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Supplement

Supplementary Paper:

- **Experts' opinion on immunity and nutrition to support key cognitive functions**
- **Evidence on the importance of gut microbiota for the immune system**
- **Immunity as key factors that influence cognitive development on children**
- **The narrative review of recent studies in understanding the relationship between gut (microbiota)-brain axis, nutrition and cognitive function**
- **Exploring key cognitive indicators for practical use by parents in community setting**

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REVIEW

Experts' opinion on immunity and nutrition to support key cognitive functions

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Abstract

The interaction of micronutrients and macronutrients has been shown to have a significant impact on children's cognitive development. Furthermore, proper nutrition helps a child's immune system avoid infection and disease, which can impair nutrient absorption and lead to deficiency. Microbiotas in the gut play critical roles in body physiology, including nutrient absorption, infection resistance and immune system development. Furthermore, it is known that the gut microbiota influences immune cell maturation. Finally, these three factors alongside with sufficient cognitive stimulation are thought to influence neurogenesis and cognitive development. A virtual meeting was held with five invited experts to gain a better understanding of the relationship between nutritional factors, the immune system and cognitive development.

Keywords: nutrition, gut microbiota, immune system, cognitive development

Introduction

Cognition is a complicated concept that encompasses a range of thought processes through which an individual registers, encodes, selects, maintains, transforms, stores, and retrieves information.[1] According to Antony and his colleagues, cognition is defined as the capacity to think, learn and remember; as a result, it provides the foundation for an individual's capacity for perception, reasoning, creativity, and problem-solving and possibly intuition as well.[2] The term "cognition" refers to a wide range of mental processes, including memory, attention and processing speed.[3] Cognitive assessment (or intelligence testing) is used to determine an individual's general thinking and reasoning abilities, which are also referred to as intellectual functioning or IQ. Intelligence testing can evaluate various aspects of your child's cognitive ability. The Wechsler Intelligence Scale for Children and the Sandford-Binet are the most commonly used tests for the Intelligent Scale for Children.[4,5]

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It appears that failing to optimize brain development early in life has long-term consequences for education, job prospects and adult mental health.[6] Among the numerous factors affecting early brain development, three stand out as having particularly profound effects: provision of optimal nutrition, reduction of toxic stress and inflammation and the presence of strong social support and secure attachment.[7]

Normal brain development requires appropriate nutrition. Childhood and early childhood are sensitive and rapid periods of brain development that coincide with the emergence of nearly all cognitive, behavioral and social-emotional functions. This is why nutrition is critical during pregnancy and infancy when the brain is forming and laying the groundwork for developing cognitive, motor and socio-emotional skills throughout childhood and adulthood.[8] Nutritional status also plays a significant role in immune competence: undernutrition, which impairs immune function and suppresses immune functions critical for host protection, can be caused by insufficient intake of energy and macronutrients and/or specific micronutrient deficiencies.[7]

Immune cells and molecules are required to shape the nervous system's circuitry and regulate its activity. During the neuronal activity, classical inflammatory cytokines such as interleukin (IL)-1b and tumor necrosis factor (TNF) are released and play a critical role in regulating synaptic transmission strength. The immune system function is critical for normal nervous system function on a systemic level. Immune system dysfunction impairs cognition and neurogenesis.[9] Recent studies also indicate that gut microbiota has a significant role on immune function and also brain development. The gut microbiota is indispensable to human health throughout the lifespan. Early-life exposures [mode of delivery (maternal microbes); infant diet (selective substrates); antibiotics (selective killing); probiotics (selective enrichment); and physical environment (environmental microbes)] result in colonization of gut microbiota, which contributes to the development of the immune system, intestinal homeostasis and host metabolism. A growing number of diseases are associated with gut microbiota disruption, including inflammatory bowel disease, necrotizing enterocolitis, diabetes, obesity, cancer, allergies and asthma.[10-12]

In community setting, detection and screening of inappropriate cognitive development are important, in which parents will play significant role. Therefore, it is important to have simple description and assessment on key parameters on cognitive function that can be easily use by parents or caregivers. There is also a need to provide a framework to show the important interrelation of nutrition, gut microbiota, immune system and cognitive development to optimize child growth and development that can be easily understand and communicated by health care professionals in daily practice to educate the parents.

A multidisciplinary expert meeting is needed to contextualize the important cognitive parameters for community and the interrelation framework of cognitive influencing factors, namely nutrition, gut microbiota and immunity.

Methods

There were five experts with different disciplinary involved in the discussion in December 2021. Two experts were pediatrician specialist (growth, development and social; allergy and immunology), one expert was clinical nutritionist, one expert was child and adolescent psychiatrist, and one expert was doctor in neuroscience. All experts had more than ten years of work experience in their respective field and were mainly academicians and medical practitioners.

The meeting was performed online via Zoom meeting platform and the discussion was conducted in two sessions. The first session was held on 2 December 2021 with the aim that experts have the same understanding of the relationship between nutrition, immunity and cognitive development through presentations of key references by each of the experts. The second session was conducted in 15 December 2021 as polling session using AhaSlides platform to have a conclusion on the key nutrition to be informed to public and parameters of cognitive development that will be easily understood and implemented by the parents or caregivers. With AhaSlides, each expert can give

simultaneous input on the most important key nutrition and key cognitive parameters and most commonly mentioned results were shown real-time.

The expert meeting was recorded, transcribed in verbatim and analyzed by the authors.

Results

From the discussions that have been carried out, all experts agree there are 3 factors that influence cognitive function and its development in children. These factors include the followings.

1. Key nutrients to support immunity and cognitive development

Optimal brain development during the prenatal period and the early years of life is contingent upon providing adequate amounts of critical nutrients during critical time periods. These times correspond to when specific brain regions are undergoing the most rapid development and have the greatest nutrient requirements.[7,13] These periods of maximum growth are also the most detrimental when a specific nutrient is deficient, particularly one that is required for basic neuronal/glial metabolic processes (e.g., protein, iron, glucose). Supplementation of a deficient nutrient after these critical developmental windows has passed typically results in incomplete recovery of the brain insult, increasing the risk of long-term neurodevelopmental deficits.[7]

Nutrition optimal for the best immunological outcomes would be nutrition that supports immune cell functions, allowing them to initiate effective responses against pathogens but also to resolve the response rapidly when necessary and avoid any underlying chronic inflammation.[14] During this period, major neurodevelopmental processes such as synaptogenesis, neurotransmitter system organization, and the onset of myelination occur, most notably in the hippocampus, which serves as the central processing area for declarative learning and memory, the visual system, and the auditory system.[15]

While all nutrients are necessary for brain development, certain nutrients (for example, protein, long-chain polyunsaturated fatty acids (LCPUFAs), iron, copper, zinc, iodine, folate, choline and vitamins A, B6 and B12) have a greater impact early in life and during critical or sensitive periods for neurodevelopment.[6,16] Nutritional deficiency timing has been shown to have a significant effect on both morphological and neurochemistry and neurophysiology brain development and has been validated through successful nutritional intervention studies in humans that result in beneficial neurobehavioral outcomes.[7,8,17-19] Certain micronutrients and dietary components play critical roles in the development and maintenance of an effective immune system over the course of a person's life, as well as in the reduction of chronic inflammation. For instance, the amino acid arginine is required for macrophages to produce nitric oxide, and the micronutrients vitamin A and zinc regulate cell division, making them necessary for a successful proliferative response within the immune system.[14] It is well established that malnutrition impairs immune function, whether caused by food shortages or famines in developing countries or as a result of malnutrition. The degree of impairment that results will vary according to the severity of the deficiency, the presence of nutrient interactions, the presence of infection, and the subject's age.[14]

Provision of nutrients is only one facet of the equation. The recipient's metabolic state, which may include illness and psychological stress, will influence how growth factors are regulated and nutrients are utilized. Thus, stress-related factors are also critical in determining the effectiveness of nutritional therapy in promoting brain growth.[7] Additionally, nutrition in early life (including breastfeeding and diet at one year) was associated with adolescents' cognitive performance, particularly on more fundamental cognitive tasks.[13]

The key nutrition to support brain development

Nutrition, health and stimulation are all known to improve children's quality of life.[20] Empirical evidence has emphasized the importance of cognitive stimulation at home, particularly in assisting children's cognitive development during

their first years of life. A low-cost home activity, such as storytelling, singing or playing with household items, can provide children with experiences that promote their early development stages.[21,22] Nutrition is recognized by all authorities as being of the utmost importance; however, it cannot be reduced to a simple discussion of micronutrients; rather, sufficient macronutrients are essential in order for micronutrients to be absorbed. DHA, folic acid, vitamin D, prebiotics and zinc are just some of the different kinds of nutrients that are mentioned by the specialists as being essential for the development of the brain. These nutrients play an important part in the development of the brain and myelination, as well as in maintaining a child's overall health, which is necessary for optimal brain development. These stand out nutrients are generally recognized as important nutrients that the general public, parents, and caregivers ought to be informed about.[23]

2. The role of microbiota on immunity and cognitive development

Important functions of the immune system include the detection and defense of the host against pathogens and other harmful threats, as well as the destruction of tumor cells. Mucosal tissue, which provides protection against the external environment, is the most important and largest immune component in the body. It is believed that early intestinal exposure to specific microorganisms reduces the incidence of inflammatory, obesity, autoimmune and atopic diseases.[18,24,25]

The microbiota plays an essential part in the stimulation, maturation, and operation of the immune system of the host. The immune system is made up of an intricate network of innate and adaptable components that are endowed with an extraordinary capacity to adapt and react to a wide variety of threats.[24]

The fetal gastrointestinal tract is believed to be sterile, with the first exposure of the immune system to commensals occurring during the passage through the birth canal and the interactions establishing the long-term mucosal and systemic immune tone.[10] However, one of the studies used super-resolution scanning electron microscopy to identify bacteria-like structures in fetal meconium of terminated pregnancies and discovered a limited number of *Micrococcaceae* and *Lactobacillus* bacteria in the fetus' intestines, which contribute to prenatal immune priming.[26] The earliest colonizing bacteria, such as *Escherichia* and *Enterococcus*, which are facultative aerobes, eventually establish an anaerobic environment. This permits the transition to obligate anaerobes, such as *Firmicutes* such as *Clostridia*, *Bacteroidetes*, and especially Bifidobacteria.[24]

On the other hand, colostrum and breast milk contain live microbes, metabolites, IgA, immune cells and cytokines, which work together to shape the breast-fed infant microbiota and the host's response to these microbes, as well as to promote the expansion of specific microbiota constituents such as *Bifidobacterium*.[10,26] These initial colonizing species are now recognized as a pioneer microbiome, one that educates the developing immune system and provides favorable conditions for colonization by subsequent microbes by producing an anaerobic environment, favorable substrates for bacterial growth and protection from the systemic immune system.[10,27]

Recent research has demonstrated that the gut microbiota, which contains more than 100 trillion microorganisms and three times the number of human genes, is critical for human health; manipulation of the intestinal microbiota can alter the release of neuroactive metabolites, which affect brain health.[28, 29] Numerous preclinical and observational studies have established that gut dysbiosis causes increased intestinal permeability, which is associated with neuroinflammation and cognitive decline.[30,31]

There is an increasing body of evidence that altering the microbiome can have an effect on the brain and behavior. Numerous studies have shown that mice fed a high-sucrose diet had significant difficulties with cognitive flexibility, working memory and the development of a spatial bias early in long-term memory training. Numerous changes in the microbiome were observed in both the high-sucrose and high-fat groups, but the high-sucrose group demonstrated more significant changes. Increased *Clostridiales* and decreased

Bacteroidales were associated with poorer performance in reversal trials assessing cognitive flexibility in the high-fat and high-sucrose diet groups. Both *Bacteroidales* and *Clostridiales* exhibited progressive changes in cognitive flexibility across diets and relationships and have been linked to autism.[32] In a study of autism and Pervasive Developmental Disorder Not Otherwise Specified (PDD-NOS) patients, the most frequently recruited population was *Clostridiales Ruminococcaceae*, which was also increased in expression in both high-energy diet groups in the current study. *Bacteroides fragilis* treatment improves gut permeability and decreases autism spectrum disorders in a mouse model of maternal immune activation.[28,32-34]

A disruption in the balance of the microbiota increases disease susceptibility. Infection, disease and antibiotics all have the potential to transiently alter the stability of the natural composition of the gut microbiota, thereby affecting the host's well-being and influencing the healthy gut bacteria, resulting in the concept of the gut–brain–microbiota.[35] The gut-brain axis is a complex bidirectional communication system between the gut and the brain that is mediated by hormonal, immunological, and neural signals. Additionally, this is a mechanism by which the gut microbiota may have an effect on neurodevelopmental processes and brain functions. Dysregulation of the gut-brain axis communication is associated with metabolic diseases, psychiatric disorders, and comorbid non-psychiatric disorders. These conditions are frequently associated with changes in the composition or function of the gut microbiota, which may also contribute to the disruption of the molecular dialogue between the gut and brain. The central nervous system (CNS), enteric innervation which includes extrinsic fibers of the autonomous nervous system (ANS) and intrinsic neurons of the enteric nervous system (ENS), the HPA-axis and the intestinal microbiota all contribute to the formation of the gut-brain axis. The HPA-axis is a component of the limbic system and is responsible for the majority of the stress response. Additionally, the HPA-axis controls a variety of bodily functions, including bowel function during digestion.[29,36,37]

Stress and its associated HPA-axis activity can have an effect on the composition of the microbiota. Alterations in the gut microbiota caused by diet-induced increases in bacteria belonging to the order *Clostridiales* and decreases in *Bacteroidales* were both associated with decreased cognitive flexibility, implying that they will have long-term effects on cognitive development.[36]

In clinical practice, dietary interventions (in the form of nutritional supplements or special diets) have frequently been used to restore intestinal eubiosis and to prevent and treat cognitive disorders. Nonetheless, the most promising strategy for reversing gut dysbiosis and preserving cognitive function appears to be probiotic, prebiotic and fecal microbiota transplantation.[38]

3. Role of immunity on cognitive development

Immunity may have an effect on cognitive development either directly or indirectly. A child with a strong immune system will be less susceptible to illness, allowing them to grow and learn more effectively, as well as perform better cognitively. Numerous studies have been conducted on the relationship between the microbiota and the immune system. However, the mechanisms by which the immune system may influence cognitive function remain unknown and lacking in evidence. The nervous system is universally regarded as the body's command center. Sensory organs and peripheral nerve fibers monitor the external environment, while receptors in the brain monitor chemical changes in the internal environment. As a result, the nervous system can be regarded as the master regulator of homeostasis. However, it does not act alone in this capacity. The immune system, via tissue-resident and patrolling immune cells, is also constantly monitoring the internal environment and attempting to maintain overall body balance.[9] These were seminal experiments that revealed the existence of an intricate network of bidirectional communication between the central nervous and immune systems indirectly. Such communication pathways had previously been hypothesized but not

demonstrated.[39] When considering brain/immune interactions, it is necessary to recognize that microglia, a type of immune cell, are also resident myeloid cells in the central nervous system that contribute to homeostasis in physiological conditions. Microglia play a critical role in embryonic development, not only in removing apoptotic debris generated by rapid cell turnover but also in promoting neuronal apoptosis. Another critical function of the microglia is synaptic spine pruning.[9,40]

Microglia are involved in synapse pruning in the hippocampus and barrel cortex during the neonatal period, as demonstrated by electron microscopy and electrical recordings. Additionally, synapses in the lateral geniculate nucleus are engulfed by microglia in a complement-dependent manner. On the other hand, microglia have been shown to induce synaptic formation in the somatosensory cortex during the early neonatal period.[40]

Microglia are classified into three types based on their morphology: resting ramified, activated and amoeboid phagocytic. The amoeboid phagocytic microglia are the predominant type in the perinatal brain. During postnatal maturation, amoeboid microglia differentiate into ramified resting microglia, which persist as a semi-permanent population with a low turnover rate in comparison to peripheral macrophages. They monitor their microenvironment as resting ramified microglia and adapt their morphology and expression of cell surface markers accordingly. They remain dormant until they are activated by injury, infection, or neurodegenerative processes, at which point they transform into amoeboid phagocytic cells.[35,41,42]

Microglia release various cytokines and chemokines upon activation, which contributes to neuropathogenesis in central nervous system inflammation. Microglial activation induced by neurodegenerative stimuli increases the release of nitric oxide and proinflammatory cytokines such as IL-1, IL-6 and TNF-, as well as the expression of major histocompatibility complex (MHC) and co-stimulatory molecules. Additionally, these cells produce free radicals such as superoxide and nitric oxide as a result of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and inducible nitric oxide synthase (iNOS) enzymes. Microglia-derived radicals, as well as their reactive reaction products, hydrogen peroxide and peroxynitrite, have the potential to harm cells and have been implicated in neurological diseases as a cause of oxidative damage and neurodegeneration. Proinflammatory mediators released by microglia appear to be critical contributors to the neurogenesis block, as nonsteroidal anti-inflammatory drug treatment restores hippocampal neurogenesis.[41]

Child's stimulation

During the rapid growth in early childhood, the brain particularly is vulnerable to external factors such as nutritional status, socioeconomic factors, and parent–child relationships.[43] Nutrition plays an important role in cell proliferation and brain growth. Healthy children with adequate nutritional needs have good immune systems and optimal brain development. Psychosocial stimulation, culture and environmental conditions also affect the process of cognitive development.[44,45]

Previous studies shown that a high quality home parenting environment has a continuous positive effect on the cognitive development of children under 5 years old may be because the high-quality home parenting environment can provide children with safe environment, learning support, emotional and verbal responsivity, and sufficient stimulation that are conducive to children's cognitive development.[45-47] Meanwhile, the reasoning ability and depressive symptoms of the mothers, as relevant factors of home parenting environment, also may have an impact on children's early development; however, the negative roles of illness, infection, and poor infant feeding practices will increase the risk of constrained cognitive development in settings with less promotion of development.[45-47]

Key indicators of cognitive development for infants and above 1 year old

Cognitive encompass visual and somatosensory perception, reasoning, memory and learning. Memory aids in the learning, retention, and

reproduction of information. Another critical aspect is attention, an integrated process by which the individual, beginning in childhood, concentrates on information necessary for growth and development. It entails a readiness to respond and an intact capacity to concentrate on a single task while avoiding distraction from other stimuli.

Another critical aspect is attention; it is an integrated process through which the individual, beginning in childhood, focuses on knowledge that is critical for growth and development. It necessitates a state of readiness to respond and the ability to focus on a single item while avoiding other distracting stimuli.

During the first year of life, the child develops the ability to construct mental structures based on expectations and body movements. It strengthens its attention skills even further by identifying and reflecting on novel aspects of its environment and applying them to the testing and organization of knowledge throughout the pre-school years.

Increasing environmental responsiveness, action and motor skills can contribute significantly to the development of the attention system. A lethargic child with delayed motor activity will have fewer opportunities to explore and concentrate on specific items or events. At that age, the operation will be inextricably linked to motor movements. Cognitive development continues as a cycle of concrete operations throughout the school years, with students developing cognitive abilities such as thinking, memory, and language. Several stimuli are appreciated concurrently during this phase, and attention capacities increase with increased understanding and memory, culminating in the development of adult intellect and hypothesized reasoning during adolescence.[1]

A healthy cognitive function is accompanied by a healthy executive function in terms of creativity, adaptability, self-control and discipline. Executive functions are comprised of three abilities: inhibition [inhibitory control, which encompasses self-control (behavioral inhibition) and interference control (selective attention and cognitive inhibition)], working memory (WM), and cognitive flexibility or shifting.[33,48-50] These abilities are critical for mental and physical health, academic and career success, and cognitive, social and psychological development. These abilities also enable us to mentally experiment with concepts, adapt quickly and flexibly to changing circumstances, pause to consider what to do next, resist temptations, maintain focus and overcome novel, unanticipated challenges.[33]

Inhibition

Inhibitory control refers to the ability to exert control over one's attention, behavior, thoughts and/or emotions in order to overcome an internal predisposition or external lure and do what is more appropriate or necessary. Inhibitory control enables us to attend selectively, focusing our attention on what we choose and ignoring other stimuli. Self-control is an aspect of inhibitory control that entails exerting control over one's behavior and emotions in order to exert control over one's behavior. Self-control is about restraining one's impulses and not acting rashly. Another aspect of self-control is the discipline required to stay on task in the face of distractions and to complete a task despite temptations to quit, move on to more interesting work, or simply have a good time. This entails compelling yourself to do something or continue doing something even when you would rather be doing something else and is related to deferring gratification or compelling yourself to forego immediate pleasure in exchange for a greater reward later.[33]

Working memory

Working memory (WM) is the process of mentally storing and manipulating information. There are two types of WM: content-verbal WM and nonverbal (visual-spatial) WM. Working memory is critical for making sense of anything that unfolds over time, as this always requires recalling previous events and relating them to subsequent events. Thus, it is necessary for comprehending written or spoken language, regardless of the length of the sentence, paragraph, or longer. Without WM, the reasoning would be impossible. WM is critical for our ability to see connections between seemingly unrelated things and to disassemble and recombine elements within an integrated whole,

and thus for creativity, as creativity entails disassembling and recombining elements in novel ways. Additionally, WM enables us to consider our remembered past and future hopes when making plans and decisions, rather than just perceptual input.[33]

Cognitive flexibility

Cognitive flexibility includes the ability to shift perspectives spatially or interpersonally. To switch perspectives, we must inhibit (or deactivate) our previous one and load (or activate) a new one into WM. Cognitive flexibility, in this sense, requires and builds on inhibitory control and working memory. Another aspect of cognitive flexibility is the ability to alter our perspective on something (thinking outside the box). Cognitive flexibility also entails the ability to adapt to changing demands or priorities, admit errors and capitalize on unexpected opportunities.[33]

According to Jean Piaget's theory of cognitive development, children progress through four distinct stages of mental development. His theory is concerned with not only how children acquire knowledge but also with the nature of intelligence. First, there is the sensorimotor stage, which lasts from birth to two years of age. Infants and toddlers acquire knowledge during this formative stage of cognitive development through sensory experiences. The interaction of the senses and the environment is the primary intellectual activity here. Children lack the ability to label experiences or to symbolize and thus remember, events and ideas. As a result, they see and feel what is happening but lack the ability to categorize their experiences.[33]

Secondly, there is preoperative stage that ranges between the ages of two and seven years.[33] During this stage, an intuitive mode of thought prevails, which is characterized by free association, fantasy and the creation of unique illogical meanings. Additionally, they frequently struggle with the concept of constancy.

Thirdly, there is concrete operational stage for those between the ages of 7 and 11. This stage marks the beginning of the development of concepts of right and wrong. Typically, these begin with specific acts and gradually become generalized. Finally, there is a formal operational stage for those aged 12 and up. The child progresses from the level of concrete operations to the final stage of formal operations at this stage. Since he is well into the socialized speech phase of language development, he is capable of considering and communicating with others' ideas.[33]

Cognitive parameters

It was proposed that there are eight key parameters of cognitive development that occur from infancy through childhood and that these parameters can be easily communicated to parents and caregivers. The cognitive development selection criteria were chosen based on the cognitive development selection criteria that were agreed upon by the experts. These cognitive development selection criteria were taken from existing references and have been used in child development within the medical field. Logic Reasoning and Decision Making, Problem Solving, Attention and Focus, Critical Thinking, Psychomotor Skills, Memory, Language and Creativity are all aspects of parameters, and they are divided into two categories. Category one is for those aged less than 2 years, and it includes attention, focus and language. Category two is for those aged more than 2 years. In addition, for children older than two years, they include memory, psychomotor, logical and reasoning skills, as well as decision-making.[23]

The relationship between microbiome, immunity and cognitive function

There is a consensus amongst all the experts that even though relationships do exist between nutrition, gut microbiota, immunity and cognitive development, there are few studies and references that explain the interrelationship of those factors as a comprehensive detail.

There are still very limited studies that link nutrition, gut microbiota and immunity to the development of cognitive function in children, despite the fact that it has been demonstrated in a number of journals that a direct relationship exists between these three factors. In this review study,

only the use of animals for research purposes has been conducted up until this point.[23]

Conclusions

There is strong evidence for the role of the gut microbiota in brain function and cognitive function that has come to light recently in research. Although a variety of factors, including health status, can influence the composition of the gut microbiota, diet is widely regarded as one of the most important influences on the human gut microbiota. As a result, all experts agree dietary interventions with the potential to improve cognitive function through neurogenesis must be investigated further.

Author contribution: All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

R.W.B., E.W., and M.S.K. are employees of Danone SN Indonesia. All other authors have no conflict of interest

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LITERATURE REVIEW

Evidence on the importance of gut microbiota for the immune system

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Abstract

Vital to the health of the host is maintaining a delicate balance in the immune system by eliminating harmful pathogens while preserving self-tolerance to prevent autoimmunity. By regulating immune homeostasis, the gut microbiota in the gastrointestinal tract provides vital health benefits to its host. It has been demonstrated conclusively that dysbiosis of these gut microbial communities can cause immune dysregulation and autoimmunity. We attempt to examine the relationship between the gut microbiota and the regulation of the innate and adaptive immune homeostasis, which can influence the development of certain disease. This literature review of recently published research and newly discovered scientific information is intended to increase awareness of the importance of maintaining a microbiota balance in the gut for immune health of the host.

Keywords: gut microbiota, innate immunity, adaptive immunity, immune system, disease

Introduction

The digestive system plays an important role in the human body's physiology and anatomy, to absorb nutrients and maintain immune homeostasis (to protect the body from potentially harmful microbes). It has a dual function that can maximize nutrient absorption while also controlling and organizing mucosal immune responses in the human digestive system.[1] When exposed to many of foreign antigens, the digestive system develops a unique and complex network of immunological and non-immunological mechanisms that act as a mucosal barrier to protect the host from pathogens while also hosting other residents microbes that perform their digestive system functions.[1,2]

The digestive system comprises of gut, organs that produce digestive secretions (liver, pancreas, and gall bladder), as well as the digestant, microflora and immune systems that are associated with it. To contribute to mucosal immune defense, the gut can be divided into three physically distinct components: the intestinal epithelial barriers, the lamina propria and gut-associated lymphoid tissue (GALT). Specialized immune cells in the digestive system promote tolerance for oral antigens (dendritic cells (DCs) and regulatory T cells (TR)). Additionally, secretory IgA on mucosal surfaces can contribute to establishing an anti-inflammatory

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environment by neutralizing immune-stimulatory antigens.[1,3,4] This process will reduce the likelihood of inflammatory responses to potentially harmful stimuli in the digestive system.

The development of the digestive system's microbiome began during the uterine phase and is constantly changing due to various factors such as prematurity, diet, hygiene and the use of medication.[5–7] Maturation of the intestinal immune system in line with the development of the gut microbiome is being observed. In order to activate their ability to ensure proper differentiation and specification, as well as the complete development of adaptive immunity, components of GALT must interact with their gut microbiome.[8,9] As a multifaceted and complex system, the immune system in the digestive system involves the interaction of multiple components, which maintain a state of non-responsiveness to non-pathogenic commensal bacteria, self-antigens and food antigens, while protecting the host against pathogenic organisms and maintaining the integrity of the intestinal mucosa. A disruption in gut homeostasis can lead to persistent or severe gastrointestinal infections, food allergies, celiac disease and inflammatory bowel disease (IBD), among other conditions.[10,11]

The complexity of this system makes it more interesting to discuss because the firm effect mechanism toward the effect of defined gut microbiota and specific immune cell function still need more clarify. In this review, we will discuss the role that the microbiota intestinal system plays in immunity and how it can be affected by both the innate and adaptive immune system pathways.

Methods

This article described the balance of gut microbiota and its correlation with immune system via innate and adaptive pathways that can impact to physical health. This literature review was built by looking for many published relevant articles from electronic databases (ex : Pubmed and Medline) in the last ten years. Variants of “gut microbiota” “innate immunity” “adaptive immunity” “immune system” “disease” were included in the research terms. Further papers were found in English, through manual search from the manual references cited in the corresponding reviews.

The balance of gut microbiota

The term "gut microbiota" refers to a community of microorganisms that are found throughout the entirety of the gastrointestinal tract and which are present in greater numbers than human body cells. Various studies indicate that gut microbiota is directly associated with both the health of the host and the regulation of host immunity, which can influence the immune response to certain diseases. This is because of the diversity of microorganisms, which makes them the most important environmental agent in the human body.[12–15]

Microorganism colonization of mucosal tissues throughout infancy is crucial for the maturity of the host immune system. These episodes in early life can have long-lasting consequences, such as promoting tolerance to environmental exposures or contributing to the development of disease later in life.[13] Due to the fact that bacteria may be isolated from the meconium of preterm infants, the host's exposure to microbiota begins in gestation and expands rapidly after delivery.

Microbiota composition is first defined by opportunistic colonization by the first types of bacteria to which a newborn is exposed. This, along with other environmental factors like food, can considerably influence the subsequent admission of microbial species into the various mucosal niches. Therefore, the mode of delivery and subsequent environmental exposures have a significant impact on the microbiota makeup of infants.[16] *Lactobacilli* are abundant in the microbiome of vaginally delivered newborns throughout their first few days of life.[17] In contrast, the microbiota of newborns whose mothers gave birth by cesarean section is depleted, and there is a delay in the colonization of the *Bacteroides* genus in these infants. On the other hand, these newborns are already colonized by facultative anaerobes, such as species of *Clostridium*.[18] It may be more difficult to establish a stable gut microbiota during an essential period of time for the development of the immune system if fewer early colonizing bacteria, particularly *Bifidobacteria*, are present.[19]

According to research published in 2016 by Odamaki et al.[20] the composition of the gut microbiota shifts with age. They discovered that the composition of the microbiome remained unchanged throughout adulthood until it reaches a point of equilibrium that, so long as it is not disturbed by external factors, can be expected to remain relatively constant throughout adulthood.[21] The phylum *Firmicutes*, which also includes *Lactobacilles* and *Clostridiales*, was found to be the most prevalent in the gut microbiota of adults, whereas the phylum *Actinobacteria*, which also includes *Bifidobacteriales*, was found to be more prevalent in samples from one year old children. After children were weaned, the relative abundance of *Actinobacteria* in their guts decreased, and by the age of three, the children's gut microbiota had developed into something more similar to an adult's gut microbiota.[21]

It has become clear that the balance of the gut microbiota in early life plays an important role in human health, and that its imbalance, also known as dysbiosis, is linked to the development of a variety of diseases. As the relationship between the gut microbiota and a variety of human health issues has become better understood, it has become clear that the gut microbiota plays an important role in human health.[22] Dysbiosis that begins in the infant stage of a person's life has a good chance of persisting into adulthood.[20]

It is of the utmost importance to take into consideration the mechanisms that contribute to the formation and maintenance of a dysbiotic state. ***Infection and inflammation****:* Dysbiosis can happen in inflammation state because it can reduces the ability of the microbiota to provide resistance to colonization by microorganisms that are invading the body. These changes happens by inflammation that was brought on a genetic lack of interleukin-10 (IL-10).[23] ***Diet and xenobiotics:*** Diet can changes composition microbiota that lives in the intestines, significantly impacted both in the short term and the long term. Other factors, such as familial transmission, pregnancy and physical injury, genetics play a role in determining the composition of the microbiota that live in the gut.[23,24] All these factors have significant contribution in maintaining health and stability immune system in gut.

Role of gut microbiota in immunity

The gut microbiota provides numerous benefits and functions to its host, such as digestion, the production of nutrients, detoxification, protection from pathogens and the regulation of the immune system, among others.[25] It is believed that the enormous and complex intestinal microbiota components play a critical role in the immune system, not only in the local intestinal immune system but also in the systemic immune response.[26] Later, these components elicit inhibitory regulatory mechanisms that are intended to maintain both mucosal and systemic immunity in balance. The presence of commensal microbes is a significant factor in the maturation of the immune system.[27]

The GALT protects us from the gut-dwelling microorganisms. The gastrointestinal system consists of the mesenteric lymph nodes, Peyer's patches, and isolated lymphoid follicles in the small intestine and colon, immune cells dispersed across the mucosal lamina propria, and intraepithelial lymphocytes. In contrast, bacteria promote robust immunity, healthy nutrition, systemic antigen tolerance, also known as mucosal tolerance, and other positive consequences. The existence of a complex microbiota is necessary for this immune response to function correctly.[2] The gut microbiota plays a critical role as a regulator in the development and function of both the innate and adaptive immune systems. It is important to understand how it works.[28] The innate immune responses signal the activation of the adaptive immune responses, and both work in tandem to eliminate the pathogens.[29]

Innate immunity

The innate immunity is a rapid and non-specific response to an infectious pathogen. Additionally, it is called the initial line of defense.[29] Physical barriers like the skin and mucous membranes, chemical barriers like enzymes and antimicrobial proteins, and innate immune cells like granulocytes, macrophages and natural killer cells

all contribute to the non-specific protection afforded by the innate immune system.[30]

Innate immune cells in GALTs identify pathogens non-specifically, begin an innate immune response, and deliver antigens to activate the adaptive immune system farther downstream. Moreover, GALTs are crucial for maintaining immunological tolerance to commensal bacteria. The dual function of GALTs is crucial for maintaining the equilibrium between the gut microbiota and the human immune system.[31] Stanisavljevic et al.[32] demonstrated that variable baseline levels of pro-inflammatory cytokines produced by GALTs from different mouse strains with distinct species of gut microbiota may contribute to the vulnerability to autoimmune disorders.

Recent investigations have demonstrated that memory is present not just in T cells, but also in monocytes/macrophages and natural killer (NK) cells.[33] Gut innate immunity is initiated by a single layer of intestinal epithelial cells (IECs) directly exposed to luminal contents and microbial metabolites.[28] Peyer's patches, which are responsible for the production of antimicrobial peptides, are activated by the gut commensal flora through the toll-like receptor (TLR) pathway. It is possible that inhibiting molecules related to the TLR pathway will make a person more susceptible to infection by enteric pathogens.[34]

In the gut, commensals produce short-chain fatty acids (SCFAs) such as butyrate, acetate and propionate. Commensals are microorganisms that help the body fight infection. When SCFAs are present in the body, they increase the number of myeloid precursors and provide protection against infection, which is necessary for immune homeostasis. This finding supports the notion that the microbiota can function as an epigenetic regulator of host physiology and as an energy source for the intestinal epithelium, both of which can influence immune responses.[31,32,35] The majority of the bacteria that produce butyrate, including *Bacteroidetes* and *Clostridia*, are anaerobes, and the low levels of oxygen found in the colon provide them with an ideal environment to thrive in.[33] SCFAs suppress inflammatory responses in human monocytes by activating pertussis toxin-sensitive (PTX-sensitive) G protein-coupled receptors (GPCRs), which results in the release of the anti-inflammatory cytokine IL-10 and the release of prostaglandin E2, both of which limit inflammatory responses.[36]

By increasing the expression of antimicrobial peptides, IL-22, IL-17 and IL-10 while simultaneously activating the inflammasome, the gut microbiota hinders the colonization and growth of invading pathogens.[37] Yao et al.[38] reported the immunological memory profile and protective actions of alveolar macrophages following infection with a respiratory virus.

Induction of immunological memory by commensal bacteria may be influenced by host genetic differences in microbiota makeup as well as pathogen exposure. While the process of intrinsic memory development should be viewed as an effective method for enhancing the host's defense, it must be carefully managed to prevent negative side effects while staying useful to the host.[39]

Adaptive immunity

Instead of being generalized to any pathogen, adaptive immunity is highly specific to a single pathogen and provides long-term protection against that pathogen. Adaptive immune responses, which are a form of defense, eliminate invading infections and any hazardous compounds they produce. Because these reactions are destructive in nature, it is crucial that they are solely specific to molecules that are foreign to the host and not to molecules that are native to the host. White blood cells known as lymphocytes, B cells and T cells are responsible for adaptive immune responses. Antibodies (immunoglobulins) are secreted by activated B cells to prevent pathogens from attaching to receptors on host cells. In response to microbes hiding inside host cells, T cells react by either killing the infected cells or assisting other cells in eliminating the microbes from the body.[29] Collaboration between commensal microbiota, intestinal adaptive immune cells, and secretory IgA facilitates tolerance for symbiotic bacteria and a mutualistic interaction between the host and the microbiota (sIgA). This ultimately leads in the preservation of intestinal homeostasis and the

capacity to mount an effective immune response against invading pathogens.[40]

Immunoglobulin (Ig) A-secreting plasma cells make up the majority of gut-associated B cells found in Peyer's patches. IgA, an immunoglobulin produced by the adaptive immune system, contributes to the diversification and balance of gut microbiota, which is necessary for immune homeostasis to be maintained.[41] Thus, the gut microbiota is a major driving force for mucosal IgA production.[42] Pathogens typically engage with antigen-presenting cells and trigger adaptive B cell and T cell responses, resulting in the generation of antigen-specific sIgAs, after entering the mucus layer.[43,44]

Adaptive T cells are the primary defenders of the host's homeostasis against immune-mediated inflammatory diseases in cellular immunity. The intestinal microbiome may promote the differentiation of T cells to initiate adaptive immune responses rapidly in response to signals from the intestinal lumen environment.[45]

The microbiota of the intestines plays a crucial role in the development of $CD4^+$ T cells both inside and outside the intestine. $CD4^+$ T cells are essential to the adaptive immune system. $CD4^+$ T cells can differentiate into four major subtypes upon stimulation: T helper 1 (Th1), Th2, Th17 and regulatory T cell (Treg). The regulation and equilibrium of T-cell subtypes are crucial in determining a person's health status. Th1 cells, for instance, are essential for the host's defense against intracellular microbial infection, whereas Th2 cells are essential for eliminating parasite infections. Th1 and Th17 responses have been associated with autoimmune diseases, whereas Th2 responses have been linked to allergic reactions.[42] *Bacteroides fragilis, Bifidobacterium longum* and *B. pseudolongum* can increase T cells and then triggers Th1 responses.[46,47] There is also a direct connection between *B. adolescentis*, a common commensal bacteria found in the human colon, and the production of homologous Th17s.[48]

Regulatory T cells (Tregs) are a crucial mediator of immune tolerance; their dysfunction can result in autoimmune diseases.[49] Tregs target the majority of immune cells to induce antigen-specific or non-specific immune tolerance via contact-dependent mechanisms, immunomodulatory cytokines (e.g., IL-10, TGF- and IL-35), or metabolic disruption of target cells.[50] *Clostridium* species induce both healthy and inflamed colonic Tregs. Other researchers have discovered that any of the five Bacteroides (*B. intestinalis, B. caccae, B. thetaiotaomicron, B. vulgatus, and B. massiliensis*) effectively induces colonic T regulatory cells (Tregs).[51,52] The development of dysbiosis and intestinal immunological abnormalities results in the development of chronic local and systemic inflammatory and autoimmune diseases.[40]

Evidence of gut microbiota influence on health and diseases

As previously stated, the intestinal microbiota plays an important role in the immune system. When the microbiota is complete and diverse, it can affect host homeostasis and make the host less susceptible to disease. The gut mucosal immune system functions normally, differentiates, functions and regulates itself as a result of proper bacterial colonization. Based on this mechanism, we may have a different perspective on microbiota and their impact on host health.[53]

Inflammatory bowel disease (IBD)

In susceptible hosts, an aberrant mucosal immune response to a commensal microbial antigen might generate an inflammatory bowel disease (IBD). It is determined by the genetically determined innate immunological responsiveness of intestinal tissue to components of the commensal microbiota, and following this process, T cells and B cells create IgG antibodies that can cause chronic inflammation in intestinal tissue and can be prevented by removing the commensal microbiota from our bodies.[53] In addition, numerous studies have demonstrated that specific gut microbiota drive the differentiation of Th17 cells that secreted IL-17 and IL-22 which have really strong impact in stimulating immune damage and autoimmune

disease by producing a potent pro-inflammatory factor.[54]

In contrast, intestinal bacteria can increase anti-inflammatory activity. *Clostridium spp, B. fragilis* and *F. prausnitzii* play a significant protective role in IBD.[55–57] Finally, an unbalanced level of several cytokines, dysbiosis from gut microbiota and impairment of the mucosal barrier can lead to mucosal inflammation and potential IBD progression.[58]

Diarrhea

Dysbiosis characterized by pathogen dominance is prevalent in diarrheal people and animals, and the interaction with gut microbiota is currently attracting a great deal of research in the field of diarrhea. Invading pathogenic bacteria inhibit the growth of normal bacteria, which results in a decrease in the total number of helpful bacteria in the digestive system.[59] Then, pathogen-produced toxic substances further cause abnormal gut function and immune responses, leading to the occurrence of diarrhea.[60] *Escherichia coli* (*E. coli*), *Shigella*, *Salmonella*, *Campylobacter*, *Clostridium difficile* (*C. difficile*) and *Aeromonas* are mainly considered to be the pathogens of diarrhea.[61]

According to the findings of a study conducted by Qin et al.[62] the abundance of *E. coli* and *Enterococcus* in children suffering from diarrhea was found to have a positive correlation with serum levels of IL-1, IL-6, IL-17 and TNF-⟨. On the other hand, the findings showed that the abundance of *Bifidobacterium* and lactic acid bacteria had a negative correlation with serum levels of IL-1, IL-6, IL-17, and TNF-⟨. Based on these findings, it was hypothesized that alterations in the composition of the gut flora could affect the release of inflammatory factors in vivo.[62]

Atopy and asthma

Atopy and asthma are complicated disorders that are influenced by the populations of microorganisms that populate the gut and respiratory systems. These communities are influenced by a range of environmental factors, including food, the administration of antimicrobials and early life exposures to local microorganisms.[63] According to the findings of a number of studies, early life is the most important period during which a microbiota dysbiosis in the gut may lead to the development of a number of respiratory diseases, because the gut microbiota has a significant influence on immune cell maturation and resistance to pathogens.[64] Colonization by *Clostridium difficile* at one month of age was associated with wheeze in the first six to seven years of life and asthma at six to seven years of age.[65]

Decrease in *Lachnospira* and an increase in *Clostridium* spp , these particular gut bacteria may prevent or promote the development of an asthmatic phenotype in pre-schoolers. In children at risk of asthma, *Lachnospira, Veillonella, Faecalibacterium* and *Rothia* levels were reduced.[66] Using methacholine challenge, Arnold et al.[67] demonstrate that *Helicobacter pylori* can also alleviate the symptoms of allergic airways disease by reducing the amount of air resistance in the stomach. *Lactobacillus* supplemetation can promote the maturation of the gut microbiota in infants at high risk of asthma. It may be a useful strategy to prevent the onset and exacerbation of asthma.[68]

Food allergy

Several bacteria, including *Lactobacilus, Bifidobacterium* and *Faecalibacterium*, have a protective effect on the host when it comes to mucosal inflammation.[69] When the flora is absent or limited to a single bacterial strain, an impaired tolerance response is observed, which prevents the development of autoimmunity (i.e., IBD) and food allergy. As a result of intestinal microbe colonization, the immune system appears to be stimulated to produce a non-allergic Th1 response, whereas IgE synthesis appears to be downregulated, which may reduce the risk of developing a food allergy.[70]

The presence of high levels of *Bacteroides fragilis* in the early stages of colonization was also associated with decreased lipopolysaccharide (LPS) responsiveness, indicating that *Bacteroides*

fragilis may have an impact on the systemic immune response.[71] Lack of *Bacteroides fragilis* and *Bifidobacteria* colonization in the gut, which is required from maternal bacteria (during the delivery process), is considered to have poor immune recognition of food, which can result in food allergy.[72] Guénolée et al.[73,74] discovered that *Lacticaseibacillus paracasei* strains could be used to induce and maintain oral tolerance in mice. This suggests that *L. paracasei* strains could be used as a probiotic to prevent infants from developing allergies, such as milk allergies.

Symbiotic microbes impact on the induction of Tregs, which suggests that there is a link between our environment and our susceptibility to allergic conditions. Mazmanian et al.[46] discovered that *Bacteroides fragilis* could maintain a healthy balance of Th1/Th2, thereby preventing the allergy process.

The influence of commensals on health and disease through the control of immune function has arisen as a topic of scientific and therapeutic importance. Preserving a delicate balance in the immune system by removing invading pathogens while maintaining self-tolerance to prevent autoimmunity is vital to the health of the body. By controlling immunological homeostasis, the gut microbiota that inhabits the gastrointestinal system confers significant health benefits on its host. Additionally, it has become clear in recent years that modifications of these gut microbial communities/dysbiosis can result in immunological dysregulation and illness (Fig.1).[26]

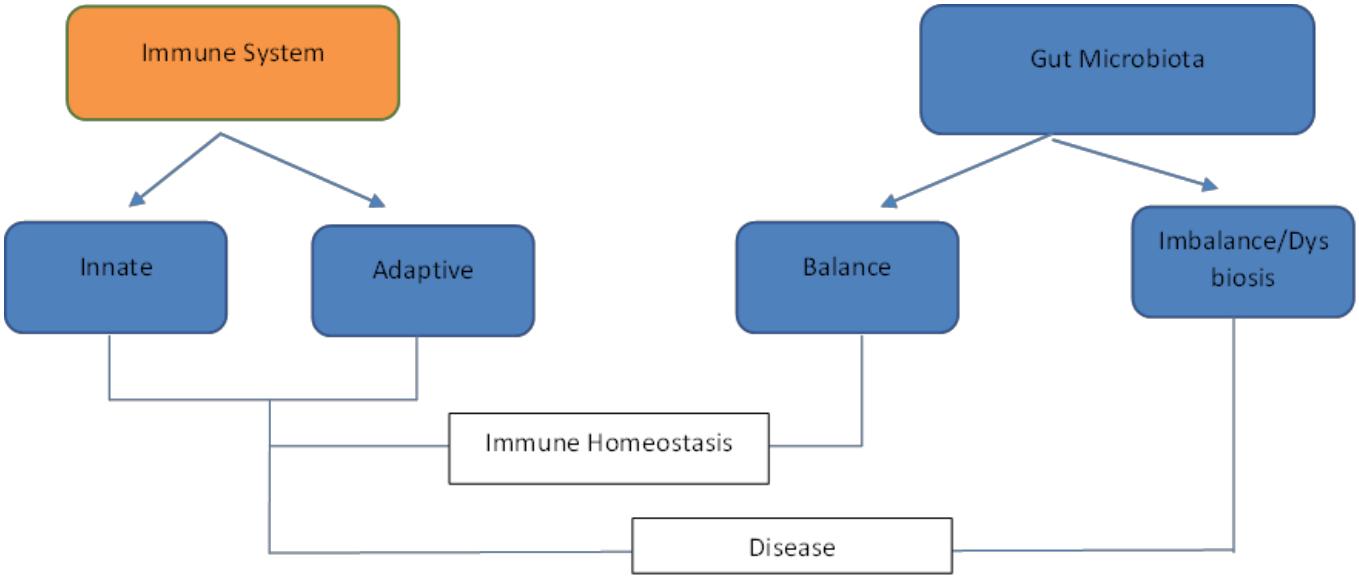

Figure 1. Relationship between immune system and gut microbiota.

Conclusions

Gut microbiota plays a very crucial part in the development of the immune system because they have strong relation each other by influencing the function. The immune system consists of two components: the innate immune system and the adaptive immune system, which can control microbes and various harmless and dangerous microbes. The digestive tract is an entry point for numerous pathogens and toxins present in the food we digest. Creating a balanced microbiome community in the gastrointestinal tract can boost immune defense. Dysbiosis can cause immunological reactions such as allergy, food allergy, inflammatory bowel disease and asthma. Physicians must be concerned about the balance

of gut microbes in the digestive system, which can induce robust immunity in their patients.

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LITERATURE REVIEW

Immunity as key factors that influence cognitive development on children

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Abstract

Immune cells in the central nervous system (CNS) of the fetus are essential for normal neurodevelopment. Innate immunity-related molecules, including cytokines, toll-like receptors and complement family, are known to be expressed in the brain. Microglia, macrophage-like immune cells that reside in the brain and spinal cord, constitute 80% of all immune cells in the brain, making them the most abundant immune cell type. Acquired immunity-related molecules, such as major histocompatibility complex and antibody receptor, are also known to be expressed in the brain. This literature review was prepared by looking for relevant papers and articles published in many electronics databases such as Pubmed and Medline between 2017 and 2022. Research has demonstrated that they play important functions in the development of the brain. Neurodevelopmental diseases, including schizophrenia, autism spectrum disorders, autism-like obsessive-compulsive behaviours and social impairment, are characterized by a disruption of a wide variety of processes in the developing brain that depend on the normal function of microglia. Enteric infections and malnutrition in the first two years of life are linked to later cognitive impairment. Multiple studies have shown that bacterial and viral illnesses have direct or indirect impacts on cognitive performance in children. The immune system is in constant communication with the central nervous system and participates in the control of behaviour and a range of other essential neurological activities throughout the lifespan.

Keywords: development, children, cognitive, immune system, central nervous system

Introduction

The development of cognitive processes is necessary for successful functioning throughout life (e.g., in school, social interactions, physical and mental health and professional careers).[1] Despite the evident importance of biological and environmental factors on cognitive development, much current neurodevelopmental research focuses on extremely early stages (e.g., prenatal/perinatal; first 12 months).[2] The functioning of immune cells in the central nervous system of the fetus in an appropriate manner and at the appropriate time is essential to normal neurodevelopment (CNS). Numerous pieces of evidence point to the fact that the interaction between the immune systems of the mother and the developing fetus has an effect on

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embryonic and fetal neuroimmunology, fetal neurodevelopment, and therefore postnatal neurodevelopment and cognitive function.[3] The CNS and the immune system possess similar properties. The most distinguishing feature of either system is its ability to transmit information with extraordinary specificity and diversity to distant parts of the body.[4] Neurodevelopment is a perfectly organized series of processes that occur during gestation and the postnatal period. During neurodevelopment, neural progenitor cells (NPCs) from the ventricular zone proliferate and move to the major regions of the brain. Traditionally acknowledged for their activities in the immune system, toll-like receptor (TLR) ligand, cytokines, complement proteins, and major histocompatibility complex (MHC) are becoming recognized for their critical roles in the developing brain. In addition, sustaining maternal and early-life immunological homeostasis is necessary for healthy neurodevelopment.[5]

It is known that cognitive function and immune system development are linked. The term "cognition" refers to a person's ability to think, acquire new knowledge, and recall previous experiences; as such, it lays the groundwork for an individual's perception, reasoning, creative problem-solving, and possibly their intuitive abilities. Cognition encompasses a wide range of processes, including attention, processing speed and memory. The cognitive domains that the cognitive assessment can examine are typically labelled as follows: Global intelligence (IQ), Memory, Language, Perception (visual, auditory tactile), Psychomotor skills, Executive functions (sometimes labelled "problem-solving). It is known that cognitive function may linked to immune system through brain development.[6]

Immune system in brain development and cognitive function

Innate immunity-related molecules, including cytokines, toll-like receptors and complement family, are known to be expressed in the brain. Acquired immunity-related molecules, such as major histocompatibility complex and antibody receptor, are also known to be expressed in the brain. In addition to this, research has demonstrated that they play important functions in the development of the brain. In addition to microglia, lymphocytes also play an important part in the formation of brain circuits and are responsible for the regulation of cognition.[7]

The immune system is in constant communication with the central nervous system and participates in the control of behaviour and a range of other essential neurological activities throughout the lifespan. Normal learning and memory processes are dependent on hippocampus neurogenesis, and abnormalities in this process can affect both spatial and non-spatial learning tasks. Immune-mediated processes contribute to healthy hippocampus neurogenesis. For hippocampus-dependent processes including spatial memory and sensorimotor gating, systemic immune cells have been shown to support brain function and plasticity.[8]

Mechanism of immunity in influencing cognitive function

Depletion of systemic CD4+ T lymphocytes led to a significant decrease in hippocampus neurogenesis, poor reversal learning in the Morris water maze and decreased production of brain-derived neurotrophic factor (BDNF). CD4+ T cells have been demonstrated to stimulate and maintain neurogenesis by affecting microglia and regulating the transit of insulin-growth factor (IGF)-1 into the brain, consequently modulating the level of brain-derived neurotrophic factor (BDNF). It is believed that brain-circulating macrophages stimulate CNS-specific CD4+ T cells by phagocytosing and processing CNS-derived self-antigens such as myelin and/or neural debris. Here, these processed antigens can be exposed to and stimulated by naive T cells in the periphery, resulting in the formation of CNS-specific memory T cells that appear in meningeal cerebrospinal fluid (CSF). They can then be re-stimulated by macrophages that monitor the brain to create neuroprotective cytokines and neurotrophic factors, so promoting normal cognitive performance, learning, and memory. Interleukin-4 (IL-4) and transforming growth factor β (TGF-β), two cytokines released by T cells,

protect neurons and neural progenitor cells. IL-4 stimulates the astrocyte expression of BDNF, which is essential for learning and cognition. Infiltrating macrophages considerably contribute to the maintenance of brain homeostasis. Together with glial cells, they regulate the brain's physiological environment by removing dead cells and cell debris, buffering toxic compounds, producing growth factors essential for cell survival and renewal, and downregulating pro-inflammatory factors including interleukin-1β (IL-1β) and tumor necrosis factor (TNF-α). The bulk of studies indicate that TNF-α has a negative impact on synaptic plasticity.[8]

The role of microglia in brain development and cognitive function

Microglia are macrophage-like immune cells that reside in the brain and spinal cord.[9] Microglia constitute 80% of all immune cells in the brain, making them the most abundant immune cell type.[10] They have different origins from other immune cells and play a crucial role in innate immunity. Microglia in the central nervous system are not formed from antecedents in the bone marrow, but rather from progenitors derived from the yolk sac. In response to stimulation, microglia are also capable of self-renewal in situ.[11] Microglia are essential for normal brain development, maturation, and homeostasis, as well as for the response to and clearance of CNS infection.[11, 13, 14] In a healthy central nervous system, resting microglia have multi-branched, lengthy processes in continual contact with neurons, astrocytes, and endothelial cells to monitor local synapses and scan for injury or infection. Microglia are activated in response to the identification of pathogens, which aids in the activation of the innate immune response.

Microglia are necessary for cognitive function. They are important in order to complement the C1q- and C3-dependent synaptic pruning that occurs throughout neuronal development and in order to sustain the normal functioning of neural networks. They can also be used as an alternative to the phrase "synaptic pruning." During the process of neurogenesis, they phagocytose apoptotic cells by interacting with the anti-inflammatory receptors Axl and Mer. It is possible that they enhance the development of learning-dependent synapses by releasing brain-derived neurotrophic factors.[11]

The term "neuroplasticity" refers to the brain's ability to compensate for and adjust to changes in the environment by altering neurons or glial cells through the processes of cell division/apoptosis and/or rebuilding synapses and neurites. As demonstrated in the brain of rats, microglial mobility is mostly dependent on cytoskeletal alterations that are mediated by motile bundles of active filaments. Active filaments are a type of cytoskeletal protein that is abundant in microglia.[13]

The role of adaptive immune system in the proliferation of brain cells

During the process of evolution, immune system cells and highly developed myelination in the nervous system almost simultaneously evolved. This occurred at the same time as jawless fish transitioned into cartilaginous fish. It would be fascinating if this wasn't just a coincidence, but rather if the two occurrences were linked together by a chain of causality in some way. The central nervous system (CNS) has lately gone through a paradigm change, transitioning from a "immune-privileged location" to a "special immune-controlled site".[7] It was proven that meningeal lymphatic vessels play a crucial role in waste elimination when mice with decreased meningeal lymphatic activity experienced cognitive impairment.[14] It was discovered in 2015 that functional lymphatic vessels line the dural sinuses and are capable of transporting fluid as well as immune cells from the cerebrospinal fluid to the deep cervical lymph nodes. This discovery was made possible by the fact that lymphatic vessels line dural sinuses. In the steady state, the majority of lymphocytes are discovered in the meninges and the choroid plexus.[7]

On the other hand, a small number of lymphocytes are also discovered in the brain parenchyma, specifically in the dorsal hippocampus fimbria and anterior olfactory nucleus.[7] Lymphocytes, which are comprised of T

cells, B cells, and natural killer (NK) cells, are relatively infrequent in the central nervous system, with roughly 10,000 per hemisphere in adult mice that have not been exposed to any pathogens. It is now well-established, despite the fact that only a relatively small number of immune cells are involved, that these cells have a substantial impact on how the brain functions. T cells in particular have been connected to a wide array of sophisticated activities in the brain, such as learning to navigate space, remembering events, exhibiting emotional behaviour, and reacting to stress. Helper T cells, also known as CD4+ T cells, are the ones that are drawn to the meninges and secrete interleukin (IL)-4 in mice that are put through the Morris water maze (MWM). Cytotoxic T cells, on the other hand, are CD8+ T cells. In order to enhance spatial learning and memory, IL-4 causes macrophages and microglia to take on an M2 (anti-inflammatory) phenotype and causes astrocytes to generate and secrete brain-derived neurotrophic factors.[7]

The importance of adaptive immunity in cognitive function was revealed by cognitive deficits in mice devoid of T cells or IL-4. Tiroyaone et al. show that type 2 cytokines play a crucial role in the control of cognitive function. They demonstrate that, similar to IL-4, IL-13 is necessary for T cell accumulation in the meninges during learning. In addition, they demonstrate that doing cognitive activities causes IL-4 and IL-13 to accumulate in the meninges of wild-trained (WT) mice. They concluded that a deficit in IL-13 impairs spatial learning, resulting in significant cognitive impairment.[15]

Evidence on the impact of abnormal immune system and cognitive function

Microglia take on a specialized phenotype during neuroinflammation and degeneration, which, depending on the stimuli and the milieu of their central nervous system (CNS), can either be neuroprotective or neurotoxic.[16] Neurodevelopmental diseases, including schizophrenia, autism spectrum disorders, autism-like obsessive-compulsive behaviours and social impairment, are characterized by a disruption of a wide variety of processes in the developing brain that depend on the normal function of microglia.[15, 21–24] An amoeboid shape of microglia and higher cytokine production are both indicators that microglia in the brains of autistic and schizophrenia patients are in a more active state than microglia in the brains of healthy persons.[21] They are the product of a complicated interaction between inherited characteristics and the environment in which they were raised.[16]

Both epidemiological and animal research have found a significant correlation between an activated immune system in the mother when she is pregnant and an increased likelihood of either of the two conditions being inherited by the child. Infections caused by bacteria or viruses, such as rubella and the influenza virus, can trigger the activation of the mother's immune system when she is pregnant (maternal immune activation, MIA).[16] Maternal Immune Activation (MIA) has been shown to have an adverse effect on the development of microglia in offspring, which has been connected to behavioural problems.[21] The research has shown that children can suffer from neurodevelopmental conditions such as autism spectrum disorder (ASD), schizophrenia, epilepsy, cerebral palsy, anxiety, and major depressive disorder. MIA also generates an inflammatory response in the fetal brain of rodents by increasing the amounts of pro-inflammatory mediators such as IL-6 and IL-17a. This is one of the mechanisms through which it does this. Critical mediators of aberrant brain development and behavioural impairments in the offspring of polyinosinic:polycytidylic acid (Poly (I:C)) caused MIA mice are maternal systemic IL-6 and its downstream signalling cytokine IL-17a. Both of these cytokines are produced by the maternal immune system.[16]

There has been very little research into the effects of infections on behaviour and mental performance. When certain conditions are present, there is a link between certain infectious diseases, such as viral encephalitis, and cognitive deficits.[22] Children aged 12 months with acute respiratory illnesses (ARI) and fever had lower cognitive scores, according to the findings of a study conducted by Azziz-Baumgartner et al.[23] It is

possible, but not certain, that this finding was related to increased levels of pro-inflammatory interleukin during illness.[23]

In addition to enteric infections and malnutrition in the first two years of life, enteric infections and malnutrition are linked to later cognitive impairment. A study evaluated the long-term effects of childhood diarrhea in the first two years of life by examining the cognitive function of Brazilian slum children. The potential mechanism as a result of early brain development is metabolically demanding. As high as 87 percent of a new-born's body's metabolic resources are consumed by the brain, compared to 44 percent at age 5 and 34 percent at age 10. Therefore, the use of metabolic resources for other purposes, such as fighting infections, will compromise the stability of brain development. This hypothesis was tested in a study that correlated the average national intelligence of 113 nations with the infectious disease burden of each nation, as measured by disability-adjusted life years lost due to infectious disease.[24] The process of "functional isolation," which occurs when a child is unable to elicit appropriate caregiving behaviour as a result of the behavioural consequences of his or her condition, and as a result, the child is unable to develop to his or her full potential, is one of the possible indirect effects of childhood illnesses. Children who are infected with the virus may display symptoms such as weakness, apathy and irritability, making it difficult for their caregivers to provide appropriate care.[25]

Conclusions

The immune system and the central nervous system (CNS) are both complex and highly structured systems that manage the entire body, with similar mechanisms of development and styles of action. A direct connection between brain activity and immune system function may explain how the immune system can be adjusted. The immune system surely affects the health status of the children. Healthy children, make them easy to receive and respond the stimulation from the environment. On the contrary, in unwell children with poor-quality immune systems, it will be hard for them to receive and respond the stimulation from the environment, thus will disrupt brain development. Aside from that, there is a review that summarizes the studies on the function of immune cells and immunological molecules, with a focus on the activity of immune cells and immune molecules in more adult brains. Multiple neurodevelopmental disorders, including autism spectrum disorder (ASD), schizophrenia, and other mental illnesses, are caused by an immune system inflammatory response that interferes with CNS development and performance. Multiple studies have shown that bacterial and viral illnesses have direct or indirect impacts on cognitive performance in children.

Author contribution: All authors have read and agreed to the published version of the manuscript.

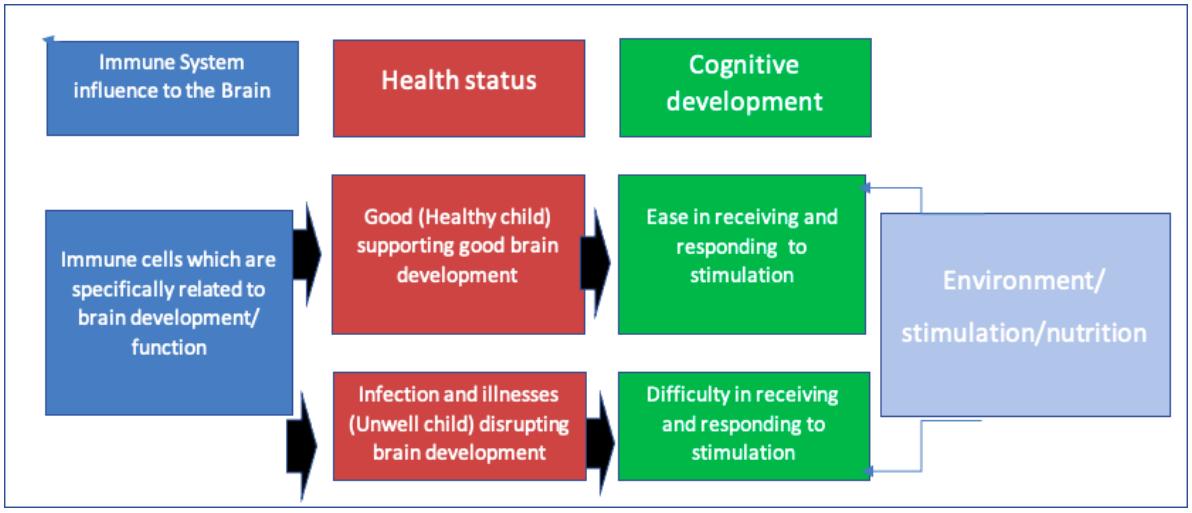

Figure 1. The role of immunity in children cognitive development

Conflict of Interest

E.W. and M.S.K. are employees of Danone SN Indonesia. All other authors have no conflict of interest

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LITERATURE REVIEW

The narrative review of recent studies in understanding the relationship between gut (microbiota)-brain axis, nutrition and cognitive function

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Abstract

The concept of the gut (microbiota)-brain axis, which influences the development and function of the gastrointestinal, immune, neuroendocrine, and metabolic systems, is gaining popularity. Recent animal studies have demonstrated that the gut (microbiota)-brain axis also plays a role in establishing cognitive function. It is known that a disruption in the environment's microbiota balance can increase disease susceptibility in children. Historically, it has been hypothesized that neurodevelopmental disorders are the results of a disruption in children's health. However, it is becoming clear that the gut microbiota and the central nervous system communicate in both directions, which could explain how microbiota affects cognitive function. Dietary factors also play important role in the central nervous system via the gut (microbiota)-brain axis, demonstrating the importance of nutrition in optimizing cognitive function. This narrative review of recently published studies and current knowledge aims to elucidate the relationship between the gut (microbiota)-brain axis and cognitive function, as well as the variables that may influence it.

Keywords: gut-brain-axis, gut microbiota, cognitive function, central nervous system, dietary factors, Nutrition.

Introduction

Over the past few years, a concept known as the gut (microbiota)-brain axis has garnered a significant amount of interest. It has been demonstrated that the quick and densely populated microbiota that contain complex forms are created after birth during the first years of a person's existence. It has been demonstrated the microbiota is involved in the developmental programming of epithelial barrier function, angiogenesis, gut homeostasis, and both innate and adaptive immunological function. Numerous studies have demonstrated that the relationship between intestinal microbiota, the gut, and the central nervous system (CNS) is essential in immunological and metabolic processes that influence human health and disease. This interaction is referred to as the gut-brain axis.[1–4] However, it has only been proven relatively

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recently that the gut-brain axis also plays an important role in the establishment and maintenance of cognitive function.[5–7]

The gut and the brain are able to communicate with one another through neuronal, endocrine, and immunological channels. Each of these pathways has its own level of complexity that is involved in homeostasis and normal physiology. Numerous studies that involved alterations in the composition of the microbiota, either as a result of bacterial infection, probiotic administration, or in germ-free mice, all demonstrate that modulating the microbiota can affect behavior and cognition. This effect was observed in studies conducted in humans and animals, including germ-free mice and germ-infected mice.[3,6–8] A recent study that was conducted with mice also suggested that changing or removing the gut microbiota has an influence on the response of the hypothalamic-pituitary-adrenal (HPA) axis to behaviors associated with stress and anxiety. These mice models with altered microbiota can be utilized to explore the influence of the change on behavior and cognitive function as a whole. [9,10] The findings of the first study to establish links between gut microbiota and cognition in human newborns are consistent with the findings of the study conducted on mice. This may be an essential first step for further research.[11]

Cognitive function and behaviour are inextricably linked to early-life brain development. In every area of the brain, development begins and accelerates during fetal life or shortly after birth; thus, maintaining developed brain areas is critical not only for promoting behavior but also for cognition. [12] While nutrients are necessary for brain growth and function, certain nutrients have significant impact in early development. Diet also plays a role in maintaining microbiota composition, which is critical for health and development. [13]

Microbial interventions through diet may be an effective strategy to address potential adverse health outcomes and cognitive deficits. Supplementation with prebiotic and/or probiotic bacteria has been extensively studied and has been shown to be beneficial in preventing altered microbiota environments (dysbiosis). When administered in sufficient quantities, probiotics and prebiotics has several beneficial physiological effects on the host's metabolism, immune system, and gastrointestinal function. [2,14] Several studies also demonstrate that probiotics, prebiotics, and the combination of a specific prebiotic and probiotic (referred to as symbiotic) all benefit cognitive function. [15–18]

The connection between the gut (microbiota) and the brain as it relates to cognitive function is one that piques the interest of researchers. The data supporting the concept has been thoroughly investigated, however the majority of the research has been conducted on animals. The objective of this review is to explain the function that the gut (microbiota)-brain axis plays in mediating changes in cognition in research including both humans and animals, as well as the factors that may influence it.

Methods

This article emphasize the connection between the gut (microbiota) and the brain and also its relation with cognitive function. This literature review was prepared by looking for relevant papers and articles published in many electronic databases such as Pubmed and Medline between 2017 and 2022. Variants of "microbiota" "cognitive function" "dysbiosis" "nutrition" "probiotics" "gut-brain-axis were included in the research terms. Further papers were found, either in English or Indonesian, through manual search from the manual references cited in the corresponding reviews.

Nutrients and Cognitive Function

Numerous aspects of the qualities of nutrients have been found to be associated with cognition, mental wellness, dysfunction, and disease. Nutrition has an effect on a number of components of brain function, including cell membranes, metabolites, enzymes, and neurotransmitters. Nutrients like fatty acids, which have receptors in the nucleus of the cell, can exert a direct influence on a wide variety of

Table 1 Nutrition and Cognitive Function [7,9,21–23]

Nutritional intervention	Impact
Polyunsaturated fatty acid (AA, DHA)	Increase brain development and function
High protein diets	Positive association with cognitive abilities
High fat diets	Increase risk of dysbiosis and impairs cognitive function such as memory and learning
Dietary factors	Influence to gut (microbiota) – brain axis

brain activities by controlling the transcription of a large number of genes that are involved in both the construction and function of the brain.[19] Intake of certain nutrients is ultimately responsible for determining the development and function of the brain. [20] It has been known for a long time that fatty acid consumption is essential for optimal development, particularly a major polyunsaturated fatty acid like DHA. Recent research conducted on piglets suggests that the amount of n-3 fatty acids consumed is not the only factor that determines optimal cognitive health; rather, it is also important to maintain a healthy balance between the amounts of n-6 and n-3 fatty acids consumed. It is possible that the Western diet, which is high in n-6 fatty acids but low in n-3 fatty acids, is a contributor to lower DHA accretion, suppression of secondary neurite formation, and impaired brain development and function.21 Several studies have demonstrated a positive association between high-protein diets and cognitive abilities in children, while high-fat diets, such as Western diets, have a negative association.[22,23]

The capacity of the majority of these dietary factors to influence behavioral processes like learning has been studied in relation to their ability to directly influence neural activity in the central nervous system (CNS) via the gut (microbiota) -brain axis. Learning is an example of a behavioral process that can be affected by these dietary factors. Recent studies have shown that one's food can have an effect on their cognitive abilities, with the gut microbiota playing an important role in the connection between the two. The results of a study on mice that lasted for three months demonstrate that a high-fat diet (50 percent lean ground beef) changes the variety of the microbiota in the gut, which in turn hinders learning and memory. [7,9] The importance of diets and nutrition for long-term cognitive function is summarized in **Table 1**.

The gut microbiota and cognitive function

It is estimated that there are between 1 x 1013 and 1 x 1014 bacteria living in the human gastrointestinal system, which is more than ten times the number of human cells found in our bodies. Our knowledge of the dynamic link that exists between the microbiota, the microbiome, and the host is quickly expanding, and this interaction is currently understood to be mutually beneficial.[3] It is now common knowledge that the microbiota in the gut play an important part in the formation and function of both innate and adaptive immune responses, as well as in the regulation of gut motility, intestinal barrier homeostasis, nutritional absorption, and fat distribution.[24] The number of species that are predicted to be present in the gut microbiota varies quite a bit; nevertheless, colonization does not take place prenatally; rather, it begins during birth when the newborn is exposed to a diverse microbiota during vaginal delivery. After the age of one year, the microbiota in the gut may have reached a stable structure that is characteristic of the microbiota in adulthood.[2,3.]

Gut (microbiota)-brain Axis. Increased susceptibility to disease can be attributed to a change in the delicate balance of the microbiota. Infection, sickness, and the use of antibiotics are all factors that have the potential to momentarily disrupt the equilibrium of the normal composition

of the gut microbiota, which in turn has a negative impact on the health of the host. Because gut bacteria have such a significant impact on overall health, it should come as no surprise that a growing body of research is focusing on the effect of enteric microbiota on the brain and behavior. This has led to the development of the idea of a connection between the gut (microbiota) and the brain, which is known as the gut–brain axis. [4] It is a well-established fact that the microbiota in the gut and the central nervous system (CNS) interact with one another. The enteric nervous system, the neuroendocrine system, the neuroimmune system, the sympathetic and parasympathetic arms of the autonomic nervous system, and the gastrointestinal tract all serve as major communication pathways between these two systems, and the gastrointestinal tract acts as a scaffold for these pathways. These components come together to produce a sophisticated reflex network, with afferents projecting to integrative cortical CNS regions and efferents innervating the smooth muscle of the intestine. Notably, there is a growing realization that this communication is bidirectional, meaning that bacteria influence CNS function, and the CNS influences microbiota composition via the effects it has on the gastrointestinal tract. It is not understood what mechanism is responsible for this communication taking place.

Microbiotas exert their impact over the gut-brain axis in a number of different ways, both directly and indirectly. In this discussion, we will cover the endocrine (cortisol), immunological (cytokines), and neurological pathways (vagus and enteric nervous system). The hypothalamus-pituitary-adrenal (HPA) axis is responsible for the regulation of cortisol secretion. This axis can have an effect on immune cells both locally and systemically (including cytokine secretion). The permeability and function of the barrier that lines the gut, as well as the make-up of the microbiota that lives there, can both be altered by cortisol's presence. However, the microbiota in the stomach and the probiotics that are taken can change the circulating cytokines, which can have a significant impact on how well the brain works. In order for the influence of the gut microbiota to be transmitted to the brain, the vagus nerve and systemic tryptophan levels are both necessary components.[3,9]

a. Endocrine Pathway

Stress and its associated HPA axis activity can influence the composition of the microbiota. Maternal separation is one type of early life stress that has been shown to increase long-term HPA axis activity.[4,25] In monkeys (6-9 months of age), maternal separation resulted in a significant decrease in Lactobacillus bacteria three days after separation, which returned to baseline by day seventh.[26] Additionally, another study demonstrates that mice that were separated from their mothers for 3 hours per day on post-natal days 2-12 have a different microbiota composition than non-separated control animals.[27] Adult mice exposed to chronic stress also exhibit altered microbiota composition. Stress also affects the levels of interleukin and chemokine in the blood, which activate the immune system. Proinflammatory cytokine changes are associated with changes in the composition of several gut microbiota.[28] Several research involving humans have shown that stress-related psychiatric diseases, such as depression, are linked to an increase in the movement of germs throughout the body. This translocation can be avoided with the use of the potential probiotic lactobacillus farciminis. This probiotic has the ability to also alleviate the psychological strain that is brought on by the HPA axis.[12] This work contributes to the expanding body of information that demonstrates the crucial function that the gut (microbiota) -brain axis plays in both the stress response and behavior.

Recent research has shown that dysbiosis, the stress response, and its link with HPA-axis activation can have an effect on behavior and cause changes such as anxiety, depression, and cognitive impairments. These findings are supported by the observation that germ-free mice (GF) have a higher baseline activation of the HPA axis in comparison to controls that have a normal microbiota composition and aren't exposed to any

particular pathogens (referred to as specific-pathogen-free mice).[10] Colonization with the feces of control animals reversed the stress response in a partial manner, whereas Bifidobacterium infantis reversed it completely.[18,27] This discovery lends credence to the idea that bacteria can play a role in the maturation of mice' cerebral stress responses.

In terms of cognitive function, A recent mouse study demonstrated that germ-free (GF) mice have a deficit in non-spatial memory and impaired working memory at baseline when compared to specific pathogen-free (SPF) controls. Acute psychological stress, which activates the HPA-axis, had no additional effect on GF mice's learning and memory. This finding suggests that in GF conditions, the HPA-axis cannot be triggered by stress, which results in an exposed neuroendocrine system. GF situations include: This impaired cognition in GF mice is related with decreased levels of two proteins that are crucial for the regulation of hippocampal-dependent memory. These proteins are brain derived neurotropic factor (BDNF) and c-FOS. Both of these factors are associated with decreased levels. In particular, BDNF is a powerful regulator of synaptic plasticity when it is present in the hippocampus during the process of neurogenesis. In contrast, c-FOS is an immediate early gene that must be present in the hippocampus in order for long-term memories to be formed.[6] When compared to SPF controls, GF mice had lower levels of BDNF messenger ribonucleic acid (mRNA) in the hippocampus than SPF mice did. This finding was consistent with what was seen in the protein investigations. When considered as a whole, these data point to the existence of a potential connection between the microbiota and the levels of BDNF or c-FOS in the process of regulating brain physiology and memory.[9] Despite the results of these research, it is currently uncertain if cognitive impairments can be normalized through the early or mature colonization of GF mice. In contrast to their SPF counterparts, GF mice have been shown in a number of subsequent studies to exhibit behavior that is analogous to that of an anxiolytic drug. The results of these studies showed that conventionalizing mice could normalize their behavior, but only in the younger stages of their lives.[8,10]

b. Immune Pathways

A recent study found that animals that were not exposed to any germs had significantly higher hippocampal concentrations of the neurotransmitter 5-hydroxytryptophan (5-HT), as well as its primary metabolite, 5-hydroxyindoleacetic acid, and the neurotransmitter dopamine. Control animals that had been exposed to germs served as a comparison.[29] It has been shown that serotonin plays an important part in cognition, and that manipulation of the serotonergic system can result in changes in cognitive function that are independent of changes in mood.[30] Plasma tryptophan concentrations, which are a precursor to serotonin, increased in germ-free mice, which suggests that microbiota can alter serotonergic transmission in the central nervous system via a humoral mechanism. It is interesting to note that the colonization of germ-free animals after weaning returned peripheral tryptophan levels to control levels; however, it did not reverse the changes in serotonin levels in the CNS during adulthood that were caused by an absence of microbiota during childhood.[29] In addition, a study conducted on humans demonstrated that treating terminal lung cancer patients with heat to kill Mycobacterium vaccae improved both their emotional health and their cognitive function. This led researchers to hypothesize that the immune response to the bacteria involved neurotransmitters such as 5-HT, which resulted in an improvement in mood.[31] The administration of *Mycobacterium vaccae* resulted in a decrease in the amount of time it took mice to complete a Hebbs-Williams-style complex maze comprised of a close-field test apparatus used to study intelligence. This indicated an improvement in the animals' ability to learn and remember new information.[32] According to the findings of these investigations, the immune system, in part by way of the serotonergic system, plays a role in moderating the influence that commensal

Table 2 Gut (microbiota) -Brain Axis and Dysbiosis Direct/Indirect Mechanism Affecting Brain & Behavior [8,10,29,31–33]

Pathway	Involved system	Evidence	Impact
Endocrine	via HPA axis activity	Dysbiosis - Long term HPA Axis Activity	Psychiatric disorder, Anxiety and Cognitive defects
Immune	via Serotonergic system	Dysbiosis - Serotonergic transmission of plasma tryptophan transmission	Impair Learning, mood changes and Memory
Neural	via Vagus Nerve	Dysbiosis - Neuronal Activation & FOS expressing cells	Anxiety

microorganisms have on the brain and cognition. When taken as a whole, these data imply that illness and stress can interact with one another and produce a synergistic effect that can change the function and behavior of the central nervous system, most notably cognitive function.

c. Neural Pathways

The vagus nerve is one route that could theoretically explain the gut (microbiota)-brain axis mechanism. Following infection, some bacteria utilize this route for gut-to-brain signaling inducing an anxiety like behavior.[33] In one study, immunocytochemistry was used to map the temporal pattern of neural activation in mice that had been infected with the food-borne pathogen Campylobacter jejuni. *Campylobacter jejuni* is known to cause illness in humans. Visceral sensory nuclei of the brainstem, such as the nucleus tractus solitarius of the vagus nerve, had elevated levels of fructooligosaccharides (FOS), but areas involved in the stress response, such as the hypothalamic paraventricular nucleus, did not. This occurred one to two days after inoculation (2 days after inoculation). In addition, the animals showed signs of increased anxiety-like behavior when they were subjected to the hole board test. The level of anxiety was found to be correlated with neuronal activation, which was measured by the number of FOS-expressing cells in the bed nucleus of the stria terminalis. This region is an essential part of the extended amygdala fear system.[34] Although such studies with pathogens do not directly address the microbiota's ability to communicate with the brain, they provide critical insights into the mechanisms by which microorganisms communicate with the brain and affect behavior. The pathways how microbiota can affect brain and behavior are summarized in **Table 2**.

Evidence on the role of Gut microbiota in Cognitive function. According to research conducted on mice, microbiotas appear to have a part to play in the appropriate regulation of behavior and brain chemistry linked with mood, anxiety, and cognition. In addition to this, it is suggested that the make-up of an individual's microbiota may have an effect on their behavior as well as their cognitive performance. The human race has only a rudimentary understanding of the connection that exists between the microbiota and the maturation of the brain in the first few years of life. In a research of toddlers, different gut microbiota compositions were found to be connected with temperament. This association was determined by the phylogenetic diversity of the microbiota as well as the abundance of certain bacterial species.[35] Other studies found that newborns whose gut microbiota included an abundance of *Bacteroides* had improved cognitive performance, particularly on visual reception and language measures. This study also found that the diversity of the microbiome at 1 year of age can predict cognitive ability at 2 years of age, with a greater diversity likely being deleterious to neurodevelopment.[5]

Additionally, corroboration links dysbiosis to autism and other neurodevelopmental disorders. Comparative analysis of the diversity and composition of the gut microbiota of children with and without neurodevelopmental disorders. According to a study, neurodevelopmental disorders and autism spectrum disorders are associated with reduced microbial diversity in children. In patients with neurodevelopmental disorders and autism spectrum disorders, it is hypothesized that the early microbiome may influence GI disturbances and accompanying cognitive and behavioral issues.[36,37]

According to one study conducted in India, GI disturbances such as diarrhea may increase the risks of adverse neurodevelopment. This study shows that increase in days of diarrhea is associated with increased risk of lower skills in fine motor and problem-solving (cognitive function). The limitation of this study is they did not differentiate diarrhea etiology is it whether due to dysbiosis or not.[38] Albeit literature shows that children with gut dysbiosis have increased risk of GI problems.[39] Additional studies in humans are needed to significantly advance our understanding of the role of microbiota in cognitive and neurodevelopment processes.

Probiotics, Prebiotics and Synbiotics Role in Preserving Cognitive Function

In clinical practice, altered microbiota environments (dysbiosis) are frequently treated with dietary interventions (nutritional supplements or special diets). The maintenance of cognitive processes is another purpose served by this dietary intervention. It is possible that the capacity of nutrition to influence behavior and learning is not entirely attributable to an effect on neuronal cells in the central nervous system, but rather may be associated with the degree to which the microbiota of the gastrointestinal tract is altered (CNS).[7] Numerous studies have attempted to establish a connection between the diversity of gut microbes and diets. These studies demonstrated that probiotic, prebiotic, and/or symbiotic supplementation is a promising strategy for reversing gut dysbiosis and preserving cognitive function.[16]

Probiotics are live bacteria that, when taken in adequate doses, can bestow a variety of health benefits on the hosts to which they are provided. In various animal models with metabolic syndrome, probiotics were able to change the composition of the gut microbiota as well as the metabolism of that microbiota, which led to an improvement in the metabolic function of those models.[17] Consumption of probiotics is also advantageous for the brain via the gut (microbiota)-brain axis in order to restore cognitive function by activating microglia.[15,16,40] The mechanism of these probiotics' beneficial effects remains unknown.

Hanstock et al [41]. examined the impact of bacterial fermentation on colonic behavior. Rats fed a high-fermentable-carbohydrate diet display enhanced hindgut fermentation, resulting in an accumulation of fermentative end products such as lactic acid and volatile fatty acid. The cumulative effect of these fermented products is an increase in anxious and aggressive behavior.[41] On the other hand, one study found that mice fed a western diet high in fat and refined sugar while receiving Lactobacillus containing probiotics exhibited increased anxiety and decreased memory.[42] Studies have shown that the probiotic agent Bacillus infantis had antidepressant-like effects and normalized peripheral pro-inflammatory cytokine and tryptophan concentrations, both of which have been linked to depression and a maternal separation model of depression. This provides additional evidence for the beneficial effects that probiotics have on behavior. [43] Recent research has demonstrated that giving mice the *Bifidobacterium* breve strain NCIMB 702258 results in greater levels of fatty acids in the brain of the mice (including arachidonic acid and docosahexaenoic acid). It is interesting to note that this effect was reliant on the strain, as it was not caused by the B. breve strain DPC 6330.44 It is well recognized that arachidonic and docosahexaenoic acids play important roles in the processes of neurodevelopment, such as neurogenesis. The concentrations of these two acids in the brain may

Table. 3 Microbiota and Cognitive Function: Effect of Dysbiosis and The Use of Supplementation [15,16,36,38,44,46]

Intervention/Condition	Effect
Increased diversity of microbiota	Predictive of better cognitive function
Gut dysbiosis in children	Increased risk of neurodevelopment disorder and autism spectrum
Use of probiotics (*Bifidobacterium breve*)	Affect Gut (microbiota)-Brain-Axis and Neurodevelopment process
Supplementation of FOS, GOS	Improve attention, executive function, and memory
Administration of clinically proven synbiotic	Improved brain function, microglia activation and restore cognitive function

influence emotions such as anxiety and sadness, as well as learning and memory.[18,44,45] This demonstrates the nuanced relationship between probiotics, diet, and their effect on microbiota, cognitive function, and behavior. Prebiotics are an indigestible kind of dietary fiber that has been shown to have a favorable effect on the host's physiology. This effect is achieved by the prebiotic's ability to stimulate the growth or activity of a select group of native bacteria. Prebiotics are fibers that, when fermented by the microbiota of the intestinal tract, encourage the growth of bacteria such as *Lactobacillus* and *Bifidobacteria* that are good to human health.[14] According to a study on the cognitive benefits of prebiotic administration, supplementation with galactooligosacharides (GOS) and fructooligosacharides (FOS) may increase cognitive function in broad domains conceptualizing attention, executive processes, or memory.46 Probiotics, namely *Lactobacillus spp* and *Bifidobacterium Breve*, exerted multiple beneficial effects on various cognitive functions, including memory, verbal learning, attention, and a variety of cognitive tests, outperforming prebiotic supplementation, possibly due to their brief administration.[16]

Prebiotic and probiotic (Synbiotics) therapy has been shown to decrease pro-inflammatory cytokines via the apoptotic pathway. Proinflammatory cytokines released by activated microglia and microglia themselves have been shown to inhibit long-term potentiation of brain synapses, resulting in cognitive decline. A recent study showed that restoring cognitive function in rats that had been fed a high-fat diet could be accomplished with the help of prebiotic xylooligosacharide (XOS), probiotic Lactobacillus paracasei HII01, or both of these together as *synbiotics*. Consuming the prebiotic XOS, the probiotic L. paracasei HII01, or the synbiotics on a daily basis for a period of 12 weeks improved brain function in obese rats. This was accomplished by lowering gut and systemic inflammation, lowering brain and hippocampal oxidative stress, increasing dendritic spine density, attenuating microglial activation, and improving hippocampal dysplasticity and brain mitochondrial dysfunction, which resulted in restored cognitive function. In addition, the researchers found that obese rats given a diet had a reduction in microglial activation and a restoration of cognitive function when they were given either prebiotic XOS, probiotic L. *paracasei* I01, or synbiotics over an extended period of time.[15] The processes that underlie the role that microglia play in cognition as well as the signaling pathways that underlie neuroglia communication particularly in humans need to be elucidated through the conduct of additional study. The influence of dysbiosis on cognitive performance, as well as the potential benefits of taking pre-probiotic supplements, are summed up in **Table 3.**

Conclusions

Given the increasing acknowledgment of the importance of the gut microbiota in complex disorders such as anxiety and cognition, it is increasingly evident that clinical translation of animal research is necessary. Clearly, modulating gut microbiota can influence behaviour,

neurophysiology, and neurochemistry. The findings of this study may pave the way for future research into the relationships between microbiota and human cognitive function. Nutritional effects and how diets improve cognitive function in humans via neurogenesis and the gut (microbiota) -brain axis are critical areas for future research. Unravelling these relationships may eventually lead to new treatment techniques for addressing established risk factors of dysbiosis, such as the promising use of prebiotics, probiotics, and synbiotics to combat cognitive deficiency.

Author contribution: All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

R.W.B., E.W., and T.S. are employees of Danone SN Indonesia. All other authors have no conflict of interest

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LITERATURE REVIEW

Exploring key cognitive indicators for practical use by parents in community setting

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Abstract

The identification of child development milestones, specifically cognitive abilities, requires parental/caregiver awareness and knowledge. With the existence of multiple cognitive abilities such as attention and focus, memory, language, psychomotor skills, logic, reasoning, decision-making, problem-solving, social/emotional, there are multiple indicators to measure children's cognitive abilities. Pediatricians are the most knowledgeable and trusted authority to routinely screen and monitor the development of healthy children. Therefore, it is crucial that parents understand their children's developmental milestones so if they encounter anomalies, they can immediately consult with the professionals. This review compiles recently published research and current knowledge to examine potential key indicators of cognitive development in infants and children that can be utilized by parents and communities in an easily understood manner.

Keywords: indicator, cognitive abilities, children more than one year old

Introduction

Cognition is the mental process individuals use to acquire and process information. It includes perception, memory, and thought, and is impacted by biological, environmental, experiential, social, and motivational variables. Changes in quality or stages are used to characterize the cognitive development process. Each stage is distinct, arranged sequentially, and builds upon the stages that came before it. Due to the biological basis of this structure, this theory asserts that cognitive capacities and developmental processes are universal, including all members of a given species regardless of their cultural or historical background.[1]

Jean Piaget (1896-1980) introduced the most widely recognized theory of cognitive development. Piaget postulated four phases of mental organization to characterize the development from infancy to cognitive maturity: sensorimotor, pre-operations, concrete operations, and formal operations. Two mechanisms govern cognitive development: organization and adaptability. Organization refers to the stages of

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development and how they unfold over time, whereas adaptation refers to the process by which children's thought processes become increasingly aligned with characteristics of their environment.[1,2]

The development of cognitive abilities is the foundation of intelligence. The dictionary defines the ability to learn, understand and deal with something new as intelligence. Intelligence is a broad concept that encompasses a wide range of factors and is still only partially understood. The most successful attempts to quantify this concept have been made using standardized intelligence tests to measure multiple areas such as problem-solving, language, attention, memory, and information processing in one test.[3]

In terms of clinical developmental screening tools, pediatricians now have various options to utilize, such as the Parents Evaluation of Developmental Status (PEDS) and the Denver-II Screening test, which are both available to them. Specifically designed for pediatricians to use in the office, the Bayley Scales of Infant Development and The Capute Scales is a promising test that assesses a child's cognitive function and language skills. Each screening instrument has its own set of advantages and disadvantages.[4,5] For the early detection of developmental delays, screening such as Denver-II and PEDS are widely utilized by health care professionals and utilized in several primary care facilities.

Research has demonstrated the critical importance of parents' and caregivers' knowledge and expectations on a child's cognitive development. Miller (1988) is the first to assert that parental beliefs are positively associated with parental childrearing practices and the development of children.[6] A recent study also demonstrated that parents with superior parenting knowledge, parenting practices, and parent-child interactions significantly influence the cognitive, linguistic, and motor development of their children. On the other hand, multiple studies have demonstrated that parents are the first institution to screen a child for developmental risks, particularly cognitive development. So, it's essential for parents to be aware and knowledgeable in watching out for their child developmental issues so they can be addressed by professionals.[7–9] Therefore, it is necessary to introduce parent-friendly cognitive indicators to increase parents' and caregivers' understanding of which aspects of a child's development deviate from those of children of the same age. In this article, we explored potential key indicators of cognitive development in infants and children that can be communicated to communities/parents/caregivers and are easily understood by them.

Methods

This article introduce a parent-friendly cognitive key indicators in infants and children to help parents, caregiver and professionals to understand child's development in easy to digest manner. This literature review was prepared by looking for relevant papers and articles published in many electronic databases such as Pubmed and Medline between 2017 and 2022. Variants of "cognitive function" "cognitive domain" "children development" "development measurement" "infants" "children" were included in the research terms. Further papers were found, either in English or Indonesian, through manual search from the manual references cited in the corresponding reviews.

Discussion

Piaget's developmental theory

According to Piaget, human cognitive development occurs in four stages. *First,* the sensorimotor stage lasts from birth to approximately two years of age. The baby develops an understanding of the world during this stage by coordinating sensory experiences such as sight and sound with physical, motoric actions.[6] At the beginning of this stage, infants exhibit only a reflex behaviour pattern. Two-year-old children are able to produce complex sensorimotor patterns and use primitive symbols at the end of the sensorimotor stage.[7] *Second*, preoperational stages occur between the ages of 2 and 7, when children begin to represent their world with words, shadows, and images. Children begin to use language during this stage; their memory and imagination are also developing. At this stage, children develop trust in themselves and express

their understanding of the relationship between the past and the future. Symbolic thoughts transcend simple associations between sensory data and physical reaction.[2,7] Between the ages of 2-4 years, there is a symbolic phase. At this stage, the child develops the ability to represent objects that cannot be seen mentally. This ability broadens children's mental worlds, as evidenced by their ability to describe people, homes, cars, and clouds randomly. Additionally, there is an intuitive thinking phase (4-7 years) during which children begin to use primitive reasoning and seek answers to various questions. According to Piaget, this stage is characterized by free, imaginative, and unique associations that occasionally make no sense.[6,8] *Third*, concrete operational stages lasts between seven and twelve years. At this stage, the child can perform operative actions, and logical reasoning takes the place of intuitive reasoning, as long as the reasoning applies to specific and concrete examples. *Fourth*, formal stages of operation begin around the age of 12 years. The child moves from concrete to abstract and more logical thinking at this stage.[2,7]

Piaget emphasizes that as children develop cognitively, they progress sequentially through four major stages. Because heredity and environment interact, it is possible for a child to exhibit characteristics of more than one developmental stage at the oldest ages. Each stage represents a significant change in cognitive processes relative to the previous stage. The stages are sequential and adhere to a consistent order. This means that the child cannot skip or miss a normal developmental stage. Several domains develop and become critical skills in cognitive development during these first two three stages, including psychomotor skills, language, memory, focus and attention, logic reasoning, problem-solving, and critical thinking. Therefore, understanding these domains are important to give sufficient experience in each stage in order to prevent developmental lag.[8]

Cognitive development for children above one year old

Multiple factors contribute significantly to the cognitive development of children older than one year. Included are logical reasoning and decision-making, problem-solving, attention and concentration, psychomotor skills, memory, and language. For cognitive development to be successful, all of these domains must be improved. Memory consists of encoding, storing, and retrieving information.[9]

Problem-solving is the process of establishing a goal, executing actions to achieve that goal, and overcoming obstacles to achieve that goal. It is a complex cognitive ability that depending on a few abilities, such as attention, perception, memory, concepts, and, in most cases, symbolic processes such as language.[1,3] The activities in which children participate become more complex as they get older, and their ability to solve problems improves. Children encode more details about a problem and allocate their attention more efficiently while encoding. As they grow older, children use information about their routine behavior and the characteristics of their surroundings to solve problems.[3,10]

Furthermore, children learn a variety of powerful thinking techniques, such as rule-based reasoning, analogies, and hierarchical classification. The ability to gather premises in order to reach a conclusion is referred to as reasoning.[11,12] Between the ages of 12 and 24 months, observing a child's ability to lift boxes to find a toy, unwrap a toy, turn pages in a book, find hidden toys, and match objects into pairs or pictures can reveal his or her problem-solving ability and reasoning. Throughout childhood, the ability to reason, to draw conclusions or inferences from facts or premises, develops.[1,3,9]

Attention management, inhibition control, decision making, planning, and working memory are all examples of Executive Functions. Attention involves the recognition and selection of particular sensory input in order to process it more thoroughly in working memory, as well as the ability to focus in one direction.[12] Over the course of early childhood, children improve their attention control and become less easily distracted. Learning requires selective attention; to learn, a person must

focus on the relevant aspects of his or her environment and ignore the irrelevant ones.[3]

Learning how to control one's attention and shift to another's attention is also crucial. Despite the fact that infants exhibit some attentional control during the first year of life, it is not until early elementary school that children demonstrate significant improvements in their ability to focus on relevant environmental features during a learning task.[10,13] Focus is the capacity to concentrate one's attention and interests on a single activity. Observing a child's focus involves looking at him or her for extended periods of time and attempting to comprehend a situation, despite having a short attention span.[11]

Psychomotor skills refer to a toddler's increasing control over their body movements and ability to manipulate objects with greater precision. This element is composed of two skills: gross motor and fine motor.[11] The wide-based, slightly stooped, and staccato gait of a 12-month-old child changes into an upright, narrow-based gait. Similarly, running develops shortly after walking, beginning as a stiff-legged approximation and evolving into a well-coordinated movement by 18 months of age that includes rapid changes in speed and direction. Over the course of a year, their fine motor skills and problem-solving abilities improved, which fuelled their desire to repeatedly practice. The development of intrinsic muscle control permits the index finger to be isolated, enabling infants to poke their fingers into small holes in order to explore. By the time they are 12 months old, the majority of infants enjoy repeatedly placing objects in containers and emptying them. In addition, they are able to pick up and bring to their mouths small food items using an advanced pincer grasp.[10,14]

Children over the age of one are in word-combination periods, during which they acquire language skills at an astounding rate. Typically, a child can use three words by the age of 13 months, and 20 words by the age of 18 months. The majority of these words are the names of familiar caregivers, as well as favorite foods and activities, and the child may begin to combine two words.[10] His receptive language abilities will be slightly more advanced than his expressive language abilities, and he will be able to comprehend more complex instructions than he can express. At this age, the toddler also imitates past events using symbols or actions. The development of the older toddler's symbolic reasoning continues to advance. The child's cognitive development is increasingly verbal, and they exhibit remarkable communication and problem-solving skills.[13] Problem-solving and fine motor skills acquired after the first year of life are dependent on the gross and fine motor skills acquired during the first year. As children form similar associations between these skills, the development of one skill promotes or facilitates the development of another.[9]

Cognitive development in the first year of life

A child's development during their first year of life can be assessed in terms of motor development and cognitive development, respectively. Initially, gross motor development proceeds through a series of prone milestones (beginning with the head up and ending with rolling), followed by sitting and finally standing. The development of fine motor skills is also evident in the first year of life, as evidenced by a stronger grasp.[10,15]

Since children under one year old is still developing, mainly for non-verbal, a few domains can be used to assess cognitive development, including problem-solving, social/emotional, and language.[3,10] There are no standardized intelligence tests for measuring infant intelligence as there are for measuring intelligence in school-age children. The primary pediatrician can make the most accurate assessment of infant intelligence by observing problem-solving and language development milestones. Language ability is the single most accurate predictor of intellectual potential; problem-solving abilities are the second most accurate predictor. It is possible to estimate verbal intelligence via language development and nonverbal intelligence via problem-solving domain skill development.[3,15]

Language abilities, which include both receptive and expressive abilities, are the most difficult to observe because infants rarely spontaneously vocalize in the clinician's office. In contrast to receptive skills, which reflect the ability

to comprehend language, expressive skills reflect the capacity to express one's own thoughts, ideas, and desires. There are numerous ways in which language can be expressed, including speech, gestures, sign language, writing, typing, and so-called "body language." Therefore, language and speech are not synonymous terms. Pre-speech periods and naming periods are the two periods found in infants younger than one year old. In terms of receptive language skills, a student may progress from alerts, orients, and responds to follows command. As for expressive language skills, infants begin to exhibit coos, smiles, and vocalizations within the first three months, and then develop reduplicate consonants, echolalia, and the ability to say "dada" and "no" prior to uttering their first words.[3,10,15]

As part of problem-solving skills, infants' complex cognitive abilities, such as concentration and memory, can be evaluated. The ability to manipulate objects to solve problems (e.g., selecting the correct opening for a circular shape on a three-piece form board) and observing how infants interact with a variety of test objects permits the evaluation of their nonverbal intelligence. Focus and memory can be predicted by observing a child's gaze, concentration, recognition, and exploration of a person or toy.[3,9,10]

Cognitive measurements by healthcare professionals in clinical settings

Identifying children with developmental delays as early as possible is essential. However, only a certified medical professional, typically a pediatrician in healthcare settings, can make an accurate diagnosis. Pediatricians may refer to other sub-specialties or disciplines, when necessary, but they are the most knowledgeable and trusted professional with whom most families interact during the first five years of a child's life. Parents view pediatricians as the authority on their child's holistic growth and development, so they visit pediatricians not only to diagnose physical illnesses, but also for advice on cognitive and mental development.[5]

The importance of development screening instruments has improved over the years, and pediatricians now have access to instruments that are both accurate and simple to use in an office setting. The American Academy of Pediatrics (AAP) recommends that all healthy children undergo developmental surveillance and are also screened for developmental delays at ages 9, 18, and 30 months to allow for early intervention.[4,5]

There is a variety of screening tools available to determine developmental delays in children. It can be classified according to the objectives of administering the test, such as the Denver-II Developmental Screening Test and the Parents' Evaluation of Developmental Status (PEDS) for general developmental screening; the Capute scales and Bayley Scales of Infant Development (BSID) for cognitive domain-specific assessment and the Modified Checklist for Autism in Toddler (M-Chat) Revised are used to assess specific developmental delays.[4] The Bayley Scales of Infant Development III is the gold standard for assessing cognitive development in children under the age of two. The BSID-III assesses infant and toddler development across cognitive, language, motor, social-emotional, and adaptive domains from 1 to 42 months of age.[16]

Pediatricians may turn to the Capute Scales when time is limited, and they need an easier-to-use screening tool than the BSID. The Capute Scales are also highly valid in their ability to assess infants and toddlers in a variety of key developmental areas.[17] There are two Capute Scales: The Cognitive Adaptive Test (CAT) and the Clinical Linguistic and Auditory Milestone Scale (CLAMS). This examination is also referred to as the CAT-CLAMS examination. CAT components differentiate between global developmental delay (cognitive, intellectual, and mental retardation) and communication difficulties, whereas CLAMS components differentiate between mental retardation, language difficulties, and a variety of autism spectrum disorders. The CAT-CLAMS is a promising test that was developed specifically for pediatricians to use in the office. It assesses a child's cognitive and language abilities independently, utilizing parental reports and direct testing of the child's abilities.[4,5] The study discovered that the CAT-CLAMS test is more convenient and faster to administer in

developmental screening, specifically language and visual-motor. It successfully assesses a variety of developmental disabilities in infants and children. [17,18]

Each screening instrument has distinct advantages and disadvantages. The method of testing may be determined by population risk factors, the amount of time available for the procedure, the availability of other developmental screening resources in the community, and the pediatrician's personal preference. For example, the Denver-II screening test is widely used but has a low sensitivity and specificity depending on how questionable results are interpreted. Additionally, each test must be administered according to specific instructions; otherwise, the results will be invalid.[4] Recent reviews of commonly used screening instruments can assist pediatricians in making screening instrument selection decisions .[5,15,19] There are several tools for assessing developmental delays, but each requires the expertise of a pediatrician and is too complicated for use in parental settings; therefore, there is a need for a community-based assessment instrument.

Key cognitive indicators for practical use in community settings

While pediatricians and healthcare practitioners already have a number of accurate screening tools to measure cognitive development and diagnose cognitive delays, but a community-based tool for parents that is accurate yet easy to understand without overwhelming the parents is quite scarce. An important new method for identifying infants and young children with developmental problems is to systematically elicit parental concern about development. Parental concerns regarding language, motor skill, cognitive, and emotional-behavioral development are highly indicative of actual issues.[4] As a result, parents also need to have an understanding of the indicators of cognitive development in order to seek out the appropriate professionals in a timely manner.[20]

Recent evidence indicates that parenting interventions that include components to directly enhance early child learning or strengthen parent–child relationships are more effective for enhancing early cognitive, language, motor, and socioemotional development than other types of interventions, including nutrition and health.[21,22] Parenting intervention programs include those that promote parents'/caregivers' knowledge, attitudes, practices, and skills regarding early child development.[23]

Recent studies have demonstrated the importance of parental belief for optimal cognitive development in children Miller's (1988) systematic review was the first to demonstrate that parental beliefs about their children's cognitive development influence parental behavior, and that parental behavior influences child development. Parents' beliefs are found to influence their judgment and knowledge of their children's cognitive abilities, and as a result, they may modify their parenting techniques.[24] On the cognitive and motor development of children, parents with greater knowledge under a responsive caregiving program exhibit greater differences than those without such knowledge.[25] In addition, the study revealed that an increase in parental/provider knowledge of child language development will result in a high-quality childcare language environment, which will contribute to better cognitive outcomes for children.[21]

Given the importance of positive parental belief on the child's holistic development, it is essential to enhance parental self-efficacy or confidence through education on child development and/or child-rearing at different stages. Confidence, often referred to as self-efficacy, describes a parent’s self-belief in their ability to perform the parenting role. Increased knowledge, abilities, and self-assurance are positively associated with child development processes and milestones. Parents will be more aware of their child's developmental milestones in a variety of cognitive domains and can consult professionals as needed if simple cognitive indicators are provided.[22]

Multiple domains can be used to screen cognitive function in community settings, according to studies, but such research is largely undertaken outside Indonesia. In a study conducted in Malaysia, the cognitive abilities of children younger than two years old are evaluated based on

their sensor development, exploration and manipulation, object relatedness, concept formation, memory, and cognitive processing.[26] A systematic review that collected data from the Philippines, Germany, France, Switzerland, and Canada on cognitive domains including language, spatial, memory, and executive function found evidence that these domains can predict cognitive function in children under the age of five.[27] One national study in the United States identifies high-priority aspects of cognition that can be measured efficiently and effectively in children between the ages of birth and three. This cognitive development measurement includes six domains: executive function skills, memory, language, processing speed, spatial and numerical processing, and social cognition.[28] Indicators of cognitive development must encompass a variety of domains in a manner that is both comprehensive and tailored to local needs. Multiple nations have developed their own indicators, which cover multiple previously introduced domains. A simplified approach to cognitive measurements may be more useful than a standard cognitive assessment used in clinical setting, making it easier to be used by parents.[28]

Several cognitive development assessment domains overlap, as suggested by Piaget's theory and the aforementioned studies. Summed up, these studies mention and highlight eight domains based on their reliability and usability: executive function (regarding focus & attention), memory, language, psychomotor, logic and reasoning, and decision-making and problem-solving. It can be concluded that there are a number of cognitive development indicators that can be used to inform and educate parents in order to facilitate effective communication regarding optimal cognitive development. Therefore, we propose a comprehensive yet streamlined cognitive development indicator for children older than one year, which includes eight key indicators: attention, concentration (focus), memory, language, psychomotor, logic, reasoning, and decision-making. As cognitive skills in children under one year old are not yet fully developed and are primarily nonverbal, five key indicators, including language, psychomotor skills, attention, focus, and memory, can be used to raise community awareness of optimal cognitive development.

Conclusions

It is a fascinating process for both the child and their parents to watch their child's cognitive development take place. Developmental surveillance and screening for developmental delays are recommended for all healthy children to avoid late intervention. In the community, it is also important to educate and inform parents about children's cognitive developments milestone. There are several skills that are essential for achieving optimal cognitive growth. We proposed 8 key indicators of cognitive development in infants and children as simplified approach to effectively communicate to parents. The indicators which can be used for children older than one year old consist of: attention, focus, memory, language, psychomotor, logic, reasoning and decision making. In the first year, considering that infants are still undergoing rapid cognitive development process, five indicators namely memory, attention & focus, psychomotor skills, and language can be used to screen their cognitive development.

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Conflict of Interest

R.W.B. and M.S.K. are employees of Danone SN Indonesia. All other authors have no conflict of interest.

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