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Interactions of innate and adaptive immunity in brain development and function

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Abstract

It has been known for decades that the immune system has a tremendous impact on behavior. Most work has described the negative role of immune cells on the central nervous system. However, we and others have demonstrated over the last decade that a well-regulated immune system is needed for proper brain function. Here we discuss several neuro-immune interactions, using examples from brain homeostasis and disease states. We will highlight our understanding of the consequences of malfunctioning immunity on neurodevelopment and will discuss the roles of the innate and adaptive immune system in neurodevelopment and how T cells maintain a proper innate immune balance in the brain surroundings and within its parenchyma. Also, we describe how immune imbalance impairs higher order brain functioning, possibly leading to behavioral and cognitive impairment. Lastly, we propose our hypothesis that some behavioral deficits in neurodevelopmental disorders, such as in autism spectrum disorder, are the consequence of malfunctioning immunity.

Keywords

Neuroimmunology; Microglia; Innate and adaptive immunity; Autism spectrum disorder; Rett; Syndrome

Introduction

The immune and nervous systems are complex systems that rely heavily on the interactions of multiple cell types for normal development and function. In the immune system, host-defense and long-term memory immunity are accomplished by the coordinated efforts of the innate and adaptive arms. The innate arm of the immune system provides a general first line of defense against pathogens, and includes phagocytes such as macrophages (brain resident

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macrophages are referred to as microglia) and granulocytes such as neutrophils. The adaptive arm, which includes T and B cells, is used to provide memory for subsequent pathogen challenges. In the nervous system, behaviors are output of integrated neural circuits that are balanced by excitatory and inhibitory neurons, supporting glia, and constant dialogue between cells. In both systems inter-cellular communications yield astounding complexity, and it is perhaps more astonishing then to consider that the systems do not exist in isolation but actually relies upon each other for normal function

The immune and nervous systems are intimately connected and each can directly influence the behavior of the other. The brain can influence immune function via glucocorticoids (Besedovsky et al., 1986) and catecholamines (Kipnis et al., 2004a, Flierl et al., 2008), as well as direct stimulation of lymphoid organs (Nance and Sanders, 2007, Rosas-Ballina et al., 2011). The immune system can likewise influence brain function by multiple mechanisms; this is quite obvious to anyone experiencing sickness behavior from infection (Hart, 1988, Dantzer and Kelley, 1989). It is thought that sickness behavior, although uncomfortable, is beneficial for clearing infections (Dantzer et al., 2008). Changes in behavior including social withdrawal, loss of appetite, lethargy, amongst others, result from elevated levels of pro-inflammatory molecules, most notably: tumor necrosis factor (TNF), interlukin-1β (IL-1β), and IL-6 (Dantzer, 2001). These molecules are produced by circulating immune cells and macrophages and affect neuronal function and behavior (Bluthe et al., 2000, Balschun et al., 2004). In addition to soluble molecules, microglia directly interact with neurons and maintain a proper excitatory/inhibitory balance (Pascual et al., 2012, Zhan et al., 2014). Disrupting these tightly controlled interactions or the imbalance in immune molecules can cause a pro-inflammatory skew and produce life-long changes in neuronal function and behavior (Hsiao and Patterson, 2012, Zhan et al., 2014). Neurodevelopment continues well after birth (Lebel and Beaulieu, 2011) and offers a large time window for immune influence. Although the mechanisms of how the immune system shapes neuronal function and behavior are just beginning to be uncovered (Kipnis et al., 2012), immune dysregulation is most evident in common neurodevelopmental disorders.

Pro-inflammatory Skew in Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a common clinical diagnosis for a heterogeneous group of neurodevelopmental disorders that is estimated to affect 1 in every 68 children (Baio, 2014). The diagnosis is clinically described by dysfunction in social behavior and language, abnormal response to sensory input, and often include repetitive behavior and cognitive disabilities (American Psychiatry Association, 2013). Direct genetic alterations can account for only approximately 10% of all ASD (Abrahams and Geschwind, 2008). Therefore, it is likely that a combination of genetic and alternative variables, such as environmental factors and immunity, contribute to the etiology of ASD.

A pro-inflammatory phenotype can be measured in numerous tissues from patients with ASD. For example, microglia have an activated morphology in numerous brain regions, most notably the frontal cortex and cerebellum, by postmortem analysis of brains from ASD patients (Vargas et al., 2005, Morgan et al., 2010). The age range of these cohorts spanned 40 years suggesting an early and prolonged chronic state of inflammation in ASD (Vargas et

al., 2005). This pro-inflammatory phenotype is not limited to the CNS and was observed in peripheral immune cells. T cells isolated from autism patients were hyperexcitable, having an exaggerated response when stimulated with the mitogen phytohaemagglutinin *ex vivo* (Ashwood et al., 2011b). Several clinical studies also measured elevated pro-inflammatory molecules, such as IL-6, in the plasma (Ashwood et al., 2011a, Ashwood et al., 2011c, Brown et al., 2014), as well as decreased anti-inflammatory molecules, such as transforming growth factor (TGF)–β (Okada et al., 2007, Ashwood et al., 2008) suggesting an overall pro-inflammatory skew.

As it stands now, pro-inflammatory profiles and ASD remain correlative and no causation has been proven. Several studies determined a correlation with diseases of the immune system and ASD (Ashwood et al., 2011a, Ashwood et al., 2011c, Brown et al., 2014). It has yet to be determined if a pro-inflammatory skew can cause ASD, however, there was an increased risk for ASD in families with maternal history for autoimmune disease (Atladottir et al., 2009); also see McDougle *et al.* in this issue for a more comprehensive review of studies linking familial autoimmune disorders and ASD (McDougle et al., 2014)) and evidence of increased gut permeability and gastrointestinal disorders in ASD patients (Buie et al., 2010, de Magistris et al., 2010, Kohane et al., 2012, Hsiao, 2014, McElhanon et al., 2014). Possibly related to these gut phenotypes, disturbances in normal gut microbiota, or dysbiosis, have been described in patients with ASD (Finegold et al., 2010, Kang et al., 2013). The healthy gut hosts a symbiotic microbiota that has been shown to be necessary for the proper development of the immune system (Kamada et al., 2013). Although neonates are more susceptible to infection at this critical developmental point, establishment of a normal microbiota is important and neonates actively suppress inflammation via $CD71^{+}$ erythroid cells to assure proper gut colonization (Elahi et al., 2013). The colonization of symbiotic bacteria is necessary for healthy intestinal homeostasis and can contribute to diseases of the gut as well as the CNS (Maloy and Powrie, 2011, Mortha et al., 2014, Wang and Kasper, 2014). The role of the gut microbiota in a gut-brain-behavior axis is only beginning to emerge (Rook et al., 2014). Dysbiosis in mice alone can lead to similar neurodevelopmental behavioral dysfunction observed in ASD. Germ-free mice had social deficits that can be corrected by colonization of the germ-free gut (Desbonnet et al., 2014). Increasing the pro-inflammatory skew of the fetal environment (discussed below) also caused dysbiosis and probiotic treatment with *B. fragilis* was sufficient to correct the leaky gut, elevated IL-6 levels, and behavioral deficits (Hsiao et al., 2013).

Pro-inflammatory skew *in utero*: Maternal Immune Activation

It is possible that these inflammatory conditions are hereditable but also that maternal conditions may affect development *in utero* (Abdallah et al., 2012, Brown et al., 2014). In fact, there was a strong association between an ASD diagnosis and maternal infections occurring in the first 2 trimesters (Atladottir et al., 2010). Also, as high as 23% of mothers with ASD children had circulating antibodies with specificity to fetal brain antigens and this specificity correlated with the offspring's repetitive behaviors (Braunschweig et al., 2008, Goines et al., 2011, Wills et al., 2011, Braunschweig et al., 2013). Pregnant mice and monkeys exposed to antibodies isolated from ASD mothers led to hyperactivity and repetitive behaviors in their offspring (Martin et al., 2008, Singer et al., 2009). Although

numerous studies have correlated maternal infection with the onset of neurodevelopmental disorders, the damage is likely due to a pro-inflammatory fetal environment rather than direct effects from the infectious agent itself (Patterson, 2002, Shi et al., 2005).

These associations between infection during pregnancy and autism risk led to the development of maternal immune activation (MIA) as a disease model, which can mimic behavioral and histological dysfunctions observed in ASD in multiple mammalian systems. Treatment of pregnant rodents or monkeys with bacterial (LPS) or viral (Poly(I:C)) mimetics resulted in autistic-like behavioral dysfunction in the offspring (Zuckerman et al., 2003, Fortier et al., 2004, Shi et al., 2005, Ozawa et al., 2006, Malkova et al., 2012, Bauman et al., 2014). Behavioral abnormalities include deficits in social and exploratory behavior, sensorimotor gating, and increased compulsive behavior (Meyer et al., 2006, Smith et al., 2007, Hsiao et al., 2013). The mechanism of MIA-induced pathology, however, remains unclear, but seems to be dependent on specific T cell populations (i.e. decreased T regulatory cells and the malfunction of $CD4^+$ T cells; (Hsiao et al., 2012). Some behavioral abnormalities were corrected when the immune systems of MIA offspring were replaced by transplanting them with wild-type bone marrow after irradiation (Hsiao et al., 2012). IL-6 is also likely involved (Smith et al., 2007). The behavioral deficits observed by MIA can be mimicked by injecting IL-6 into pregnant dams, and administration of an IL-6 neutralizing antibody or use of IL-6 deficient mice was sufficient to prevent the deficits caused by poly(I:C) injections (Smith et al., 2007).

Taken together, it appears that the immune profile in ASD is skewed to a pro-inflammatory phenotype and that a pro-inflammatory skew may interact with brain development. Although the cause for ASD is currently unknown, several large studies have revealed an association with genes involved in synaptic dysfunction (Zoghbi and Bear, 2012, Ebert and Greenberg, 2013). This begs the question; can a pro-inflammatory skew in the fetal environment hinder synaptic function?

The behavioral dysfunction after MIA is likely due to a number of underlying changes in normal brain function. Pathological changes in brain histology, chemistry, and electrophysiology after MIA highlight the importance of the fetal environment on the development of proper brain circuitry. MIA caused crude anatomical changes, such as enlarged ventricles and small hippocampal volumes, a region critically important for cognition (Li et al., 2009, Piontkewitz et al., 2009). Whether these changes are a consequence of neuronal cell death is questionable and mixed results have been published (Zuckerman et al., 2003, Meyer et al., 2006, Oh-Nishi et al., 2010). However, measurements of neuronal function suggest synaptic and overall network dysfunction in MIA offspring. Multiple neurotransmitter systems, including the dopaminergic, GABAergic, glutamatergic, and serotonergic systems, are imbalanced (Dickerson and Bilkey, 2013). Although heterogeneity exists in the data, MIA seems to cause an overall decrease in neuronal activity; in the hippocampus, excitatory input to pyramidal cells in CA1 were decreased (Zuckerman et al., 2003) as well as decreased baseline synaptic transmission and LTP in the Schafer collaterals (Ito et al., 2010). In the cortex, markers for glutamatergic synapses were decreased (Elmer et al., 2013). It is likely that MIA affects multiple brain regions and leads to an imbalance in overall network integration. Decreased synchrony between the prefrontal

cortex and the hippocampus suggests long-range network dysfunction (Dickerson et al., 2010). This is particularly interesting as the prefrontal cortex plays a role in social behavior of humans and mice (Wang et al., 2011, Gariepy et al., 2014) and has be implicated in ASD (Itahashi et al., 2014, Jung et al., 2014, Stoner et al., 2014). These data demonstrate the lasting consequences of an *in utero* pro-inflammatory environment on neuronal function and behavior in the rodent.

Overall, dysregulation of the immune system in development, most notably a skew to a more pro-inflammatory phenotype, can adversely affect normal brain development. Furthermore, at least a subset of ASD cases are linked to maternal infections, but the exact detrimental components of these infections, the genetic traits that confer vulnerability, and the percent of autism cases associated with them remains unknown. It seems likely that ASD is an umbrella term for diseases of multiple etiologies, maternal infection being one. How a pro-inflammatory skew actually perturbs neuronal development is unclear, but many immune factors can affect neuronal function. Several immune-related molecules (such as complement proteins (Stevens et al., 2007) and MHC-I (Huh et al., 2000)) have pleotropic functions in the brain where they can directly affect synaptic function in the CNS (Boulanger, 2009, Garay and McAllister, 2010). Moreover, it has also been shown that circulating immune cells themselves can alter neuronal function and behavior.

T cell Deficiency and Brain Function

Numerous techniques, both genetic and pharmacological, have been used to investigate the role of the adaptive immune system in normal brain physiology. Our lab (Kipnis et al., 2012) was among the first to assign a beneficial role for T cells in cognition and behavior (Kipnis et al., 2004b, Cohen et al., 2006, Ziv et al., 2006, Brynskikh et al., 2008, Wolf et al., 2009). After training for a cognitive task, $CD4^+$ T cell numbers increased in the meninges surrounding the brain, and blocking this increase was sufficient to cause cognitive impairment (Derecki et al., 2010). Moreover, surgical excision of CNS-draining deep cervical lymph nodes also resulted in abnormal immune repertoire in the meningeal spaces and correlated with impaired learning behavior (Radjavi et al., 2014). Along these lines, immune compromised mice have impaired cognitive and emotional behaviors that have been attributed specifically to $CD4^+$ T cells. Severe combined immunodeficiency (SCID), $Rag1^{-/-}$, and $Rag2^{-/-}$ mice (which lack T cells and B cells), nude mice (which lack mature T cells), and OTII mice (which lack T cells recognizing self-antigens) all demonstrated impaired learning and memory (Kipnis et al., 2004b, Ziv et al., 2006, Brynskikh et al., 2008, Derecki et al., 2010, Radjavi et al., 2014). Replacing $CD4^+$ T cells was sufficient to prevent this cognitive deficit, demonstrating that a functional T cell pool is necessary for normal brain function (Derecki et al., 2010). Interestingly, repopulation of T cells from IL-$4^{-/-}$ mice did not improve cognition in T cell deficient mice, revealing the role of IL-4 as a major mediator of pro-cognitive immunity (Derecki et al., 2010). The deficits caused by $CD4^+$ T cell depletion are not limited to cognitive deficits. RAG-$1^{-/-}$ mice, which lack T and B cells, had compulsive behavior and deficits in nest building that was fixed by repopulating $CD4^+$ T cell pools (Rattazzi et al., 2013). Further experiments showed that antigen specific T cells, most likely effector-memory T cells, were needed for proper cognition (Baruch et al., 2013, Radjavi et al., 2014). These data demonstrate that not only are T cells needed for normal

brain function, but specific populations of T cells in a distinct compartment are needed. How is it that peripheral immune cells communicate with the brain? A functional blood-brain barrier exists early in development (Ek et al., 2012) and no peripheral immune cells are detected within the normal brain parenchyma. Our data suggest that the communication between immune cells and the CNS occurs at the barriers between the brain and the periphery, i.e. the meningeal spaces (Kipnis et al., 2012). Taken together that IL-4 producing T cells can benefit cognition, it is possible that IL-4 produced by T cells in the meninges and cerebrospinal fluid prevents a pro-inflammatory skew of CNS myeloid cells, which may impact normal neuronal function (Figure 1). A lack or malfunction of T cells could, therefore, result in a lack of regulation of meningeal myeloid cells allowing their pro-inflammatory skew. In line with this hypothesis, injecting macrophages treated with IL-4 *ex vivo* into SCID mice ameliorated the pro-inflammatory skew of their meningeal myeloid cells and improved cognitive function, even in the absence of functional T cells (Derecki et al., 2011). Interestingly, both decreased T cell numbers (Warren et al., 1990, Yonk et al., 1990, Saresella et al., 2009) and dysfunction (Ashwood et al., 2011b) have been associated with some cases of autism spectrum disorders. Thus, if T cell malfunction results in a pro-inflammatory skew of meningeal myeloid cells that lead to impaired cognitive function, it is plausible that T cell malfunction or scarcity in autism may underlie some of the cognitive impairment associated with autism spectrum disorders.

Besides meningeal macrophages, microglia and astrocytes may also respond to meningeal cytokine contents and acquire a pro-inflammatory skew in the absence of T cells. For instance, astrocytes express the IL-4 receptor and astrocyte cultures respond to IL-4 by producing BDNF and NGF (Brodie et al., 1998, Derecki et al., 2010). Likewise, it is not surprising that microglia express the IL-4 receptor and control local inflammation through IL-4 signaling under multiple circumstances (Suzumura et al., 1994, Ponomarev et al., 2007, Fenn et al., 2014).

Microglia in Development and Disease

Microglia are the professional phagocytes of the CNS. They are of myeloid origin, populate the CNS early in development (~E9.5) (Ginhoux et al., 2010, Schulz et al., 2012) and are most probably maintained by local proliferation (Ajami et al., 2007). They are similar to other tissue resident macrophages but have evolved to maintain local neurons and circuits (for a more in depth review on microglial function see Bilimoria *et al.* is this issue (Bilimoria and Stevens, 2014)). In the healthy brain, microglia are classified as resting but their processes are very active and they continuously survey their surroundings (Nimmerjahn et al., 2005). It has recently been shown that microglia processes actually contact and engulf synaptic elements (Wake et al., 2009, Tremblay et al., 2010, Paolicelli et al., 2011, Schafer et al., 2012), suggesting that microglia may play a role in synaptic plasticity. In development, deletion of the microglial fractalkine receptor ($CX3CR1^{-/-}$) transiently decreased microglia in the hippocampus and aberrantly increased synaptic activity and susceptibility to induced seizures (Paolicelli et al., 2011). By 40 days after birth, most of these readouts were normalized suggesting a delay in synaptic pruning. Conversely, another study showed increased microglia in layer V of the cortex in mice deficient for the fractalkine receptor (Ueno et al., 2013). They also observed an increase in layer V apoptotic

neurons. Microglia deficient for CX3CR1 were still able to engulf apoptotic neurons but were unable to offer neurotrophic support to surrounding neurons. Both of these studies highlight the important role of microglia on neuronal function. This idea was most elegantly extended by looking at functional connectivity in CX3CR1$^{-/-}$ mice (Zhan et al., 2014). These mice had reduced connectivity between prefrontal cortex and hippocampus (by resting-state fMRI and EEG) and ultimately decreased social behavior and repetitive grooming. The direct effect of adult microglia on neuronal function was determined in a recent study, where conditional elimination of microglia in adulthood decreased the frequency of both NMDA and AMPA receptor-mediated miniature excitatory postsynaptic currents (mEPSCs) and resulted in cognitive impairments (Parkhurst et al., 2013). These and other studies hint at a role for microglia in homeostasis, sculpting or “pruning” circuits in the developing and mature brain by targeted phagocytosis. Despite these data that microglia affect pruning and behavior, acute depletion of microglia in adulthood with PLX3397 (which targets Csf-1R, KIT, and FLT3; Plexxikon, Inc.) had minimal effects on behavior (Elmore et al., 2014). In fact, mice treated with PLX3397 for 3 weeks showed improved learning curves in the Barnes maze (a measure of learning and memory). This is contradictory when a more abrupt technique was used to deplete microglia (i.e. CX3CR1 CreER:R26iDTR; (Parkhurst et al., 2013)) These mice had deficit in novel object recognition and classical fear conditioning. Perhaps this contradiction is due to the time course of microglia cell death and the ability of astrocytes (or other non professional phagocytes) to clean up cell debris.

The context in which microglia choose and engulf synaptic elements is under active investigation. Data suggests microglia engulf synaptic elements in an activity dependent manner. In the developing visual cortex, microglia tended to contact smaller spines (which are considered to be relatively transient than their larger more stable counterparts) (Tremblay et al., 2010). Over time, the small spines that were contacted by microglia were often eliminated. During dark adaptation and re-introduction to light, microglia tended to contact active spines and contain more synaptic-like inclusions, suggesting a role of microglial phagocytosis in synaptic remodeling (Tremblay et al., 2010). Another model even earlier in visual development, the establishment of ocular dominance at post-natal day 5, offers a unique system to investigate microglial phagocytosis in synaptic remodeling. In the lateral geniculate nucleus (a relay point in the visual system), microglia engulfed presynaptic terminals from retinal ganglion cells (Schafer et al., 2012). Manipulating neuronal activity with tetrodotoxin (decreasing) or forskolin (increasing) demonstrated that microglia preferentially engulfed inputs originating from the less active neurons. Microglial engulfment depended on the complement protein C3 and its microglial receptor CR3. Deleting either decreased engulfment by ~50% and impaired the formation of normal eye dominance patterns. C3 localized at synapses and this was dependent on upstream complement protein C1q and the cytokine transforming growth factor beta (TGF-β) (Bialas and Stevens, 2013). Whether C3 can selectively target a synapse for phagocytosis or whether many synapses are targeted and stronger synapses are able to offer “don’t eat me” signals have yet to be determined.

In addition to the engulfment of synapses, microglia also engulf apoptotic neurons. Apoptotic cell death of neuronal stem cells is needed for proper brain development.

Genetically blocking apoptosis altered a delicate proliferation/death balance and leads to an abnormally expanded nervous system and is often embryonic lethal (reviewed in (Boya and de la Rosa, 2005)). Neurogenesis continues throughout life and most of our current knowledge of how the immune system can affect development stems from the studies looking at postnatal neurogenesis. Microglia make contact with apoptotic neurons and promote cell apoptosis during development (Marin-Teva et al., 2004, Peri and Nusslein-Volhard, 2008, Wakselman et al., 2008). Apoptotic puncta were observed in the microglial branches (Sierra et al., 2010) and inhibiting phagocytosis increased apoptotic cells in the hippocampus (Lu et al., 2011). Further, inhibiting phagocytosis, either genetically or pharmacologically, decreased neurogenesis (Lu et al., 2011).

Microglial dysfunction can contribute to numerous neurodevelopmental disorders. As mentioned above, microglia had an activated morphology in ASD by postmortem analysis (Vargas et al., 2005, Morgan et al., 2010). While our understanding of the contribution of defective microglial in the early stages of disease pathogenesis is growing, the precise mechanisms are still not fully understood.

Rett syndrome is a neurodevelopmental disorder in which patients are often diagnosed with ASD based on their clinical symptoms. The disorder is caused by mutations in the methyl-CpG binding protein, Mecp2 (Van den Veyver and Zoghbi, 2001). Deletion of Mecp2 in mice led to severe pathology and death at ~8 weeks of age (Guy et al., 2001). Microglia isolated from Mecp2 null mice have defects in activation and phagocytosis suggesting they may contribute to the pathology (Derecki et al., 2012). Repopulating Mecp2-null mice with wild-type microglia (by bone-marrow transplantation or expression of a wild type Mecp2 in myeloid cells (including microglia) by genetic manipulation) was sufficient to attenuate disease progression. Repopulating with wild-type microglia has benefited other pathological behavior associated with ASD, such as repetitive behavior. For example, in the brain, HoxB is expressed by microglia (Chen et al., 2010) and deletion of HoxB in mice caused pathological grooming. This grooming pathology was efficiently rescued by repopulating the mice with wild-type microglia.

Communication Between the Innate and Adaptive Arms of the Immune System

It is becoming evident that both the innate and adaptive immune systems can affect the developing brain. Several clinical studies revealed a strong link between a pro-inflammatory skew and ASD (Ashwood et al., 2011a, Ashwood et al., 2011c, Brown et al., 2014). Elevated levels of pro-inflammatory cytokines and a pro-inflammatory phenotype of microglia were observed in post-mortem ASD patients (Vargas et al., 2005, Morgan et al., 2010). Mouse models, such as MIA, suggest that a pro-inflammatory skew in the fetal environment can cause behavioral changes that last well into adulthood (Hsiao and Patterson, 2012). Therefore, on one hand, immune activation seems to deleteriously affect brain development; on the other hand, presence and normally functioning T cells are is necessary for proper brain function (Derecki et al., 2010, Baruch and Schwartz, 2013, Radjavi et al., 2014). How can these seemingly opposite effects of immune activation be reconciled? It is likely that a delicate balance exist between proper activation needed for

beneficial immune maintenance and deleterious over-activation of immune cells that results in neuronal dysfunction.

Just as the immune system and nervous system communicate, the innate and the adaptive arms of the immune system closely interact to maintain proper immune balance. If the cells of the innate and the adaptive arms are not well regulated, brain function and development can be affected. This is exemplified in mice deficient for T cells. SCID mice had increased levels of pro-inflammatory cytokines, TNF and IL-12, in innate myeloid cells ($CD11b^+$) of their meninges. When injected into the circulation, anti-inflammatory macrophages (treated with IL-4) sufficiently recovered the pro-inflammatory skew and cognitive deficits of SCID mice (Derecki et al., 2011). These data suggest that T cells provide beneficial regulation by preventing a pro-inflammatory skew of innate myeloid cells and possibly microglia. Since T cells, residing in the meninges, and microglia, residing in the parenchyma, are physically separated, more work is needed to understand how these two compartmentalized cells communicate.

The behavioral deficits in ASD and other neurodevelopmental disorders are pathological and can be severe but it is intriguing to hypothesize that the immune system can contribute to the heterogeneity of normal human behavior. Neuroanatomical imaging studies on attention-deficit/hyperactivity disorder imply that behavioral abnormalities may be due to deviations in developmental timing and trajectories (Giedd and Rapoport, 2010). These same developmental patterns were linked with the severity of hyperactivity and impulsive behavior of normal developing children. In mice, prenatal exposure to a pro-inflammatory skew causes a delay in cortical development (Soumiya et al., 2011). Perhaps, subtle prenatal changes in the skewing of the fetal environment can play a role in sculpting our unique personalities.

Concluding remarks and take-home message

The immune system has profound effects on brain development and function. A pro-inflammatory skew of immune cells has been linked to many neurodevelopmental disorders, such as ASD, and MIA in animals can cause behavioral deficits in offspring. Although a dysregulated inflammatory environment is detrimental in development, functioning T cells are needed for immune homeostasis and proper brain function. $CD4^+$ T cell numbers are decreased in some ASD patients and T cells from patients and mouse models have exaggerated responses when stimulated. Mice lacking T cells have cognitive deficits and a pro-inflammatory skew of their meningeal myeloid cells, suggesting that T cells actively support normal function of tissue-resident myeloid cells and prevent them from unleashing pro-inflammatory molecules that can disturb normal brain development and function.

We propose that immune dysfunction in ASD and possibly other neurodevelopmental disorders, is not simply a manifestation of the pathology, but contributes to the development of the disorder. A healthy immune system is known to support brain function, and an altered one known to result in cognitive impairment. Furthermore, without the normal homeostatic functions of brain resident microglia the ability to cope with pathology is likely hindered. A gap in brain maintenance resulting from this failing support mechanism (the immune

system) and an increased demand for this support (due to an ongoing disease), further fuels the pathology.

We further suggest that a malfunctioning T cell compartment in development leads to dysregulation and a pro-inflammatory skew of meningeal myeloid cells and microglia. This leads to an increase in pro-inflammatory molecules surrounding the parenchyma resulting in altered synapses, neural circuits, and ultimately behavior. It is plausible that decreased numbers or malfunction of T cells can contribute to the etiology of ASD and this link needs to be further scrutinized. Drug accessibility of the immune system and its feasible replacement make the immune system an intriguing new therapeutic target in neurodevelopmental disorders.

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Highlights

- Well-regulated immune system is needed for proper brain function
- Immune imbalance impairs higher order brain functioning
- Immune deficiency leads to cognitive impairment
- Behavioral deficits in autism might be the consequence of malfunctioning immunity

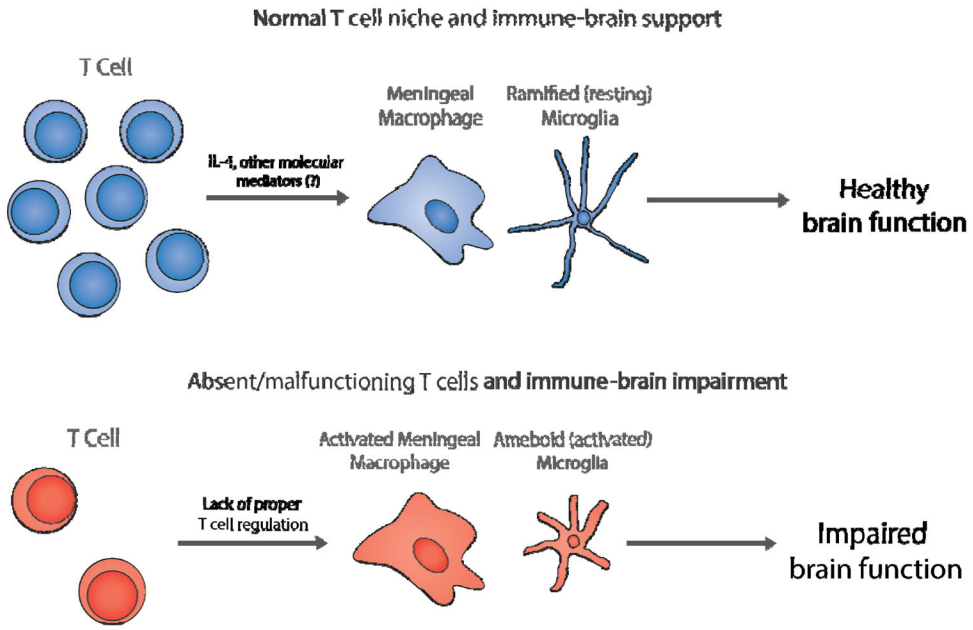

Figure 1. T cells influence brain function by regulating the activation status of local myeloid cells

Top, In the T cell niche surrounding a healthy brain, T cells regulate meningeal macrophages, and possibly microglia, by the release of IL-4 and other pro-cognitive molecules. Resting microglia survey the brain parenchyma and support a healthy environment for brain development. **Bottom,** When T cells are absent, or malfunctioning, meningeal macrophages and microglia become activated and unleash pro-inflammatory molecules. This pro-inflammatory milieu is detrimental to normal brain function and may contribute to the developmental abnormalities in ASD.