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Neuroinflammation: The Devil is in the Details

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Abstract

There is significant interest in understanding inflammatory responses within the brain and spinal cord. Inflammatory responses that are centralized within the brain and spinal cord are generally referred to as “neuroinflammatory”. Aspects of neuroinflammation vary within the context of disease, injury, infection or stress. The context, course, and duration of these inflammatory responses are all critical aspects in the understanding of these processes and their corresponding physiological, biochemical and behavioral consequences. Microglia, innate immune cells of the central nervous system (CNS), play key roles in mediating these neuroinflammatory responses. Because the connotation of neuroinflammation is inherently negative and maladaptive, the majority of research focus is on the pathological aspects of neuroinflammation. There are, however, several degrees of neuroinflammatory responses, some of which are positive. In many circumstances including CNS injury, there is a balance of inflammatory and intrinsic repair processes that influences functional recovery. In addition, there are several other examples where communication between the brain and immune system involves neuroinflammatory processes that are beneficial and adaptive. The purpose of this review is to distinguish different variations of neuroinflammation in a context-specific manner and detail both positive and negative aspects of neuroinflammatory processes.

Keywords

neuroinflammation; microglia; astrocytes; lipopolysaccharide; sickness behavior

Introduction to Neuroinflammation

Neuroinflammation is defined as an inflammatory response within the brain or spinal cord. This inflammation is mediated by the production of cytokines, chemokines, reactive oxygen

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species, and secondary messengers. These mediators are produced by resident CNS glia (microglia and astrocytes), endothelial cells, and peripherally derived immune cells. There are immune, physiological, biochemical, and psychological consequences of these neuroinflammatory responses. Moreover, the degree of neuroinflammation depends on the context, duration, and course of the primary stimulus or insult (Figure 1). For instance, inflammation can lead to recruitment of immune cells, edema, tissue damage and potentially cell death. The term neuroinflammation, however, is not universally equivalent. Therefore, the primary goal here is to discuss different degrees of neuroinflammation and describe pathways that represent positive and negative aspects of neuroinflammatory processes in the context of the insult.

Microglia: Central Players in Neuroinflammation

Microglia are the focal point for any discussion of neuroinflammation. This is because these innate immune cells perform the primary immune surveillance and macrophage-like activities of the CNS, including the production of cytokines and chemokines. Indeed, much of the innate immune capacity of the CNS is mediated by microglia. These cells are resident CNS cells that reside in both the white matter and gray matter of the brain and spinal cord. Overall, microglia comprise 10% of the CNS population. Microglia develop early in embryogenesis from myeloid precursor cells in the embryonic yolk sac, and migrate to the area of the CNS around embryonic day 8.5 (Ginhoux *et al.* 2010). In fact, microglia have the same progenitor as the rest of the long-lived tissues macrophages of the body (Alliot *et al.* 1999). Consistent with this idea, microglia are long-lived cells that have limited turnover from the myeloid cells of the bone marrow during the course of a lifetime (Ajami *et al.* 2007, Ginhoux *et al.* 2010). These cells are not replaced from myeloid cells of the bone marrow. Nonetheless, when depleted, microglia turnover is possible from a potential progenitor source within the CNS (Elmore *et al.* 2014). The rate at which microglia would normally be turned over in the absence of pharmacological or genetic depletion is still unclear, yet microglia appear to have a relatively low overall turnover rate (Ajami et al. 2007, Ginhoux et al. 2010). This low turnover would make them susceptible to the potentially pro-inflammatory effects of age, injury or stress.

Microglia have an active role in immune surveillance. For instance, elegant two photon imaging studies show that microglia use their processes to actively survey their microenvironment (Nimmerjahn *et al.* 2005, Davalos *et al.* 2005). Other immune related activities include the propagation of inflammatory signals that are initiated in the periphery (Dantzer *et al.* 2008). These responses are pivotal in the coordinated communication between the immune system and the brain. For example, in infection or disease, microglia become ‘activated’ and function as inflammatory cellular mediators. Activated microglia rapidly alter their transcriptional profile and produce inflammatory cytokines and chemokines. Depending on context, the production of cytokines and chemokines can facilitate the recruitment of leukocytes to the brain (Zhou *et al.* 2006). Active microglia also undergo cytoskeletal rearrangements that alter the pattern of receptor expression on the cell surface. In addition, these alterations allow for microglia to migrate towards sites of injury or infection (Russo & McGavern 2015) and potentially increase their phagocytic efficiency (Davalos *et al.* 2005). In general, microglial activation and the increased expression of

cytokines are intended to protect the CNS and benefit the host organism. Nonetheless, amplified, exaggerated, or chronic microglial activation can lead to robust pathological changes and neurobehavioral complications such as depression and cognitive deficits (Norden & Godbout 2013).

The Degrees of Neuroinflammation and Neuroinflammatory Signaling

Neuroinflammatory responses are mediated by several key pro-inflammatory cytokines (IL-1β, IL-6, and TNFα), chemokines (CCL2, CCL5, CXCL1), secondary messengers (NO and prostaglandins) and reactive oxygen species (ROS). Many of these mediators are produced by activated resident CNS cells including microglia and astrocytes (Norden *et al.* 2016). In addition, endothelia cells and perivascular macrophages (Dunn *et al.* 2006) are also important in interpreting and propagating these inflammatory signals within the CNS. Neuroinflammation remains difficult to summarily define, and will be discussed here as the presence of cytokines/chemokines/secondary messengers within CNS tissue. Illustrating the broadness of this definition, there is evidence of active microglia and production of cytokines in early brain development (Salter & Beggs 2014). Moreover, active microglia provide support, synaptic pruning and immunological activities within the CNS (Schafer & Stevens 2013). In addition, a recent report indicates that IL-1 signaling is important in the repopulation of depleted microglia from a local progenitor source (Bruttger *et al.* 2015). Furthermore, enhanced neuroinflammatory signaling between T-cells and resident CNS cells are implicated in normal memory and learning (Derecki *et al.* 2010, Ziv *et al.* 2006). These examples represent a degree of neuroinflammatory cytokine production that acts on other cells to influence cellular biochemistry, physiology and development. Such instances do not represent pathological “neuroinflammation”, often a term with negative connotation, but rather demonstrate a way in which signals are communicated to or within the CNS.

Highly destructive or pathological neuroinflammation is associated with activation of CNS glia with significant cytokine and chemokine production, infiltration of peripheral immune cells, edema, increased blood-brain barrier (BBB) permeability and breakdown (Hawkins & Davis 2005, Michael *et al.* 2015, Monahan *et al.* 2008). There is also primary damage caused by the mechanical and physical damage of the infection, injury, or insult. In addition, there can be vascular occlusion, ischemia, cell death, and other secondary inflammatory components from these insults. This degree of neuroinflammation has been associated with CNS infection (Goldman *et al.* 2001), stroke (Liesz *et al.* 2011), or disease (Linker *et al.* 2002, Walter *et al.* 2007). In many of these examples the insults are life threating, can elicit neuroinflammatory processes with more pathological components, and are associated with negative functional outcomes. In addition, this high degree of inflammation has primary and secondary damage, and can also have chronic neuroinflammatory components that may never resolve. This degree of neuroinflammation is associated with immune responses induced by autoimmune disease like multiple sclerosis (MS), modeled in mice with experimental autoimmune encephalomyelitis (EAE) (Linker *et al.* 2002). In this example there is activation of CNS glia, cytokine and chemokine production, infiltration of peripheral immune cells, and presence of auto-reactive T-cells (Reboldi *et al.* 2009, Samoilova *et al.* 1998). Here there is significant autoimmune reaction against myelin basic protein which leads to demyelination of axons. In addition, over time this inflammation becomes chronic

and results in loss of axons (Lovas *et al.* 2000). The immediate and chronic phases of this response have a notable impact on myelin physiology, including functional disability caused by the loss of myelin and axonal fragmentation. A notable chronic type of neuroinflammation is associated with Alzheimer's disease (Sokolova *et al.* 2009, Walter et al. 2007). AD disease progression consists of protein mis-folding, activation of CNS glia, infiltration of peripheral immune cells, neuronal damage and death, and neuronal atrophy over time (Bucciantini *et al.* 2002, Sokolova et al. 2009). These represent examples of the ebb and flow of chronic neuroinflammatory processes that contribute to tissue damage over time. Such tissue damage to axons and neurons in MS and AD has significant functional outcomes. This degree of neuroinflammation is chronic, progressive and increasingly destructive over time. Notably, these classic examples of neuroinflammation are reviewed elsewhere (Gold *et al.* 2006, Mrak *et al.* 1995, Tansey & Goldberg 2010) and are difficult to discuss in the context of the positive aspects of neuroinflammation. Additionally, the benefits of inducing phagocytic activity in neurodegeneration have been extensively reviewed by Sokolowski and Mandell (2011).

There can also be transient neuroinflammation that involves activation of resident glia and the production of several neuroinflammatory cytokines including IL-1β, TNFα, and IL-6. This induction of neuroinflammatory cytokines can be elicited as a part of coordinated CNS interpretation of peripheral infection or insult. In this context, activation of CNS glia and the production of cytokines and chemokines lead to physiological and behavioral responses that are beneficial to the host organism (Imeri & Opp 2009). It is important to highlight that this is a transient response and is not associated with significant infiltration of adaptive immune cells into the brain, blood-brain barrier breakdown or cell death. Interpretation of psychological stressors also has a similar neuroinflammatory profile, with glial activation and cytokine and chemokine production. Both of these interpretations occur in the absence of tissue pathology. In addition, others have harnessed this form of transient immune activation as a way to promote immune conditioning. For example, transient activation of the immune system prior to injury or infection (euflammation) is associated with reduced inflammatory profiles and increased neuroprotection (Tarr *et al.* 2014). Overall, this type of neuroinflammation represents the process of immune to brain signaling events that influences behavior.

Classic Examples of Neuroinflammation in the Context of Central Nervous System Trauma

There is a significant degree of neuroinflammation associated with brain and spinal cord injury. With CNS injury, there is activation of resident glia (microglia and astrocytes), moderate cytokine and chemokine production, and infiltration of peripheral immune cells (Werner & Engelhard 2007). In addition, there is cellular recruitment, increased blood brain barrier permeability and edema. Brain injury may consist of non-penetrating and penetrating injuries, both of which involve a direct, physical consequence on the CNS which leads to significant post-injury symptoms and long-term complications. Additionally, both brain and spinal cord injury involve an acute, beneficial initial inflammatory response (David & Kroner 2011, Woodcock & Morganti-Kossmann 2013) which becomes damaging should it

persist too long. Penetrating brain injuries have more direct CNS tissue damage and more intermediate inflammation. Nonetheless, both penetrating and non-penetrating injuries can have secondary and chronic phases of inflammation that are considered maladaptive.

Neuroinflammation after Traumatic Brain Injury

One example of CNS injury is traumatic brain injury. TBI is defined by a complex assortment of heterogeneous physical insults to the head, resulting in biochemical injury to the brain and surrounding structures. TBI includes biphasic injuries and are described by their primary and secondary components (Maas *et al.* 2008, Osier *et al.* 2014). In brief, the primary injury caused by mechanical disruption of macro- and microscopic structures within and associated with the brain, resulting in tissue damage. Depending on the type of injury this can include overt tissue damage from a penetration injury or diffuse axonal injury from accelerating and rotational forces. Secondary injury is associated with tissue pathology and cell dysfunction leading to progressive damage extending long after the initial primary injury. For instance, the secondary injury with TBI is associated with cell death, neurotransmitter excitotoxicity, electrolyte imbalances, mitochondrial dysfunction, and ischemic injury (Maas et al. 2008).

Myriad studies indicate that both focal (penetrating) and diffuse (non-penetrating) TBI induce significant inflammatory processes in the brain mediated, in part, by resident microglia and astrocytes (McCrea *et al.* 2003, Lifshitz *et al.* 2007b, Tang *et al.* 1997, Woodcock & Morganti-Kossmann 2013). Following TBI, microglia respond to damaged cells, other activated glia, and peripherally derived stimuli after the breakdown of the blood brain barrier (Abdul-Muneer *et al.* 2013, Blixt *et al.* 2015). Active microglia rapidly induce the expression and release of cytokines and chemokines after injury (Kumar *et al.* 2015, Witcher *et al.* 2015). Microglial activation after injury is also associated with alterations in morphology and redistribution of cell-surface markers. For instance, a recent study identified “jellyfish” microglia by two-photon microscopy (Corps *et al.* 2015) that were detected after TBI was induced via pressure on a thin skull preparation. These microglia were highly activated, moved to the area of damage, and phagocytosed particulate matter associated with tissue damage (Corps et al. 2015). Active microglia also increase surface expression of Iba1 and CD68 and have a de-ramified morphology after diffuse TBI induced by midline fluid percussion injury (mFPI) (Bachstetter *et al.* 2013). Another study showed that morphological changes in microglia following diffuse TBI were dependent on intact p38α MAPK signaling, a pathway that also induces pro-inflammatory cytokine production (Bachstetter *et al.* 2011). Diffuse TBI induced by mFPI results in transiently elevated IL-1β, TNFα, and CD14 in the cortex and hippocampus of mice within 4 hours (Fenn *et al.* 2014). Moreover, microglia have increased IL-1β, CD14, iNOS, and arginase expression 24 hours after diffuse TBI compared with sham-injured controls (Fenn *et al.* 2015). Therefore, TBI results in the induction of both inflammatory (M1) and repair (M2) cascades associated with macrophage and microglia profiles (Kumar *et al.* 2013). Similar induction of both inflammatory and repair related mediators including iNOS, CD86, CD68, CD11b, IL-10, chitinase, TGF-β, and arginase are induced after focal brain injury by controlled cortical injury (Loane *et al.* 2014, Turtzo *et al.* 2014, Wang *et al.* 2013). Thus, both diffuse and focal head injuries drive a concordant inflammatory and repair response by microglia.

Along with resident microglia, there are other myeloid cells within the injured CNS that contribute to acute neuroinflammation. Differentiating the contribution of resident microglia from infiltrating macrophages can be difficult, particularly in the context of penetrating brain injury. This is because once monocytes differentiate into brain macrophages they are nearly indistinguishable from microglia by histology due to similarities in surface marker expression. Nonetheless, activation of microglia following TBI results in production of chemokines including CCL2, which attract monocytes and granulocytes to the site of injury (Semple *et al.* 2010). Notably, antagonism of the CCL2 receptor, CCR2, reduces inflammation and improves cognitive function 1 month after TBI induced by controlled cortical impact injury (CCI) (Morganti *et al.* 2015). Penetrating injury causes microglia/macrophages to associate with the axon initial segment within 3 hours (Baalman *et al.* 2015) and diffuse brain injury induces microglia to form tight clusters and long rod-like structures in the cortex within 7 days (Ziebell *et al.* 2012). Both of these cell types are rapidly activated and have central roles in mediating neuroinflammatory responses after injury.

Clinical evidence supports the idea that microglial and macrophage activation occurs rapidly following TBI. In autopsy of patients who have died following severe TBI, activated microglial morphologies were detected 2-10 days after injury (Velazquez *et al.* 2015). In addition, increased cerebrospinal fluid (CSF) levels of ferritin and soluble CD163, markers of macrophage and microglial activation, were elevated in pediatric patients within 3 days of severe TBI (Newell *et al.* 2015). Additionally, plasma levels of microglial activation products MMP-9 and galectin-3 were elevated within 8 hours of mild TBI in adults (Shan *et al.* 2016). Clinically, the detection of inflammatory proteins in CSF or blood may be useful biomarkers of microglia/macrophage-mediated inflammation.

In summary, microglia are rapidly activated and have both pro-inflammatory and neuroprotective roles immediately after TBI. The majority of anti-inflammatory interventions in rodent models of head injury reduces inflammation and improves functional recovery. Therefore, the reduction in acute neuroinflammation in TBI is interpreted to be beneficial. In several examples of TBI in rodents, minocycline, an anti-inflammatory agent and purported microglia inhibitor, reduced inflammation and improved functional recovery after TBI (Haber *et al.* 2013, Kovesdi *et al.* 2012). In addition, intravenous administration of methylene blue (MB), an anti-inflammatory agent (Oz *et al.* 2011), reduced expression of inflammatory mediators in the brain 1 day post-injury (Fenn et al. 2014). Notably, this reduction blocked the development of a TBI-associated depressive-like phenotype 7 days later. Another paper showed that MB treatment increased neuronal survival in a controlled cortical impact model of injury (Talley Watts *et al.* 2016). There are many examples of therapies that reduce the activation profiles of microglia and improve functional recovery (Kumar & Loane 2012). Another is issue is the degree to which inflammation fails to resolve, instead persisting chronically after injury. Evidence suggests that such a prolonged neuroinflammatory response mediated by microglia and macrophages is significantly detrimental after CNS injury. Therefore treatment strategies that can lower acute inflammation after TBI may have a long term benefit.

Neuroinflammation after Spinal Cord Injury

Another example of traumatic CNS injury is spinal cord injury (SCI). SCI is characterized both by the acute and focal contusion, as well as by an extensive secondary injury composed of ischemia, excitotoxicity, and inflammation (David *et al.* 2012). The initial, acute period of inflammation is characterized by an influx of neutrophils and monocytes into the damaged region of the spinal cord (Pineau *et al.* 2010). In the secondary phase of inflammation, there is continued degeneration that occurs over a period of months and is driven by lymphocytes (Ankeny *et al.* 2006). The cells of the CNS including microglia, astrocytes, neurons, and oligodendrocytes respond quickly to SCI, upregulating IL-1β and TNFα within hours (Yang *et al.* 2004, Yang *et al.* 2005, Bastien *et al.* 2015). There is activation of microglia in the cord, even distal from the site, associated with tissue reorganization and impediment of functional recovery (Hansen *et al.* 2013). Additionally, there is a significant contribution of peripheral immune cells to inflammation following SCI. For instance, there is rapid infiltration of neutrophils after injury, the presence of which is transient and disappears by 3 days post-injury (Fleming *et al.* 2006). Monocytes are recruited to the injured cord, as well, with lymphocytes found within the spinal cord after a far longer period of time, reaching their peak concentration in mice at 42 days (Ankeny et al. 2006, Sroga *et al.* 2003) and in humans after several months (Fleming et al. 2006). Thus, there is a significant and long lasting contribution of peripheral immune cells to the inflammatory environment within the spinal cord after injury.

The infiltrating peripheral myeloid cells play a large role in the secondary degeneration of SCI. A reduction in neutrophils present in the spinal cord has led to improved recovery (Bao *et al.* 2004, Bao *et al.* 2008, Gris *et al.* 2004), while depletion of macrophages via clodronate liposomes reduced damage to the tissue at the contusion site (Popovich *et al.* 1999). New evidence suggests that these myeloid cells are not inherently damaging, but that they may be driven toward a more inflammatory phenotype by the presence of cytokines such as TNFα and IL-1β (Genovese *et al.* 2008, Zong *et al.* 2012) and free radicals (Bao et al. 2004, Bao et al. 2008). Antagonism of the IL-1 receptor at early time points following SCI, and sequestration of TNFα via administration of soluble tumor necrosis factor receptor superfamily member 1A (TNFR1), reduced apoptosis (Ferguson *et al.* 2008, Nesic *et al.* 2001). Additionally, the increase in expression of TNFα caused spontaneous demyelination via activation of macrophages and microglia (Probert *et al.* 2000). Overall, the presence of peripherally derived myeloid cells in the spinal cord contributes to prolonged tissue damage after SCI.

Positive Aspects of Neuroinflammation

Cytokine-Mediated Sickness Behavior

Now that classic neuroinflammation has been discussed in the context of CNS injury, we can discuss that there are other degrees of neuroinflammation that are beneficial and adaptive. A key component to this argument is that the immune system and the brain communicate with one another and that this communication is bi-directional. For instance, challenges to the peripheral immune system are sensed by the CNS. This immune activation is conveyed to the brain using several neural and humoral pathways. This “inflammation” is interpreted and

propagated within the brain. Key areas of communication include the neurovascular unit (endothelium), brain stem, and circumventricular organs of the brain (Hansen *et al.* 2001, Laflamme *et al.* 1999, Lacroix *et al.* 1998, Ching *et al.* 2007). This communication results in microglial propagation of cytokines and chemokines within the brain (Henry *et al.* 2009, Chen *et al.* 2012) and allows for functional communication between the immune system and the brain.

In the context of a peripheral immune challenge, one consequence of the propagation of neuroinflammatory cytokines is the induction of sickness behavior. A coordinated response mediated by the neurovascular unit (Serrats *et al.* 2010) and resident glia (Henry et al. 2009, Norden *et al.* 2014) propagates cytokine and secondary signals that cause the physiological and behavioral components of the sickness response including fever, hypophagia, lethargy, listlessness, decreased activity, and reduced social interaction (Dantzer et al. 2008). These behavioral changes are evolutionarily adaptive and necessary to reallocate the host's resources and to fight infection (Berg *et al.* 2004, Bluthe *et al.* 2000). Disruptions to this response have a negative effect on morbidity and mortality (Corona *et al.* 2013). Thus, this response is beneficial to the host organism when properly controlled and resolved.

Neuroimmune communication, signal propagation, and behavioral output are cytokine-mediated and several neuroinflammatory cytokines, such as IL-1β, TNFα, and IL-6, play a key role in the induction and maintenance of this response. It is important to clarify that the duration of cytokine exposure is short and the effect is transient, characterized by temporary activation of both microglia and astrocytes (Norden et al. 2016). This response is tightly regulated and quickly resolved, indicating that the CNS is designed to handle this level of neuroinflammation as a beneficial response (Norden & Godbout 2013). Such immune to brain communication occurs without breakdown of the BBB, entrance of peripheral immune cells, or overt neuropathology (Dantzer et al. 2008). Additionally, sickness behaviors are evolutionarily conserved, indicating their importance to recovery after infection. Thus, this is one broad example of how communication between the immune system and the brain results an acute inflammatory response that is adaptive and beneficial.

Immune Conditioning or Euflammation

Another positive aspect of inflammation is immune conditioning (Chen *et al.* 2013, Tarr et al. 2014). One example of immune conditioning is euflammation, defined as the induction of peripheral inflammation in the absence of sickness behavior. This is induced by repeated subthreshold *Escherichia coli* i.p. injections on three consecutive days which create a euflammation induction locus (EIL). The doses of *E.coli* incrementally increase, and are administered at 2.0×10^7, 25×10^7, and 100×10^7 CFUs. This low level challenge beneficially "conditions" the immune system and leukocytes within the EIL release less cytokines upon subsequent immune stimulation (Chen et al. 2013, Tarr et al. 2014). This reduction in inflammatory signal propagation is contrasted by increased phagocytic potential of macrophages within the EIL.

This immune condition of inflammation was associated with minimized sickness behavior compared to mice exposed to a single *E.coli* dose. Additionally, leukocytes plated from inside the EIL displayed decreased cytokine mRNA expression, and leukocytes from outside

the EIL displayed increased cytokine mRNA expression, when stimulated with LPS (Tarr et al. 2014). Locomotor deficits and piloerection were absent after euflammation conditioning (Chen et al. 2013, Tarr et al. 2014). Additionally, anhedonia, anorexia, and adipsia, more subtle markers for sickness (Andonova *et al.* 1998, Borowski *et al.* 1998, Riediger *et al.* 2010), were all resolved faster in the pre-conditioned mice (Tarr et al. 2014). The difference in sickness behavior following euflammatory treatment was attributed to changes in the phenotype of myeloid cells and a reduction in their inflammatory profile. Cells associated with the immune response ($CD11b^+$/MHC II^+, $CD11b^+$/$TLR4^+$, $CD11b^+$/$CD86^+$) were reduced within the EIL, but are increased in the blood and the spleen (Tarr et al. 2014). In addition, cultured peritoneal leukocytes had reduced production of IL-1β, IL-6, and IL-10 mRNA when stimulated with LPS (Tarr et al. 2014). This is a phenotype similar to the development of endotoxin tolerance. Outside of the EIL, blood leukocytes instead increase their expression of IL-1β, TNFα, and IL-10, a phenotype similar to trained immunity. This duality is unique to euflammation, combining the profiles previously described as endotoxin tolerance (Biswas & Lopez-Collazo 2009) and trained immunity (Netea 2013).

Related to these points, there are other examples of immune conditioning relevant to CNS injury. In this context, studies have aimed to precondition the CNS and protect against traumatic CNS injury. This preconditioning can be induced in a wide variety of manners, such as via LPS injections, the use of anesthetics such as isofluorane, and exposure to hypo- and hyperthermia (Baughman *et al.* 1988, Ota *et al.* 2000, Tasaki *et al.* 1997). For example, repeated LPS exposures lead to preconditioning of the CNS. Conditioned microglial activation can lead to the ensheathing of cortical neurons and the subsequent reduction in inhibitory axosomatic synapses, a neuroprotective function after traumatic brain injury caused by cryo-injury (Chen et al. 2012). The mechanism of action for this function is still under investigation, but it is hypothesized to be similar to the protective benefits offered by the synaptic stimulation of NMDA receptors and their anti-apoptotic signaling pathway through CREB activation (Hardingham *et al.* 2002). This process is paralleled by the activated microglia transiently and preferentially reducing GABAergic signaling (Chen et al. 2012). Overall, immune preconditioning may drive a unique microglial profile that is more anti-inflammatory or repair that allow for protection from the hyper-inflammatory conditions associated with traumatic CNS injury.

Signaling in Memory

There are also example of the benefits of neuroinflammatory signaling in brain development and plasticity. As outlined in the introduction, this represents neuroinflammatory signaling as opposed to true neuroinflammation discussed for CNS injury. For instance, recent studies in learning and memory have detailed the involvement of a complex cytokine network during LTP (del Rey *et al.* 2013). The major cytokines involved in these studies, IL-1β, IL-6, and TNFα, are produced by several cell types, including immune cells. A similarly diverse cellular population responds to these immune signals. These cells include neurons, both within and outside the hippocampus, and astrocytes, which are involved in the maintenance of synapses (Elmariah *et al.* 2005, McAfoose & Baune 2009, Ullian *et al.* 2004). Both IL-1β and IL-6 are overexpressed in the hippocampus after LTP induction, and they produce opposing effects in that IL-1β bolsters learning while IL-6 inhibits it (Goshen & Yirmiya

2009, Schneider *et al.* 1998). In addition to these two primary cytokines, TNFα, IL-1 receptor antagonist (IL-1RA), and IL-18 are also implicated in learning and memory. All of these cytokines have important roles in learning processes, an often overlooked property of classically inflammatory molecules.

Cytokine expression in the hippocampus displays regional specificity. The hippocampal increases mentioned above are complimented by additional changes in expression in the pre-frontal cortex (PFC). The effect of IL-1 upon neuronal activity can be elucidated through the study of IL-1 receptor 3 (IL-1R3). This shortened protein is preferentially expressed in neurons, opposed to the classical IL-1R1 expression on immune cells (Qian *et al.* 2012). In conjunction with the IL-1 receptor accessory protein B (IL-1RACPb), both of which are found preferentially within tissue of the nervous system, IL-1R3 activation increases voltage-gated potassium current. The discovery of IL-1R3 has led to clearer explanations of how IL-1 signaling can induce neuronal activity in the absence of NF-κB pathway activation (Qian et al. 2012). In sum, IL-1R1 and IL-1R3 activity helps to illuminate the increasingly complex role of IL-1 signaling in learning and memory. Additionally, this demonstrates the importance of cytokine signaling in the CNS even during such basic, homeostatic conditions as LTP induction.

Another route to learning and memory alteration by cytokines may lie in their modulatory effect on neurotransmission. In this context the source for the cytokines, particularly IL-1β and IL-6, is glia including astrocytes (John *et al.* 2003). Astrocytes receive neuronal signals and reciprocating by activating NF-κB pathways to affect neuronal plasticity (del Rey et al. 2013, Freudenthal *et al.* 2005, Kaltschmidt *et al.* 2006, Meffert *et al.* 2003). IL-1 and IL-6 also exert opposite effects on molecular signaling: IL-1 enhances AMPA- or NMDA-mediated transmission, while IL-6 inhibits glutamate release and synaptic plasticity (Kawasaki *et al.* 2008). In addition, IL-1 stimulates aminergic release in the hippocampus (Kabiersch *et al.* 1988). There is also evidence that immune cells, especially T cells, communicate to resident cells and are critical to normal memory and learning processes (Ziv et al. 2006, Kipnis *et al.* 2012). Thus, neuroinflammation signaling in this context is interpreted have a beneficial role in brain development, memory, and learning processes.

Promotion of Repair Processes

As discussed above, traumatic injuries provide illuminating examples of true neuroinflammation involving contribution of both resident microglia and recruited leukocytes. Following SCI or TBI extensive inflammation is reported, composed of both resident microglia and peripheral macrophages recruited by chemokines. Most of the evidence indicates that the reduction of acute inflammation of infiltrating immune cells into injury sites is beneficial to the injured. Notably, an important observation from SCI and TBI is that active neuroinflammation also coincides with active intrinsic repair responses (Gensel *et al.* 2009, Kigerl *et al.* 2009). Thus, injury induces inflammatory responses and repair responses at the same time. The classical view of neuroinflammation in traumatic injury is that of chronic, unchecked microglial and macrophage activation, cytokine release, and tissue damage and degeneration. Nonetheless, there is a balance and an “alternative activation” (M2) profile of microglia/macrophages has been characterized since 1992 (Stein

et al. 1992). Interestingly, this balance between classic (M1) and alternative (M2) activation states in the CNS is influenced by the method of entry of the infiltrating leukocytes to the CNS (Shechter *et al.* 2013). Clearly the acute neuroinflammatory response to injury must serve a purpose. One example of this is the recruitment of macrophages to combat excitotoxicity via glutamate uptake (Rimaniol *et al.* 2000). Secondly, the recruitment of immune cells helps to complete the wound healing process as infiltrating macrophages help to clear debris caused by the injury. Indeed, phagocytosis of the dead cells and myelin is required in order to foster a microenvironment conducive toward repair and regrowth (Barrette *et al.* 2008, Kotter *et al.* 2001, Popovich et al. 1999). For example, due to myelin's growth-inhibitory properties, its removal is paramount for axon regeneration to occur in SCI. M2-type macrophages, induced by IL-4 or IL-13, can simultaneously promote angiogenesis and suppress the inflammation caused by SCI. In addition, these M2 cells promote long-distance axon regeneration even within inhibitory environments (Kigerl et al. 2009, Sica *et al.* 2006). They are also able to foster the generation of oligodendrocytes via the activation of TLR4 receptors (Schonberg *et al.* 2007). To summarize, alternative activation of microglia and macrophages is paramount for intrinsic repair after SCI and these cells help to promote myelin clearance and oligodendrocyte regeneration.

As noted above, immune responses can benefit the tissue repair process after traumatic CNS injury. Several lines of evidence indicate that bolstering M2-repair responses of microglia and macrophages is beneficial. For instance, M2 re-direction of macrophages with Azithromycin promotes tissue sparing and locomotor recovery after SCI, as shown by the anti-inflammatory effects of azithromycin treatment in mice (Zhang *et al.* 2015b). Recent studies have shown that active microglia upregulate the receptor for IL-4, which directs activated microglia toward a more M2a or repair profile (Fenn *et al.* 2012). Thus, a shift in inflammatory balance towards a profile that is more supportive of repair would be beneficial in the context of CNS injury. In fact, IL-4 may be produced by $CD4^+$ T-cells that enter the injury site (Walsh *et al.* 2015). IL-4-producing T-cells provide a neuroprotective signal on neurons directly (Walsh et al. 2015) and may also provide IL-4 to the resident microglia. For instance, a recent study using adult and aged (20 months) mice showed that microglia of adult mice enhance IL-4Rα on the cell surface after SCI (Fenn et al. 2014). This induction, however, was not detected on aged microglia after SCI. This was associated with less IL-4-dependent reprograming of microglia and reduced arginase induction in the microglia of aged mice compared with adult microglia after SCI (Fenn et al. 2014). In addition, microglia from aged mice had reduced expression of IL-1β and CCL2 in the injured cord and a differential recruitment of macrophages. In a related study, aged mice (14 months) had reduced IL-10 expression after SCI. This IL-10 reduction in the aged was associated with reduced presence of M2 regulatory macrophages, less tissue sparing, and worse functional recovery (Zhang *et al.* 2015a). In sum, cytokine pathways that re-direct activated microglia and macrophages toward a more M2-type profile help turn the tide of inflammation from damage toward repair.

Negative Aspects of Neuroinflammation

Stress

While the neuroinflammation derived from the communication between the immune and the brain is beneficial, certain circumstances can throw off this balance. A good example of this is the response to chronic or traumatic stressors. Traumatic or chronic stressors appear to promote a more neuroinflammatory profile that involves both resident microglia and bone marrow-derived macrophages (Wohleb *et al.* 2014a). A myriad of studies with rodents indicate that microglia play a major role in response to chronic or traumatic stressors, activating and releasing inflammatory signals (Frank *et al.* 2007, Frank *et al.* 2006, Tynan *et al.* 2010b, Wohleb *et al.* 2012, Wohleb *et al.* 2011a, Wohleb *et al.* 2013). For example, repeated social defeat induces activation of microglia and increased pro-inflammatory cytokine and chemokine expression in the brain (Wohleb et al. 2012, Wohleb et al. 2011a, Wohleb et al. 2013). These inflammatory inductions are paralleled by increased Iba1-immmunoreactivity of microglia, particularly in stress responsive regions of the brain (i.e., fear and threat appraisal centers) (Tynan et al. 2010b, Wohleb et al. 2011a). Other stressors including foot shock and unpredictable stress also provide evidence of the activation of resident microglia (Frank et al., 2007). The connection between stress appraisal and activation of microglia has been attributed to noradrenergic signaling (Gyoneva & Traynelis 2013, Johnson *et al.* 2005), and inflammasome activation and the release of ATP (Iwata *et al.* 2013).

In repeated social defeat (RSD), threat interpretation and microglial activation is also associated with the recruitment of inflammatory monocytes from the bone marrow to the brain. This is relevant because it provides a means by which the immune system can relay signals back to the brain and influence behavior. In RSD, sympathetic activation induced the production of pro-inflammatory ($Ly6C^{hi}/CD45^{+}$) monocytes (Wohleb *et al.* 2011b, Heidt *et al.* 2014, Powell *et al.* 2013) that are released into circulation. These cells traffic to the brain, including within specific stress-responsive brain regions (Wohleb et al. 2011b, Tynan *et al.* 2010a) that are spatially coupled to neurovascular facilitation of monocyte recruitment (Sawicki *et al.* 2014). The recruitment of these monocytes following chronic stress promotes the development of prolonged anxiety-like behavior (Wohleb *et al.* 2014b, Wohleb et al. 2013). Notably, when either monocyte release from the BM or monocyte recruitment to the brain is blocked, induction of anxiety is inhibited. For instance, β-adrenergic receptor antagonists, benzodiazepines, and antidepressants that modify neuronal adaptation prevent many of the neuroimmune and behavioral responses to psychosocial stress, including anxiety and social avoidance (Ramirez *et al.* 2016, Wohleb et al. 2011a, Wohleb et al. 2013). In addition, mice deficient in CCR2 or IL-1R1 do not develop anxiety after RSD (Wohleb et al. 2013). Overall, the prevention of macrophage trafficking to the brain blocks the induction of stress-related anxiety in mice (Wohleb et al. 2014a, Wohleb et al. 2013). Thus, stress-induced neuroinflammatory responses serve as an important link between immune dysfunction and development of mood disorders.

This is relevant because in clinical evidence indicates that individuals exposed to chronic stress show persistent cognitive and emotional dysregulation that contributes to deterioration

of overall mental health and quality of life (Baum *et al.* 1993, McEwen 2013). For instance, studies with caregivers (Caswell *et al.* 2003, Mackenzie *et al.* 2007) and college-age students (Keinan *et al.* 1999) demonstrate that chronic stress is strongly associated with cognitive impairments and accelerated cognitive decline (Vitaliano *et al.* 2011). Additional studies also report associations between stress-induced neuroinflammatory activation and psychological disturbances. For example, elevated pro-inflammatory cytokines (Janelidze *et al.* 2011), increased microglia activation (Schnieder *et al.* 2014), and increased brain macrophages (Torres-Platas *et al.* 2014) were all detected within specific brain regions of depressed suicide victims. Thus, stress-induced neuropsychiatric disturbances may involve impaired neuroplasticity caused by microglial activation, monocyte recruitment, and enhanced neuroinflammatory signaling.

Aging

The normal aging process provides a key example of the disruption in the communication and balance between the brain and the immune system. In this case, there is a myriad of alterations in both peripheral immune cells and brain cells. Notably, the number of microglia in the dentate gyrus of aged mice is inversely correlated with the number of stem/progenitor cells (Gebara *et al.* 2013). In the brain, a higher inflammatory profile of microglia in rodents, canines, non-human primates, and humans has been reported. Several mediators associated with immunity are increased including MHC II, CD68, CD11b and CD11c, TLRs, and CD86 (Frank et al. 2006, Godbout *et al.* 2005, Griffin *et al.* 2006, Lucin & Wyss-Coray 2009, Stichel & Luebbert 2007). Aged microglia also have altered morphological profiles associated with de-ramification, shorter processes, and fewer branching arbors (Choi *et al.* 2007). In addition, there is an increase in inflammatory genes for cytokines such as IL-1β and IL-6 (Godbout et al. 2005, Sierra *et al.* 2007, Xie *et al.* 2003), and a corresponding decrease in anti-inflammatory genes of cytokines including IL-10 and IL-4 (Maher *et al.* 2005, Ye & Johnson 2001). Recent transcriptome analysis of the aged brain (Youm *et al.* 2013) sorted aged microglia confirmed a higher inflammatory profile with an mRNA signature of less TGFβ-related responsiveness.

One interpretation of this increased inflammatory profile of microglia with age is that these cells are primed or sensitized. This ‘priming’ profile of microglia is represented threefold: 1) increased expression of markers and mediators of inflammation, 2) decreased threshold and time for activation, and 3) increased response and inflammation following this activation (Henry et al. 2009, Norden & Godbout 2013). It is clear that the inflammatory status increases with age (Chung *et al.* 2009). Recent studies have also used positron emission tomography (PET) to evaluate microglial activation in humans. The ligand PK [11C] (R)PK11195 binds to translocator protein (TSPO) receptors that are expressed in mitochondria of activated microglia. PET imaging using this compound showed increased TSPO in older individuals, indicating that microglial activation was elevated with age (Schuitemaker *et al.* 2012). Taken together, the increase of inflammatory mediators and altered phenotype of microglia with age indicates that microglia develop a primed phenotype and that this may contribute to the heightened inflammatory status of the aged brain.

A consequence of an increased primed profile in the aged brain is the hyper-activation of microglia in response to immune challenge. For instance, peripheral immune challenge with lipopolysaccharide or *E.coli* causes an exaggerated and prolonged neuroinflammation in aged rodents compared to adults. In aged mice, peripheral LPS challenge results in elevated mRNA levels of IL-1β, IL-6, and TNFα (Abraham *et al.* 2008, Godbout et al. 2005), which remained elevated for 24 and 72 hours (Godbout *et al.* 2008b). The prolonged exaggeration of IL-1β in microglia coincides with a similarly prolonged downregulation of fractalkine receptor (CX3CR1) (Wynne *et al.* 2010). Evidence points to primed microglia as the major arbiters of this inflammation, as MHC II^+ microglia had a robust increase IL-1β protein expression following LPS stimulation (Henry et al. 2009). Similarly, microglia isolated from aged mice display elevated TNFα, IL-1β, IL-6, IL-12, TLR2, and indoleamine 2,3-dioxygenase (IDO) mRNA after LPS when compared with adult controls (Henry et al. 2009, Sierra et al. 2007). These changes in cytokine production are also present in aged mice following minor surgery and mild psychological stress (Buchanan *et al.* 2008, Rosczyk *et al.* 2008). Furthermore, the induction of IL-1β after immune challenge was greater in MHC II^+ microglia of aged mice compared to MHC II^- microglia (Henry et al. 2009). These studies indicate that these primed MHC II^+ microglia produce inflammatory cytokines, to an exaggerated and prolonged degree, after peripheral immune stimulation.

As discussed above, cytokine-mediated sickness behavior is a necessary and beneficial response to infection. An unchecked, amplified, or prolonged response, however, affects behavioral and cognitive processes (Jurgens & Johnson 2010). In the studies discussed above, LPS stimulation, either peripheral or central, caused protracted neuroinflammation in the brain of aged rodents. This was accompanied by a protracted sickness response notably characterized by persistent anorexia, lethargy, and social withdrawal (Godbout et al. 2005, Abraham et al. 2008, Huang *et al.* 2008). An exaggerated sickness response was also detected in older rats following subcutaneous *E.coli* injection. The aged rats displayed an altered febrile response characterized by a blunted and delayed increase of core body temperature followed by a notable and protracted increase of inflammatory cytokines in the brain (Barrientos *et al.* 2009b). Similar to the extended sickness behaviors in aged BALB/c mice, the increase of inflammatory cytokines were driven by exaggerated microglial IL-1β (Henry et al. 2009). Indeed, i.c.v. infusion of IL-1 receptor antagonist (IL-1RA) reversed the extended LPS-induced sickness behavior in aged mice (Abraham & Johnson 2008). These findings indicate that the exaggerated sickness response in aged rodents was caused by the exaggerated and prolonged production of IL-1β by primed microglia.

Following an immune challenge, there is also evidence of the development of depressive-like behavioral complications and cognitive deficits in aged rodents. For example, in aged BALB/c mice, peripheral LPS stimulation caused prolonged depressive-like behavior 72 h after injection in aged mice after acute (Godbout *et al.* 2008a) and chronic (Kelley *et al.* 2013) immune challenge. In addition, injection of LPS caused an amplified cytokine response in the hippocampus of older mice that was paralleled by impaired hippocampal-dependent spatial memory (Chen *et al.* 2008). Moreover, infection by *E.coli* led to prolonged production of IL-1β in the hippocampus of aged rats (Barrientos *et al.* 2009a) and reduced long-term contextual memory examined by context-dependent fear conditioning and Morris water maze (Barrientos *et al.* 2006, Barrientos et al. 2009a). When aged mice were fed a diet

supplemented with resveratrol, a potent anti-oxidant, LPS-induced neuroinflammation and working memory deficits were attenuated (Abraham & Johnson 2009). Increased cytokine production in the aged brain after peripheral innate immune challenge is also associated with impaired cognitive function. Taken together, when there is a primed or sensitized profile of microglia the normal communication between immune system and the brain is impaired. The normally acute neuroinflammatory signaling events are instead amplified and prolonged, and cognitive and behavioral deficits develop in aged mice that are not detected in healthy adults.

Chronic Microglial Activation after Traumatic Brain Injury

As discussed, acute neuroinflammation has both positive and negative influences of functional recovery and repair processes after injury. Thus, it can be difficult to state whether inflammation is negative or positive. The majority of clinical and experimental data, however, indicates that neuroinflammation has a negative effect when it is prolonged. For instance, a pro-inflammatory profile of microglia persists long after injury and is evident in diffuse, penetrating, and repeated head injuries. Furthermore, persistent changes in microglia and astrocytes after penetrating TBI, such as increased MHC II expression in rats 16 days post-injury, are caused by CCI (Holmin *et al.* 1995). CCI-injured rodents also display an increased inflammatory profile of microglia up to 1 year after injury (Loane et al. 2014). Microglia in the lesion border more highly express several pro-inflammatory mediators such as MHC II, CD68 and NADPH oxidase (NOX2) in the cortex and thalamus, persisting 12 months after injury. In the same brain regions, YM-1, an alternative activation marker (M2) was transiently up-regulated 1 week later, but was reduced over time and was undetected at 3 and 12 months after injury. This supports the notion that in the midst of heightened inflammatory status and progressing gliosis, reparative mechanisms are down-regulated. Additionally, CCI-initiated inflammatory marker expression elevation on microglia and macrophages is associated with increased lesion volume expansion and loss of neurons in the hippocampus (Loane et al. 2014). Such tissue damage and elevated inflammatory mediators are mediated by microglia and macrophages, persist over time, and are consistent with other models of focal or penetrating brain injury (Shultz *et al.* 2013, Huang *et al.* 2014).

There is evidence of a persistent, primed, pro-inflammatory microglial profile after diffuse head injury. Reliable experimental models of this non-penetrating, diffuse injury include mFPI, closed head impact (CHI), and blast injuries (Xiong *et al.* 2013). Injuries by mFPI are administered by a fluid-filled pulse directly at the brain midline without disrupting the dura, causing global undulation of brain tissue. This causes mild neuronal pathology including diffuse axonal injury (Lifshitz *et al.* 2007a) and transient neurological deficits (Morales *et al.* 2005) that mimic clinical complications after mild to moderate concussive head injuries in human patients (Lifshitz 2009). Moderate mFPI in rodents causes activated microglia and an altered microglial phenotype, such as increased MHC II and CD68 expression, that persists 1 week to 1 month post-injury. (Ziebell et al. 2012). Moreover, these microglia have a unique rod-like morphology and train arrangement along axon tracks and are predominantly detected in the primary sensory barrel fields of rats (Ziebell et al. 2012). A related study in mice has shown that mFPI increases mRNA and protein expression of MHC II on microglia in the brain up to 1 month post-injury (Fenn et al. 2014). Furthermore, there subtle changes

in microglial morphology are evident in the parietal cortex and hippocampus, both of which are brain regions affected by the diffuse injury. These increases in MHC II expression on microglia 30 days post-injury were detected in mice that had returned to baseline behavior. Overall, these data provide evidence that there are pro-inflammatory microglial profiles of microglia that develop and are maintained after brain injury.

An inflammatory glial profile that persists after TBI is paralleled in human patients following moderate or severe TBI. For example, increased CD11b and CD68 microglial expression has been shown in blunt head trauma patients at short- and long-term time points, up to 16 years post-injury (Gentleman *et al.* 2004). Another study has demonstrated that densely-packed, reactive ($CR3/43^+$ or $CD68^+$) microglia are detectable 1-18 years after a single moderate or severe TBI (Johnson *et al.* 2013). Recent developments in magnetic resonance imaging (MRI) techniques have been used to examine microglial activation in human brains after TBI *in vivo*. As described above, PK [11C](R)PK11195 ligand is expressed on activated microglia. Higher PK binding was detected in TBI patients in the thalamus, occipital lobes, putamen and posterior limb of internal capsule (Ramlackhansingh *et al.* 2011). Notably, chronic microglial activation increases in cell populations further from a focal lesion, being most prominent within subcortical structures such as the thalamus and putamen. Furthermore, although the time post-injury for those studied ranged from 11 months to 17 years, no correlation was found between PK binding and the time since the head injury. These findings indicate that chronic microglial activation persists for months to years after the initial insult in human patients.

Evidence for Microglial Priming and Microglia Reactivity after Central Nervous System Injury

Discussed above in the aging section, a central component of microglia priming is microglial hyper reactivity following immune stimulation. Reactivity of microglia to secondary immune challenge is also evident after CNS injury. For example increased expression of CD68 in resident microglia is maintained after optic nerve (ON) crush injury. Induction of an immune response with peripheral LPS administration 28 days after ON crush significantly increased expression of IL-1β, TNF-α, and IL-6 (Palin *et al.* 2009). This heightened inflammatory response after LPS suggests that ON crush prompts development of primed $CD68^+$ microglia. Moreover, MHC II mRNA and protein were elevated in microglia 1 month after injury induced by midline fluid percussion injury (Fenn et al. 2014). Secondary LPS challenge induced exaggerated expression of IL-1β, TNFα, and CCL2 specifically in microglia from TBI (30 dpi) mice compared to controls (Fenn et al. 2014, Muccigrosso *et al.* 2016). This exaggerated microglia activation following immune challenge in TBI mice was associated with prolonged social withdrawal and depressive-like behavior that was not detected in control mice injected with LPS (Fenn et al. 2014). Moreover, the LPS challenge also significantly impaired memory recall in TBI mice but not controls (Muccigrosso et al. 2016). Thus, CNS injury is a “priming event,” leaving microglia in an activated state, capable of hyper-responsiveness with subsequent immune activation.

Microglial priming may also be a factor in repeated TBI, where the initial injury is the priming event and subsequent injuries result in exaggerated inflammatory responses and

progressive pathology (Mouzon *et al.* 2014, Weil *et al.* 2014, Aungst *et al.* 2014). This idea has not been investigated specifically, yet it is clear across the literature that even a single TBI has long-lasting glial affects and repeated TBI exacerbates the neuroinflammatory response. For example, Mouzon et al. (2014) showed morphologically reactive astrocytes and microglia (thick processes and hypertrophied cell soma) were evident in cortices and hippocampal regions 6 months after single and repeated closed head TBI (5 hits with 48h interval). Inflammation persisted at 12 and 18 months and was associated with spatial learning deficits that were worse following repeated traumas compared to single TBI (Mouzon et al. 2014). The cognitive changes 12 and 18 months after injury were associated with white matter damage and increased Iba1 labeling, but were not associated with neurodegenerative pathology. The time frame allotted in between injuries may also be an important factor. Another study looked at pathological outcomes after a single and repeated closed head TBI (2 hits) with a 3 or 20 day interval (Weil et al. 2014). One month after the last hit, repeated TBI with a shorter interval induced an enhanced neuroinflammatory response, more robust axonal degeneration and poorer performance in spatial learning and memory task. Therefore, multiple injuries can augment neuroinflammation and functional decline. Overall, microglia display increased reactivity to subsequent stressors after traumatic brain injury, leading to affective disorders, cognitive impairments, and increased cytokine production.

Concluding Remarks

The concept of neuroinflammation is broad and encompasses two large areas of biological science in the nervous and immune systems. We are just now beginning to parse out the positive and negative aspects of immune system-nervous system interaction, as illustrated in Figure 1. It is difficult to make generalized conclusions about the positivity or negativity of neuroinflammation when considering systems as nuanced as those discussed in this review. Additionally, due to the complexity of the subject, we are unable to probe each topic discussed here as deeply as is necessary. Perhaps the best way to sum up the state of the field is that its study requires careful consideration of context. Complete removal of inflammatory cells has been shown to be an unreliable treatment for degenerative diseases or mood disorders, while modification of the M1/M2 polarization has shown more promise. Rather than ask whether neuroinflammation is a friend or a foe, the science of neuroimmunology should instead study the individual situations and specific contexts in which the neuroinflammation is occurring.

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List of Abbreviations Used

AD	Alzheimer's Disease
BBB	blood-brain barrier
BM	bone marrow

CCI	controlled cortical impact
CCL	chemokine (C-C motif) ligand
CCR	chemokine (C-C motif) receptor
CD	cluster of differentiation
CFU	colony-forming unit
CHI	closed head injury
CNS	central nervous system
EAE	experimental autoimmune encephalomyelitis
EIL	euflammation induction locus
i.c.v.	intracerebroventricular
i.p.	intraperitoneal
i.v.	intravenous
IFN	interferon
IL	interleukin
iNOS	inducible nitric oxide synthase
LPS	lipopolysaccharide
LTP	long-term potentiation
M1	classically activated macrophage
M2	alternately activated macrophage
MB	methylene blue
mFPI	midline fluid percussion injury
MHC	major histocompatibility complex
MS	multiple sclerosis
NOX	NADPH oxidase
ON	optic nerve
RSD	repeated social defeat
SCI	spinal cord injury
TBI	traumatic brain injury
TGF	transforming growth factor

TLR	toll-like receptor
TNF	tumor necrosis factor
TSPO	translocator protein

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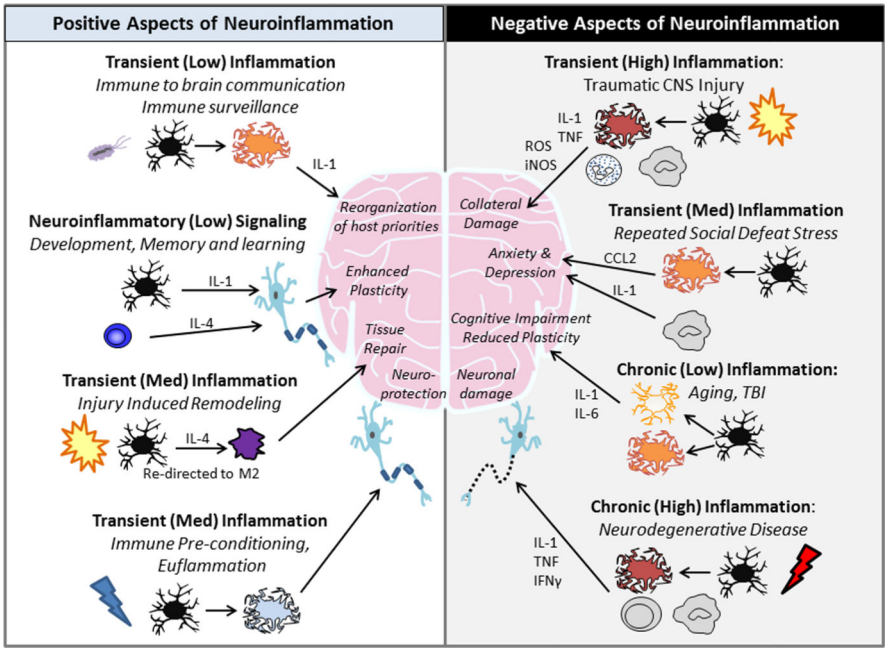

Figure 1. Positive and Negative Aspects of Neuroinflammation

The intensity and duration of inflammation account for much of whether immune signals are supportive or destructive to the central nervous system. On the left, we show examples of brief and controlled inflammatory responses that are generally considered beneficial to the host organism. For instance, immune-to-brain signals after infection lead to the subsequent reorganization of host priorities and induction of sickness behaviors. Additionally, there is an important maintenance role of IL-1 and IL-4 on learning and memory. Following traumatic CNS injury, IL-4-driven repolarization of macrophages (M2) has been proven to be highly effective in promoting recovery and axonal regrowth. Immune preconditioning, or euflammation, provides a method for training the innate immune system toward a more neuro-protective phenotype. Conversely, on the right we demonstrate various maladaptive inflammatory responses. Chronic, uncontrolled inflammation is characterized by increased production of cytokines (IL-1 and TNF), reactive oxygen species (ROS), and other inflammatory mediators (inducible nitric oxide synthase). These markers are highly evident following trauma to the CNS, and are accompanied by significant recruitment and trafficking of peripheral macrophages and neutrophils to the site of injury. The transient inflammation after repeated social defeat stress also leads to monocyte and macrophage recruitment and causes anxiety and depression. Additionally, a low-level and chronic inflammatory response driven by IL-1 and IL-6 is caused by aging, follows the acute phase of CNS trauma, and leads to reduced neuronal plasticity and cognitive impairments. A higher degree of chronic inflammation is greatly damaging to the nervous system and is characteristic of neurodegenerative diseases.