



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 be 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-1 β (IL-1 β) 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.

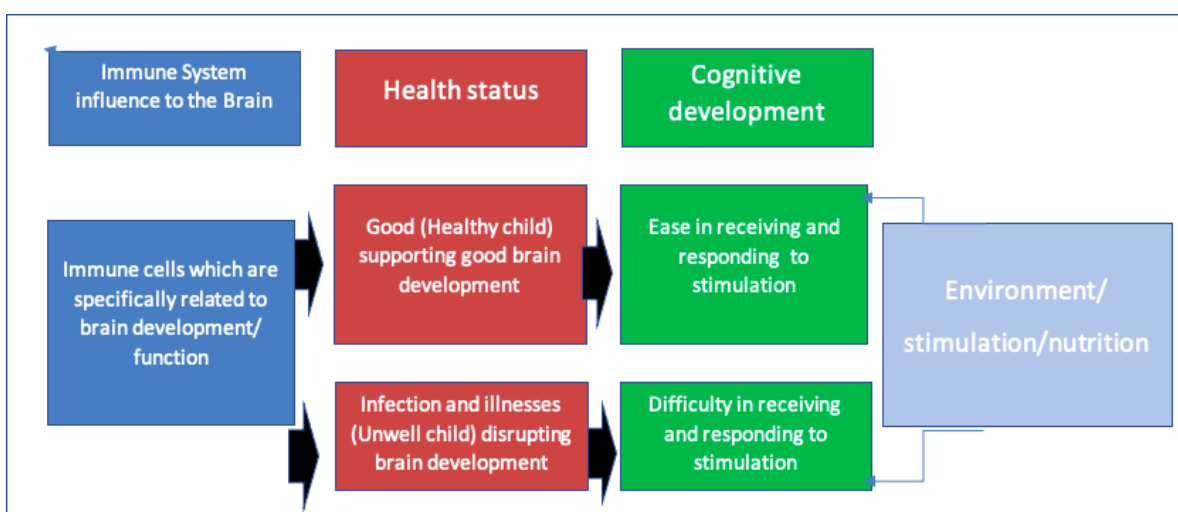


Figure 1. The role of immunity in children cognitive development

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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References

1. Vandenbroucke L, Spilt J, Verschuere K, Piccinin C, Baeyens D. The classroom as a developmental context for cognitive development: A meta-analysis on the importance of teacher–student interactions for children’s executive functions. *Rev Educ Res*. 2018;88(1):125–64.
2. Mollon J, Knowles EEM, Mathias SR, Gur R, Peralta JM, Weiner DJ, et al. Genetic influence on cognitive development between childhood and adulthood. *Mol Psychiatry* [Internet]. 2021;26(2):656–65. Available from: <http://dx.doi.org/10.1038/s41380-018-0277-0>
3. Prins JR, Eskandar S, Eggen BJL, Scherjon SA. Microglia, the missing link in maternal immune activation and fetal neurodevelopment; and a possible link in preeclampsia and disturbed neurodevelopment? *J Reprod Immunol* [Internet]. 2018;126(June 2017):18–22. Available from: <https://doi.org/10.1016/j.jri.2018.01.004>
4. Ott JA, Castro CD, Deiss TC, Ohta Y, Flajnik MF, Criscitiello MF. Somatic hypermutation of T cell receptor α chain contributes to selection in nurse shark thymus. *Elife*. 2018;7:1–31.
5. Pronovost GN, Hsiao EY. Perinatal Interactions between the Microbiome, Immunity, and Neurodevelopment. *Immunity* [Internet]. 2019;50(1):18–36. Available from: <https://doi.org/10.1016/j.immuni.2018.11.016>
6. Connor DJ, Norman MA. Chapter 4 Assessment of Cognitive Status. 2014;85–117.
7. Morimoto K, Nakajima K. Role of the Immune System in the Development of the Central Nervous System. *Front Neurosci*. 2019;13(September).
8. Di Benedetto S, Müller L, Wenger E, Düzel S, Pawelec G. Contribution of neuroinflammation and immunity to brain aging and the mitigating effects of physical and cognitive interventions. *Neurosci Biobehav Rev* [Internet]. 2017;75:114–28. Available from: <http://dx.doi.org/10.1016/j.neubiorev.2017.01.044>
9. Li JT, Zhang Y. TREM2 regulates innate immunity in Alzheimer’s disease. *J Neuroinflammation*. 2018;15(1):1–7.
10. Korin B, Ben-Shaan TL, Schiller M, Dubovik T, Azulay-Debby H, Boshnak NT, et al. High-dimensional, single-cell characterization of the brain’s immune compartment. *Nat Neurosci* [Internet]. 2017;20(9):1300–9. Available from: <http://dx.doi.org/10.1038/nn.4610>
11. Labzin LI, Heneka MT, Latz E. Innate Immunity and Neurodegeneration. *Annu Rev Med*. 2018;69(October 2017):437–49.
12. Wang X, Xuan W, Zhu ZY, Li Y, Zhu H, Zhu L, et al. The evolving role of neuro-immune interaction in brain repair after cerebral ischemic stroke. *CNS Neurosci Ther*. 2018;24(12):1100–14.
13. Franco Bocanegra DK, Nicoll JAR, Boche D. Innate immunity in Alzheimer’s disease: the relevance of animal models? *J Neural Transm*. 2018;125(5):827–46.
14. Da Mesquita S, Louveau A, Vaccari A, Smirnov I, Cornelison RC, Kingsmore KM, et al. Functional aspects of meningeal lymphatics in ageing and Alzheimer’s disease. *Nature* [Internet]. 2018;560(7717):185–91. Available from: <http://dx.doi.org/10.1038/s41586-018-0368-8>
15. Brombacher TM, Nono JK, De Gouveia KS, Makena N, Darby M, Womersley J, et al. IL-13–Mediated Regulation of Learning and Memory. *J Immunol*. 2017;198(7):2681–8.
16. Smolders SMT, Kessels S, Vanganswinkel T, Rigo JM, Legendre P, Brône B. Microglia: Brain cells on the move. *Prog Neurobiol* [Internet]. 2019;178. Available from: <https://doi.org/10.1016/j.pneurobio.2019.04.001>
17. Fernández de Cossío L, Guzmán A, van der Veldt S, Luheshi GN. Prenatal infection leads to ASD-like behavior and altered synaptic pruning in the mouse offspring. *Brain Behav Immun*. 2017;63:88–98.
18. Paolicelli RC, Jawaid A, Henstridge CM, Valeri A, Merlini M, Robinson JL, et al. TDP-43 Depletion in Microglia Promotes Amyloid Clearance but Also Induces Synapse Loss. *Neuron* [Internet]. 2017;95(2):297–308.e6. Available from: <http://dx.doi.org/10.1016/j.neuron.2017.05.037>
19. Salter MW, Stevens B. Microglia emerge as central players in brain disease. *Nat Med* [Internet]. 2017;23(9):1018–27. Available from: <http://dx.doi.org/10.1038/nm.4397>
20. Thion MS, Garel S. Microglia Under the Spotlight: Activity and Complement-Dependent Engulfment of Synapses. *Trends Neurosci* [Internet]. 2018;41(6):332–4. Available from: <http://dx.doi.org/10.1016/j.tins.2018.03.017>

21. Zengeler KE, Lukens JR. Innate immunity at the crossroads of healthy brain maturation and neurodevelopmental disorders. *Nat Rev Immunol* [Internet]. 2021;21(7):454–68. Available from: <http://dx.doi.org/10.1038/s41577-020-00487-7>
22. Connolly KJ, Kvalsvig JD. Infection, nutrition and cognitive performance in children. *Parasitology*. 1993;107(S1):S187–200.
23. Azziz-Baumgartner E, Gonzalez R, Davis W, Calvo A, Olson N, Grant L, et al. Lower cognitive scores among toddlers in birth cohorts with acute respiratory illnesses, fevers, and laboratory-confirmed influenza. *Influenza Other Respi Viruses*. 2022;16(1):101–12.
24. Ijaz MK, Rubino JR. Impact of infectious diseases on cognitive development in childhood and beyond: Potential mitigational role of hygiene. *Open Infect Dis J*. 2012;6(1):65–70.
25. Kvestad I, Taneja S, Hysing M, Kumar T, Bhandari N, Strand TA. Diarrhea, stimulation and growth predict neurodevelopment in young North Indian Children. *PLoS One*. 2015;10(3):1–13.