Gut microbiota play a crucial role in the development and functionality of both innate and adaptive immune responses, as well as in intestinal barrier homeostasis, nutrient absorption, and gut motility.<sup>25,26</sup> The metabolites derived from the microbiota can be absorbed and transported by blood before crossing the blood-brain barrier.

The microbiota normally has a balanced composition that allows for a healthy gut and

body. A disruption of this balance can result in disease susceptibility.<sup>27</sup> The microbiota composition can be substantially affected by diet, infection, disease, and antibiotics, resulting in instability.<sup>28</sup> Dysregulation of the microbiome (dysbiosis) has been correlated with a number of inflammatory and autoimmune conditions.<sup>29,30</sup> Anomalies in gut microbiota composition have been associated with obesity, type 2 diabetes, inflammatory bowel disease, and allergies.<sup>31,32</sup> There is a growing body of literature focussing on the impact of gut microbiota on brain and behaviour, resulting in the emergence of the concept of the gut-brain axis.<sup>10,27,33</sup> CNS pathologies like autism, anxiety, depression, and alcohol dependence have been related to gut dysbiosis.<sup>34</sup>

### **The Enteric Nervous System**

The enteric nervous system consists of a mesh-like system of neurons that governs the function of the gastrointestinal system. It can operate autonomously and is described as a “second brain.” It communicates directly with the CNS through the parasympathetic (via the vagus nerve) and sympathetic (via the prevertebral ganglia) pathways. The enteric nervous system includes efferent, afferent, and interneurons, which allow it to carry reflexes in the absence of CNS input. The vagus nerve interfaces with the parasympathetic nervous system to increase stomach acidity, gut motility, and digestive juice secretion, and it plays a role in regulating heart rate, sweating, inflammation, neurogenesis, and glucose homeostasis. It is responsible for the coordination of peristalsis; it is also responsible for controlling the anti-inflammatory reflex. Parasympathetic outflows from the vagus nerve inhibit macrophage activation, thereby controlling the immune response. The sympathetic system has an inhibitory effect on the gut, inhibits intestinal motor function, and decreases gut secretions. Under conditions of stress, the sympathetic system is over-activated, and the integrity of

the gut epithelium is destroyed, with resultant gut motility and secretion changes. The stress-induced changes alter the habitat of resident bacteria and promote alterations to microbiota composition.<sup>26</sup>

The enteric nervous system makes use of more than 30 neurotransmitters, including dopamine, serotonin, and acetylcholine, which are produced by the gut flora. In excess of 90% of the body’s serotonin and about 50% of the body’s dopamine lies in the gut. The gut flora also release molecules that can directly activate the vagus nerve, which transmits information about the state of the intestines to the brain.<sup>24</sup> The cholinergic anti-inflammatory pathway that signals through the vagus nerve also affects gut epithelium and flora. Therefore, a bi-directional communication network exists, where the gut flora influence the brain, and the brain influences the gut flora.

### **Immunity and the Microbiota**

The human immune system and the microbiota interact with each other in such a way that each modulates the other. Microbial imbalance is characterized by an increase in potentially inflammatory microbes and is associated with a breakdown in immune system homeostasis.

Pathogenic microbiota and bacterial metabolites are able to stimulate the secretion of pro-inflammatory cytokines (IL-1, IL-6, and IL-18) by intestinal epithelial cells, intestinal dendritic cells, and macrophages.<sup>35</sup>

Microbiota alteration, by disrupting intestinal permeability, may trigger migration of intestinal bacteria into the systemic circulation (microbial translocation), which might contribute to systemic inflammation. This may lead to a breakdown of the blood-brain barrier and to neuroinflammation, which is associated with many neuropsychiatric disorders, including depression, anxiety, schizophrenia, and ASD.<sup>24</sup>

Intestinal microbes regulate the function of macrophages that reside in the lamina propria of the intestine. Normally, these macrophages

produce interleukin (IL)-10 and dampen the production of pro-inflammatory cytokines by dendritic cells. Without the commensal bacteria, there is significantly less production of IL.<sup>10,36</sup> Once the innate and adaptive immune response is disrupted, pro-inflammatory cytokine activity ensues. Increased serum levels of pro-inflammatory cytokines have been implicated in diseases like rheumatoid arthritis, IBD, and multiple sclerosis.<sup>37</sup>

### **The Hypothalamic-Pituitary-Adrenal (HPA) Axis**

The HPA axis is a complex set of direct influences and feedback interactions among three anatomical components. These include the hypothalamus, which secretes corticotropin releasing hormone (CRH); the anterior pituitary, which secretes adrenocorticotrophic hormone; and the adrenal cortex, which secretes cortisol. The HPA axis controls reactions to stress and regulates body processes, including digestion, the immune system, emotion, and mood. Release of CRH is influenced by stress, physical activity, illness, serum cortisol levels, and the circadian rhythm. The HPA axis integrates physical and psychosocial influences to allow an organism to adapt effectively to its environment in order to optimize survival. Increased production of cortisol during stress results in increased availability of glucose to facilitate fight or flight. Cortisol also suppresses the metabolic processes of the immune system to increase the availability of glucose. While glucocorticoids have many useful functions, excessive production is damaging. Bi-directional communication exists between the HPA axis and the immune system. Proinflammatory cytokines are released into the circulation and can pass through the blood-brain barrier, where they can interact with the brain and activate the HPA axis. This in turn modulates the immune response with high levels of cortisol, resulting in decreased immunity and inflammatory reactions and minimizing tissue damage from inflammation.

While the majority of research focuses on the impact of the microbiome on CNS function and stress perception, there is also evidence to show that stress and the associated activity of the HPA axis can influence the composition of the gut microbiota.<sup>38</sup> Studies show that chronic psychosocial stress decreases amounts of good bacteria like *Bacteroides* spp in the gut and increases pathogenic bacteria like *Clostridium* spp.<sup>39</sup>

Chronic stress also disrupts the intestinal epithelium, which usually acts as a barrier, preventing pathologic bacteria, viruses, and fungi from leaking out of the gastrointestinal tract. Pro-inflammatory cytokines can induce epithelial damage, causing leaky gut syndrome. The presence of this foreign material in the bloodstream induces an inflammatory response. Chronic inflammation that has the potential to spread to the joints, skin, thyroid, and brain can have long-term health implications, including anxiety, depression, mood swings, autoimmunity, and changes in cognition, IBS, and allergies.<sup>40,41</sup> A study by Dinan et al.<sup>42</sup> shows that patients with IBS, a chronic inflammatory bowel disorder, have higher basal cortisol levels than healthy controls.

Mice that were subjected to a water-avoidance stress developed intestinal inflammation and alterations in gut microbiota.<sup>43</sup> Maternal separation is an early life stressor that can cause long-term increases in the activity of the HPA axis.<sup>44</sup> The findings of the study by O'Mahony indicate that early life stress not only affects the expression of genes relevant to the stress response, but also has an effect on proprioception, microbiota composition, and glucocorticoid plasma levels.<sup>41</sup>

### **Germ-Free Mice Studies**

Most research on the microbiome has focussed on using the germ-free (GF) animal model. Germ-free mice have no microorganisms living in or on them. They are raised within germ-free isolators to control their exposure

to viral, bacterial, or parasitic agents. GF mice are used in the study of the direct effects of the microbiota on cognitive, emotional, and physiological state of the organism. Studies on immunity and inflammation are effectively done using this GF model. A landmark study by Sudo et al.<sup>45</sup> showed that GF mice have altered HPA axis function, which can be reversed with specific bacterial strains early in life.

Germ-free mice, who lack normal T cells, are immunocompromised with respect to infection but relatively resistant to induction of autoimmunity. When certain bacteria are inoculated into the intestines of the mice, they become more immune to infectious organisms, but they also become more susceptible to autoimmune disease.<sup>46</sup>

Studies show that GF mice display a range of deficits in gut and brain chemistry, neurodevelopmental processes, and anxiety, as well as in social behaviours. Researchers compared control GF mice and mice that were inoculated with gut microbiota to investigate significant differences in cerebral concentration of metabolites known to modulate brain activity. They found that commensal microbiota are not only important for normal immune system function, but also for brain development, and that this regulation has explicit time constraints or developmental windows.<sup>47-49</sup>

### **Neurodevelopment and Microbiome**

The gut microbiota undergoes a period of maturation until the age of 2-3, when an adult-like microbiota structure is established. This occurs parallel to neurodevelopment. During this period, the microbiota is unstable and vulnerable. Any perturbations in the microbiota may potentially impact neurodevelopment, with long-lasting effects into adult life.<sup>50</sup> There appears to be a developmental window during which the gut flora can influence the developing brain.<sup>48,51</sup> The microbiota has been shown to modulate neurotrophins and proteins in brain development and plasticity. Brain-derived

neurotrophic factor (BDNF) is a neurotrophin that is important in promoting neurogenesis and neuronal survival. Gut microbiota appear to influence BDNF. A reduction in the level of BDNF in the hippocampus in GF mice, as well as after the administration of antibiotics, has been shown to contribute to working memory impairment.<sup>52</sup>

Specific gut flora are involved in the production of the neuroendocrine system, which impact mood, cognition, and neurodevelopment: *Lactobacillus* spp and *Bifidobacterium* spp can produce GABA; *Escherichia* spp, *Bacillus* spp, and *Saccharomyces* spp can produce noradrenaline; *Candida* spp, *Streptococcus* spp, *Escherichia* spp, and *Enterococcus* spp produce serotonin; *Bacillus* spp produce dopamine; *Lactobacillus* spp produce acetylcholine.<sup>53</sup>

The dopamine and norepinephrine pathways, which project to the prefrontal cortex and striatum, are responsible for modulating cognitive control of behaviour, motivation, and reward perception. Over 90% of circulating serotonin (5-HT) is produced by the intestine. Serotonin modulates gastrointestinal functions of bowel motor and secretory activities, as well as CNS regulation of mood, appetite, and sleep. Serotonin also has some cognitive functions, including memory and learning. Tryptophan is an essential amino acid and is a precursor to the neurotransmitter serotonin. Gut microbial colonization and development of the gut microbiota occurs in parallel with cognitive development and overlaps with the development of the serotonergic system.

Short-chain fatty acids, such as butyrate, acetate, and propionate that are produced by microbial fermentation of dietary fibre in the gut, are known to have neuroactive properties. In animal studies, propionate has been shown to induce neuroinflammatory processes that cause behavioural alterations. Propionate is also a preservative found in food products that has been shown to exacerbate autism spectrum disorder symptoms.<sup>54</sup>

## Neurodevelopmental Disorders

Neurodevelopmental disorders constitute a group of conditions characterized by developmental deficits of the CNS that usually have an early onset. They vary from mild to severe and lead to impairments in personal, social, academic, and occupational function. Both genetics and environmental factors are believed to contribute to their manifestation.<sup>55</sup>

The two neurodevelopmental disorders that this paper will discuss are autism and ADHD. Both of these have a gut-brain axis connection and appear to be shaped by interplay of both genetics and the environment. They are conditions that are on the rise, and novel insights into the aetiology of their pathologies and potential treatments will shape future management of these disorders. Visual efficiency and visual processing difficulties are frequently observed in this population, as well as cognitive and perceptual motor anomalies.

### Autism and the Gut-Brain Axis

Research into neurodevelopmental disorders like autism highlights the integration of pathways across multiple body systems that together can impact brain, behaviour, and cognition. Autism spectrum disorder (ASD) is a serious neurodevelopmental disorder that affects one in 45 children in the United States, with a similar prevalence in countries around the world. Mechanisms underlying its aetiology and manifestations remain poorly understood. ASD is diagnosed based on the presence and severity of qualitative impairment in social interaction and communication as well as restricted, repetitive or stereotyped patterns of behaviour, interests and activities. Immune dysregulation and gastrointestinal issues are common comorbidities.<sup>56</sup>

Autistic individuals have difficulty processing and responding to information from their senses, with the frequency of visual problems being high. They tend to have difficulty with maintaining eye contact, tracking, and visual

attention.<sup>57</sup> Staring at spinning objects, side viewing, fleeting peripheral glances, difficulties with coordination of central and peripheral vision, and visually defensive behaviours have been noted. Anomalies in visual perception of figure ground, face perception, form constancy, and motion processing have been described.<sup>58,59</sup>

ASD-associated genes encode for features of the immune system, and mutations in those genes are associated with the ASD phenotype. Immune dysregulation and gastrointestinal disturbances in ASD are of interest due to the many studies reporting ASD-associated abnormalities in the peripheral nervous system, enteric nervous system, and neuroimmune system.

There have been a growing number of studies demonstrating the importance of the microbiota-gut-brain axis in the development of autism spectrum disorder. The comorbidity of neurodevelopmental deficits and intestinal symptoms has been investigated. Children with ASD were found to be six to eight times more susceptible to bloating, constipation, and diarrhoea than were control children. The gastrointestinal (GI) symptoms were also strongly correlated with the severity of autism.<sup>10,60</sup> Excessive sensory responsiveness and anxiety were highly associated with GI problems, and each could serve as a predictor for chronic GI problems in ASD.<sup>61</sup>

There are links between certain bacteria from the gut microbiota and ASD phenotypes. The microbiota is well positioned at the interface between genes and environment, as both its composition and function are dependent on genetic background and are shaped by environmental factors, including age, infection, diet, and maternal health. Early life changes in the microbiota can have lasting effects on the health and disease of the individual.<sup>56</sup>

A large percentage of ASD patients have a history of extensive oral antibiotic use, which

disrupts the protective microbiota, creating a favourable environment for colonization by opportunistic pathogens. This can lead to the proliferation of anaerobic bacteria in the gut.<sup>62</sup> These bacteria produce certain metabolites that contribute directly to behaviours observed in autism. *Clostridium tetani* produces a potent neurotoxin, the tetanus neurotoxin, which is transported from the gut via the vagus nerve to the brain, where it disrupts neurotransmitter release, causing behavioural patterns seen in autism.<sup>63</sup> A metabolic product of *Clostridium*, HPHA, depletes catecholamines in the brain, inducing autism symptoms. This supports the correlation between the aetiology of autism and the bacteria *Clostridium*, providing further support for the theory that the integrity of the gut microbiome is closely related to the pathology of autism.<sup>64</sup>

Short chain fatty acids (SCFAs), the critical mediators within the gut-brain axis, can cross the blood-brain barrier and modulate brain activity directly. One study showed that children with ASD had much lower levels of total SCFAs in their stool sample.<sup>60</sup> Deficient integrity of the gut epithelium and increased intestinal permeability are also reported in ASD, resulting in leaky gut syndrome and its associated pathologies.<sup>56</sup>

Researchers have provided evidence to support gut microbiota as a likely contributor to autistic behavioural abnormalities. There are multiple animal studies, and to a lesser extent, large-scale studies with human subjects. Further randomized double-blind clinical studies are needed in order to determine the role of the microbiota-gut-brain axis in ASD. Restoring the balance of the gut offers potential therapeutic treatment options for autistic patients, and further investigation into these options needs to be explored.<sup>65</sup>

### **ADHD and the Gut-Brain Axis**

ADHD is currently the most prevalent neurodevelopmental and neurobehavioral disorder

in childhood, affecting about 5% of children worldwide, although this figure appears to be advancing rapidly. It is characterized by inappropriate levels of hyperactivity, impulsivity, and attention problems. Despite many years of research, its aetiology, diagnosis, and treatment are still poorly understood and remain a challenge.

Several studies support the idea that individuals with ADHD have visual perceptual anomalies compared with the general population. In these studies, a group with ADHD presented with spatial bias as part of impaired perceptual-attentional-action coordination. Adults with ADHD were impaired in a letter cancellation task.<sup>66,67</sup>

Children with ADHD appear to suffer from visual hypersensitivity and photophobia, as well as poor balance performance, postural control, and coordination.<sup>68</sup> Vestibular input and proprioception from eyes, neck, and body is integrated with visual information to form a map that is used to navigate the body successfully in space. This sensory process helps us direct our eyes when we look at things. Children with ADHD who suffer from vestibular or proprioception processing problems and who have difficulties maintaining visual attention will experience visual perceptual difficulties when navigating through space as well as when attempting near-centred tasks.<sup>68,69</sup>

ADHD is diagnosed based on clinical symptoms. Treatment is traditionally based on a combination of psychotherapy and pharmacotherapy. A large percentage (20-33%) of subjects may have an inadequate response to treatment, and pharmacotherapy has been associated with negative side effects and doubtful long-term efficacy.<sup>70</sup>

Family studies suggest a high genetic component for ADHD. A 2- to 8-fold increased risk of ADHD in parents and siblings of children with the disorder has been demonstrated.<sup>71</sup> A dysfunction in neurotransmission (dopamine, noradrenaline, and/or serotonin deficits) plays

an important role in the pathophysiology of ADHD, but precise underlying mechanisms that lead to these neurological alterations have not been adequately identified. Most of the studies performed to decipher the aetiology of ADHD have focussed on the human genome in the risk of developing the condition. Our second genome, the genome of our microbiota, has been overlooked and may play a crucial role in neurotransmission and neuronal plasticity.

The risk of ADHD has been associated with many perinatal factors, including delivery mode, gestational age, type of feeding, maternal health, and early life stressors. This supports the idea that ADHD is a multifactorial disorder triggered by environmental factors in genetically susceptible individuals.<sup>72</sup> Many of these environmental factors have also been shown to influence early gut microbiota composition. The perinatal period is a key period in the establishment of the microbiota of the infant and has been considered a window of opportunity for influencing brain development via modulation of the gut microbiota.<sup>73</sup> Preterm neonates who are at higher risk of developing ADHD and who have more severe ADHD symptoms seem to lack two of the main bacterial genera present in healthy full-term infants. Preterm birth also elevates the risk of infection, which increases the frequency of antimicrobial use, resulting in less-diverse microbiota.

### **Infant Nutrition and Childhood Diet**

The gut microbiota is shaped by infant nutrition in early life, mainly by the type of feeding, the time of introduction of solid food, and the pattern of food introduced. Diet is considered to be one of the most important factors impacting human gut microbiota composition and functionality.<sup>74</sup> It has recently been demonstrated that information regarding dietary-induced changes to microbiota may be transmitted to the brain and result in changes to learning and memory.

A recent study in a large cohort showed that unhealthy maternal and early postnatal dietary patterns elevated the risk of behavioural and emotional problems in the offspring.<sup>75</sup> A shift away from traditional lifestyles has been linked to changes in diet and in the microbiota composition, as well as increased rates of depression and other mental health disorders. Specific diets have been suggested to reduce symptoms of ADHD and ASD, including sugar-restricted, preservative-free, oligoantigenic elimination, and fatty acid supplements. It has also been suggested that deficiencies in certain minerals, such as zinc, iron, magnesium, and iodine, and dietary intake of long-chain polyunsaturated fatty acids (PUFAs) may have an impact on the development and the symptoms of neurodevelopmental disorders in children.<sup>76</sup>

Western diets, which are rich in saturated fats and simple sugars, are known to be contributors to gut dysbiosis. Rural or traditional diets, which are rich in complex carbohydrates, are associated with increased beneficial bacteria species in the gut microbiota. Western diets are high in consumption of omega-6 PUFAs relative to the consumption of anti-inflammatory omega-3s. Decreased consumption of omega-3 PUFAs has been associated with many inflammatory-related conditions, including psychiatric disorders. Omega-3 PUFAs have been shown to be protective against depression, dementia, and age-related cognitive decline.<sup>77,78</sup> Omega-3 levels have been shown to be reduced in children with ADHD, according to a recent meta-analysis.<sup>79</sup> Omega-3 may also regulate the levels of neurotrophins, especially BDNF, as well as HPA axis activity. Dietary supplementation appears to provide modest but significant evidence of clinical efficiency for improving symptoms of ADHD.<sup>79</sup> Diets rich in polyphenols have been suggested to maintain normal brain function.<sup>80</sup> Increasing evidence suggests that food allergies in children and adults are associated with behavioural problems and

neuropsychiatric disorders. Dietary-based treatments have been shown to reduce ADHD-like behaviours.<sup>81</sup>

The impact of refined sugars and food colourants has been investigated in the literature. A number of well-designed studies suggest a potential role of certain nutrients in cognitive functioning in children and adolescents. In several instances, it has been shown that the strongest effect of nutritional manipulations on cognitive efficiency and behaviour are obtained in young people with poor nutritional status. These observations confirm that poor nutritional status is likely to have deleterious influence on both cognition and behavioural adaptation.<sup>6</sup> As yet, there have not been studies that have shown a direct relationship between refined sugar consumption and hyperactivity. However, the impact of diet on the microbiome as a subject is a new and evolving one, and further studies might show a strong relationship between the composition of the gut microbiota and sugar consumption, with its resultant impact on attention and behaviour. Dietary intake has been shown to modulate gut microbial activity. Evidence suggests that sugar substitutes, especially fructose, condition the microbiota, resulting in the acquisition of a Westernized microbiome with altered metabolic capacity.<sup>82</sup>

## Conclusion

This review highlights the integration of pathways across multiple body systems that together can impact cognition, behaviour, and neurodevelopment. It suggests that changes in the microbiome-gut-brain axis may contribute to the various pathologies of neurodevelopmental disorders like autism and ADHD. The extent of the role of the gut microbiome in influencing brain function and behaviour via the gut-brain axis is only recently beginning to be understood and is a new and developing area of interest in the fields of cognitive neuroscience, psychology, neuro-

gastroenterology, and integrative medicine. Any changes affecting neural pathways in the brain will have an impact not only on how we visually perceive the world, but also on how we project ourselves in space and time through visually guided movement. Given our role as primary care practitioners and as optometrists who view the eye, brain, and body in an integrative manner, this burgeoning field of study should be incorporated into our existing body of knowledge.

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Sacho B. The gut-brain axis and its relationship to attention, cognition, and visual perception. *Optom Vis Perf* 2019;7(2):101-12.