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# The role of Western diets and obesity in peripheral immune cell recruitment and inflammation in the central nervous system

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ABSTRACT

As the prevalence of obesity and chronic disease increases, the role of nutrition is taking center stage as a potential root cause of not just metabolic-related illnesses, but also of disorders of the central nervous system (CNS). Consumption of a modern, westernized diet, such as a high fat diet (HFD) that contains excess saturated fatty acids (SFAs), refined carbohydrates, and ultra-processed ingredients has been shown to induce neuroinflammation in multiple brain regions important for energy homeostasis, cognitive function, and mood regulation in rodents, non-human primates, and humans. This review article summarizes the literature showing Western diets, via SFA increases, can increase the reactivity and alter the function of multiple types of immune cells from both the innate and adaptive branches of the immune system, with a specific focus on microglia, macrophages, dendritic cells, and T-cells. These changes in immune and neuroimmune signaling have important implications for neuroinflammation and brain health and will be an important factor in future psychoneuroimmunology research.

## 1. Introduction

Obesity and unhealthy diet consumption are one of the biggest risk factors for developing a number of disorders of the central nervous system (CNS) (Oddy et al., 2018). Specifically, increased consumption of dietary fats and refined carbohydrates has led to increases in adiposity and circulating saturated fatty acids (SFAs), which can act as signaling molecules at the basis of several disease states (Fatima et al., 2019; Volk et al., 2014). With advancements in our understanding of the sophisticated communications between the digestive, immune, and nervous systems, the mechanisms through which food impacts brain and behavior are being elucidated, with neuroimmune signaling being a leading candidate (González Olmo et al., 2021). There are a myriad of cells involved in mediating neuroimmune signaling that are all susceptible to direct modulation by ingested nutrients (Chapman and Chi, 2017; Gianfrancesco et al., 2019; Nadjar et al., 2017; Reynolds et al., 2012). Thus, the goal of this review is to briefly summarize the existing literature on cell types involved in neuroinflammation and how consumption of modern, processed diets that lead to excess SFAs and obesity influence their function and, ultimately, the function of the brain.

## 2. Diet and neuroinflammation

Divergence from an evolutionarily relevant diet to the consumption of a modern, westernized diet, such as a high fat diet (HFD) that contains excess SFAs, refined carbohydrates, and ultra-processed ingredients has been shown to induce neuroinflammation in multiple brain regions important for energy homeostasis, cognitive function, and mood regulation in rodents, non-human primates, and humans (González Olmo et al., 2021). Neuroinflammation is defined as an inflammatory process, typically characterized by increased levels of cytokine, chemokine, and reactive oxygen species, in the brain or spinal cord (DiSabato et al., 2016). Consumption of these "Western diets" can indirectly impact brain function by altering the gut microbiota, increasing intestinal inflammation and permeability, and ultimately impacting gut-brain communications via the vagus nerve (González Olmo et al., 2021). However, these ingested nutrients, and their metabolites, can also impact brain function by crossing the blood brain barrier (BBB) and interacting directly with neurons and glia in the brain (González Olmo et al., 2021). Importantly, these circulating nutrients that have been absorbed into the bloodstream also interact with peripheral immune cells (Chapman and Chi, 2017; Gianfrancesco et al., 2019; Nadjar et al., 2017; Reynolds et al., 2012), which can also directly and indirectly contribute to the neuroinflammatory milieu (Prinz and Priller, 2017). The rest of this review will focus on how nutrients abundant in the Western diet, specifically SFAs, impacts the function of central and peripheral immune cells and what that could mean for brain health in an effort to highlight its importance for the future of psychoneuroimmunology research. Importantly, any

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mention of Western or HFDs throughout this review are referring to 45% and 60% HFDs accompanied with a moderate amount of carbohydrates and should not be confused with a ketogenic diet, which evokes very different responses in the brain than Western diets due to the elimination of carbohydrates.

## 3. Brain-resident and infiltrating immune cells

### 3.1. Microglia

Microglia are myeloid cells derived from erythromyeloid progenitors in the yolk sac and enter the nervous tissue early during embryonic development and serve as the resident innate immune cell of the brain parenchyma (Matcovitch-Natan et al., 2016). In a physiological state, homeostatic microglia survey the brain microenvironment and, upon encountering an immune challenge, release either pro- or anti-inflammatory cytokines and can engage in the phagocytosis of invading pathogens or other debris that has accumulated in the brain (Lannes et al., 2017). Even in their homeostatic or surveying state, microglia serve a variety of functions in the healthy brain, including aiding in neuronal signaling, synapse formation, remodeling, and plasticity, as well as vasculature remodeling and blood flow regulation (Dudvarski Stankovic et al., 2016; Pont-Lezica et al., 2011; Wake and Fields, 2012). In regards to the resident immune response, astrocytes, which have bi-directional communication with microglia, and border-associated macrophages also play a role in conjunction with microglia and have been extensively reviewed elsewhere (Escartin et al., 2021; Liddelow et al., 2020; Prinz et al., 2021).

In addition to responding to classic immune threats like invading viruses, bacteria, or other pathogens, which are rare, microglia also respond to brain-specific injuries like stroke or traumatic brain injury (Lannes et al., 2017). Interestingly, microglia appear to be highly susceptible to modulation by dietary lipids and other nutrients that are taken up by the brain (Butler et al., 2020; Nadjar et al., 2017; Sobesky et al., 2014; Spencer et al, 2017, 2019). Preclinical models have shown that SFAs consumed via HFDs can cross the BBB via transport-protein mediated mechanisms (Pifferi et al., 2021). Once in the brain, SFAs can activate toll-like receptors (TLRs), which are located on the surface membrane of innate immune cells like microglia (Nadjar et al., 2017). The ability of SFAs to activate TLRs is consistent with the observation that saturated fatty acyl chains are located on the immunostimulatory domain of lipopolysaccharide (LPS), the endogenous TLR ligand and byproduct of gram-negative bacteria (Lancaster et al., 2018).

A diet-induced neuroinflammatory response was first observed in the hypothalamus in a seminal 2005 study by De Souza and colleagues (De Souza et al., 2005). Here, they showed mice fed a HFD for 16 weeks had increased proinflammatory cytokine expression and nuclear factor kappa B activation in the hypothalamus (De Souza et al., 2005). Subsequent work has extended the original findings regarding diet-induced neuroinflammation by showing that even short-term (3-day) HFD consumption can elicit a proinflammatory response in the hypothalamus as evidenced by increased proinflammatory cytokines and increased microgliosis (Thaler et al., 2012). Moreover, microglia have been causally linked to diet-induced hypothalamic inflammation in that microglia depletion that coincided with HFD consumption resulted in a blunting of the hypothalamic inflammatory response (Valdearcos et al., 2014).

Multiple *in vitro* studies have suggested that microglia respond directly to palmitic acid, the most abundant dietary SFA, via TLR4 activation which results in proinflammatory gene expression (Duffy et al., 2015; Wang et al., 2012; Yanguas-Casás et al., 2018). As an extension of this previous work, we have recently shown that microglia isolated specifically from both the hippocampus and amygdala of rats have increased expression of cell-surface markers indicative of increased reactivity, such as cluster of differentiation 11 b (CD11b) and MHCII, following palmitic acid treatment (Butler et al., 2020). These data pair nicely with *in vivo* data from our lab showing HFD impairs memory function and leads to increased inflammation in these same brain regions in aged rats (Spencer et al, 2017, 2019).

### 3.2. Macrophages

Macrophages are innate immune cells involved in the detection and destruction of invading pathogens, as well as antigen presentation to adaptive immune cells. Tissue-resident macrophages, similar to microglia, develop from yolk-sac progenitors and invade developing tissues (Stremmel et al., 2018). And while macrophages can also develop from bone marrow-derived monocytes, tissue-resident macrophages typically persist by local self-renewal (Hashimoto et al., 2013). Like brain-resident microglia, data show that SFAs can also activate peripheral macrophages via TLR4-medidated mechanisms (Håversen et al., 2009; Shi et al., 2006) and induce the activation of the nod-like receptor 3 (NLRP3) inflammasome in both human and murine monocyte-derived macrophages (Gianfrancesco et al., 2019; Karasawa et al., 2018). However, recent macrophage data have provided new evidence that casts doubt on whether or not SFAs act as true TLR4 agonists. Using multiple experimental approaches ranging from computational modeling to *in vitro* and *in vivo* techniques, Lancaster and colleagues (Lancaster et al., 2018) show that palmitic acid and LPS activate distinct intracellular signaling pathways in human monocyte-derived macrophages and that palmitic acid does not induce TLR4 dimerization, a critical step in canonical TLR4 activation by LPS. They do, however, show that while not a direct agonist, TLR activity is necessary for palmitic acid's inflammatory effect in macrophages and that this occurs via a TLR priming mechanism that mediates palmitic acid metabolism and changes in gene expression, lipid metabolic pathways, and lipid membrane composition (Lancaster et al., 2018). Regardless of SFAs' role as a traditional TLR agonist, there is now overwhelming evidence that SFAs directly activate both microglia and peripheral macrophages to induce a proinflammatory phenotype.

In addition to stimulating microglia in the brain and macrophages in the periphery, diet-induced obesity can lead to the trafficking of peripheral monocyte-derived macrophages into the brain. This macrophage infiltration was observed in the hypothalamus in male mice fed a HFD for 12 weeks (Lainez et al., 2018). In this study, hypothalamic macrophage infiltration was associated with decreases in post-synaptic density 95 (PSD95) protein expression and neuronal spine density in the hypothalamus, suggesting that diet-induced inflammation and peripheral immune cell recruitment may lead to functional changes in synapse formation (Lainez et al., 2018).

Peripheral monocyte-derived macrophage infiltration has been observed in other areas of the brain, including the hippocampus where it can have a direct impact on cognition. Specifically, obesity in mice devoid of the receptor for leptin, which is an energy homeostasis-regulating hormone released by adipocytes, led to increased BBB breakdown and macrophage infiltration to the hippocampus, promoting hippocampal inflammation and impairments in synaptic plasticity and learning and memory. Importantly, stabilization of the BBB via pharmacological inhibition of PKCβ prevented macrophage infiltration and cognitive impairments (Stranahan et al., 2016). An important distinction here is that the role of diet was not investigated in this study as the researchers employed a genetic model of obesity, which could have mechanisms distinct from diet-induced obesity, though chronic inflammation is a hallmark of both.

While the majority of studies investigate HFD-induced obesity models, HFD in the absence of obesity can still induce inflammatory changes and lead to cognitive impairments, especially in the context of aging. Indeed, short-term (3-day) HFD consumption causes increased proinflammatory cytokine levels in the hippocampus and amygdala of aged, but not young, rats and this inflammatory response is associated with significant impairments in hippocampal- and amygdalar-dependent memory (Spencer et al., 2017). Moreover, 3-day HFD significantly alters microglial morphology in aged rats *in vivo*, as well as phagocytosis function and the expression of genes associated with microglial priming

and reactivity in microglia isolated from aged animals (Butler et al., 2020; Spencer et al., 2019). These data demonstrate that diet alone, independent of obesity, can impact neuroinflammation and cognitive function in aged animals, though the underlying cellular mechanisms are still relatively unknown. Importantly, these studies focused on resident microglia and did not consider the contribution of macrophages or other infiltrating immune cells from the periphery.

### 3.3. Dendritic cells

Dendritic cells (DCs) originate from bone marrow-derived monocytes and are the professional antigen presenting cell (APC) of the innate immune system and are typically the first responders to an immune challenge (Wu and Liu, 2007). In addition to antigen presentation to T and B lymphocytes of the adaptive immune system, DCs are important for macrophage recruitment and activation (Stefanovic-Racic et al., 2012). One hallmark of diet-induced obesity is immune cell infiltration to adipose tissue, which contributes to the chronic inflammatory phenotype present in obesity. DCs appear to play a critical role in mediating this process as HFD-fed animals show an increase in DC presence in adipose tissue and liver, which is necessary for subsequent macrophage infiltration and immunophenotype in these tissues (Stefanovic-Racic et al., 2012).

Similar to microglia and macrophages, it appears HFD impacts DC function via direct interactions with SFAs. DCs derived from HFD-fed mice exhibited increased MHCII and TLR4 expression, as well as an increased proinflammatory cytokine response to LPS when compared to DCs isolated from chow-fed mice (Chen et al., 2014). In an additional set of experiments, palmitic acid treatment of DCs was shown to mimic the effects of HFD by increasing MHCII expression and potentiating responses to LPS (Chen et al., 2014). These effects were dependent on SFA-induced activation of the NLRP3 inflammasome and TLR4 signaling. These findings are consistent with data we recently published showing palmitic acid mimics the effects of HFD on microglia, with both HFD-derived and palmitic acid-treated microglia showing increased MHCII and NLRP3 expression (Butler et al., 2020). Taken together, these findings suggest DCs and microglia share similar responses to HFD and SFAs, which could have important implications for brain function.

It has been known for quite some time that cells with functional characteristics of bone marrow-derived DCs have been identified in the inflamed brain (Fischer and Reichmann, 2001; Karman et al., 2004). In recent years, advances in transcriptomics has shown that these presumed DCs in the brain serve functions that are distinct from resident microglia/macrophages under various pathological conditions, mostly in regards to antigen presentation (Gallizioli et al., 2020; Malo et al., 2018). In support of this notion, in an elegant set of experiments using high dimensional single-cell mapping and conditional MHCII ablations across each of the APCs in the CNS, it was revealed that DCs sample antigens from the healthy, steady-state brain parenchyma and migrate out of the CNS to present antigen to peripheral T-cells (Mundt et al., 2019). Together, these data expand the scope of conventional neuroimmunology, which mostly focused on the functional role of resident microglia.

The role of diet and/or obesity on DC infiltration and sampling of CNS antigen is unknown. However, increasing evidence suggests obesity is a risk factor for multiple sclerosis (MS), a CNS autoimmune disease in which infiltrating immune cells, including DCs, and antigen presentation, are critical aspects of the pathology (Hedström et al, 2012, 2014; Munger et al., 2013). In preclinical models, HFD has been shown to exacerbate neuroinflammation and behavioral symptoms in experimental autoimmune encephalomyelitis (EAE), a rodent model of MS. HFD-fed EAE mice showed increased microglial activation, IL-6 and CCL2 expression, and expansion of Th1 and Th17 cells relative to chow-fed EAE mice (Ji et al., 2019). While the exact mechanisms are unknown, given the consistently replicated finding that HFD and SFAs increase antigen presentation machinery, such as MHCII, on innate immune cells, it is tempting to hypothesize a direct SFA mechanism in driving antigen presentation in this context.

The role of DCs in the aged brain is also of interest for future research. Our lab has shown in multiple experiments that aging alone is sufficient to increase MHCII in the rat brain, specifically in the hippocampus (Frank et al., 2006; Spencer et al., 2017). Interestingly, 3-day HFD further potentiates this age-associated increase in MHCII in the hippocampus (Spencer et al., 2017). We have attributed primed microglia as the cell type responsible for this MHCII increase, especially since microglia isolated from aged rats also show increased MHCII gene expression (Butler et al., 2020). However, in addition to resident microglia, a recent study attributes increased antigen presentation in the aged brain to peripherally-sourced APCs, namely DCs and monocyte-derived macrophages (Honarpisheh et al., 2020). Thus, future experiments are needed to further delineate the cell type-specific contribution of antigen presentation in aging and the role of diet and obesity in this process. Overall, it appears HFD and SFAs directly activate multiple types of innate immune cells, both in the periphery and the brain, via parallel mechanisms involving TLRs and inflammasome signaling and increasing antigen presentation machinery.

### 3.4. T-cells

T-cells belong to the adaptive branch of the immune system and play integral roles in immune memory and host defense against pathogens. Briefly, $CD4^+$ naïve helper T-cells (Th cells) are produced by the thymus and, in general, await activation by APCs of the innate immune system (mostly dendritic cells and macrophages) (Smith-Garvin et al., 2009). Depending on the signal from the APC, Th cells will differentiate into either Th1, Th2, or Th17 cells and migrate to non-lymphoid tissues (Ruterbusch et al., 2020). Th1/17 cells are proinflammatory, and further propagate the activity and recruitment of innate immune cells, such as macrophages, as well as release their own proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α), interferon gamma (INF-γ), interleukin 2 (IL-2), and IL-17 (Ruterbusch et al., 2020). Th2 cells release cytokines such as IL-4, IL-5, and IL-13, and are therefore considered anti-inflammatory (Ruterbusch et al., 2020). In addition to Th cells, $CD8^+$ T-cells are also involved in the adaptive immune response and are considered cytotoxic T-lymphocytes (CTLs). While Th cells form their immunological synapse with MHCII on innate immune cells, which is essential for their activation, CTLs bind to MHC I, which is expressed by all nucleated cells as a means to present proteins made inside the cell (Smith-Garvin et al., 2009). Thus, CTLs are critical for the elimination of virus- or bacteria-infected cells.

Like other immune cells, T-cells are subject to modulation by ingested nutrients and metabolic state of the organism. For example, HFD consumption increases proinflammatory Th1/Th17 differentiation of naïve Th cells and subsequent infiltration to non-lymphoid tissues, particularly adipose tissue where they contribute to the chronic proinflammatory environment observed in obesity (Chapman and Chi, 2017; Gerriets and MacIver, 2014; Winer et al., 2009). Since Th1 differentiation can be induced by signals from TLR4-activated innate immune cells (Chen et al., 2020; Kim et al., 2018), this could be one potential mechanism driving diet-induced Th1 differentiation considering TLR4 is involved in HFD-mediated innate immunity, though this has yet to be tested directly. Alternatively, similar to innate immunity, diet-induced Th1 differentiation could be the result of direct interactions with SFAs. Indeed, direct palmitic acid exposure to naïve Th cells mimics HFD-induced Th1 differentiation that is mediated via a phosphoinositide 3-kinase (PI3K) p110δ-Akt signaling pathway (Mauro et al., 2017). Moreover, this SFA-mediated mechanism was independent of innate immune cell activity as HFD increased Th1 numbers regardless of whether or not they were co-cultured with DCs. In fact, DCs isolated from HFD-fed mice were surprisingly less effective at promoting *ex vivo* Th1 differentiation compared to chow-fed controls (Mauro et al., 2017). While these results may be counterintuitive, they nevertheless support the claim that HFD

**Fig. 1.** Michael J. Butler, PhD. I studied psychology and biology at Florida State University during my undergraduate years and went on to pursue my PhD in neuroscience at Florida State. For my graduate work, I trained under Dr. Lisa Eckel and studied the neuroendocrine control of food intake and regulation of energy homeostasis in female rats, with a focus on estrogen receptor signaling. One of my projects investigated the impact of estradiol on microglia function in female rats that were fed a high fat diet and this sparked my interest in neuroimmunology research. Following the completion of my PhD in 2019, I began a postdoctoral research position at the Institute for Behavioral Medicine Research at the Ohio State University Wexner Medical Center working with Dr. Ruth Barrientos. Here, I've focused on delineating the underlying mechanisms driving diet-induced neuroinflammation and cognitive decline in aged animals. My goal is to build a program of research at the intersection of immunology, neuroscience, and nutrition in an effort to understand how the food we eat impacts our immune system and brain function. Through my research I also want to be an effective science communicator and make advanced and nuanced scientific concepts more accessible to non-scientists. Through this outreach, it is my hope to improve science literacy and build trust in the scientific community. In my free time, I enjoy hiking, rock climbing, and snowboarding, as well as spending time with my friends and family.

functionally dysregulates innate immune responses that can have downstream consequences for adaptive immunity. However, further research is required to delineate the relative contribution of innate immune cell function and SFA signaling to diet-induced T-cell activation.

In recent years, the role of T-cells in neuroimmunology has gained increased attention, especially in the context of natural aging and various pathologies. For instance, in MS, T-cells infiltrate the brain and engage in bi-directional communication with resident microglia, with each

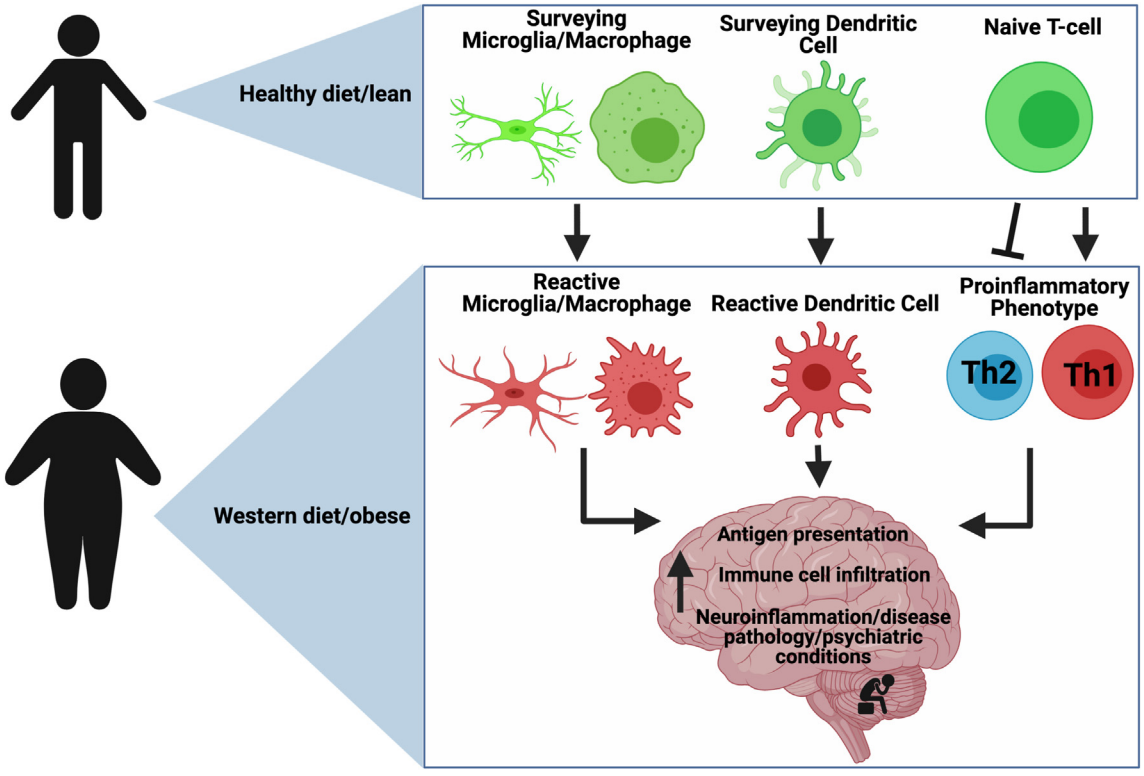


**Fig. 2.** The consumption of Western diets and obesity leads to increased inflammation in the periphery and the brain via increased activation and priming of both microglia, macrophages, and dendritic cells of the innate immune system. Moreover, a bias towards $CD4^+$ Th1 polarization, relative to Th2, and reactivity of $CD8^+$ cytotoxic T-cells occurs in obese animals fed a HFD. These alterations in immune cell function can lead to increased neuroinflammation, which ultimately impacts brain health and function.

promoting the proinflammatory function of the other, facilitating neuroinflammation and MS symptomology (Strachan-Whaley et al., 2014). While typically observed in low numbers in the steady-state parenchyma, T-cells do play an important role in CNS immune surveillance and even potentially alter cognitive function by regulating hippocampal neurogenesis (Ziv et al., 2006). That said, T-cell infiltration to the naturally aged parenchyma has been shown in several species, including rodents, non-human primates, and humans, with functions that could ameliorate or exacerbate neuroinflammation, depending on the phenotype (Batterman et al., 2021; Coder et al., 2017). Indeed, both proinflammatory Th1/Th17 cells and CTLs, as well as anti-inflammatory Th2 cells, have been identified in the aged brain (Gemechu and Bentivoglio, 2012; Xu et al., 2010). Importantly, little is known about the mechanisms of T-cell recruitment to the aged brain and the dual effect of aging and HFD consumption on T-cell recruitment to the brain is completely unexplored, providing an exciting new area of research for diet-brain interactions. T-cell recruitment to the brain has also been observed in neurodegenerative disease, such as Alzheimer's and Parkinson's disease. However, the role of T-cells in these pathologies are not yet clearly defined (Prinz and Priller, 2017), again providing exciting new directions for neuroimmunology research.

## 4. Conclusion and future directions

Overall, there is a compelling body of evidence that ingested nutrients from a HFD can directly impact the function of multiple types of immune cells from both the innate and adaptive branches of the immune system in both the periphery and the brain. Given that peripheral immune signals can have direct and indirect impacts on brain inflammation and function, understanding how nutrition impacts these cells will be critical to understanding the neuroinflammatory and behavioral milieu brought on by diet. Unfortunately, like most biomedical research, the majority of work has been conducted in male subjects. This is concerning given that sex hormones like estrogens and progesterone impact immune cell function and neuroinflammatory signaling, as well as weight gain in diet-induced obesity models (Barrientos et al., 2019; Hwang et al., 2010; Lovejoy and Sainsbury, 2009). Moreover, women are at an increased risk for developing numerous pathologies, including depression, anxiety, and neurodegenerative disease, which highlight the importance of including sex as a biological variable in future work (Barrientos et al., 2019; Mazure and Swendsen, 2016). Moving forward, understanding the specific roles and interactions between these infiltrating and resident immune cells of the brain, and related sex differences, will be critical for psychoneuroimmunology research (Fig. 1). Lastly, due to the breadth of studies that focused on Western diet-induced increases in SFA-mediated neuroimmune signaling, discussion of other aspects of nutrition, such as consumption of polyunsaturated omega-3 fatty acids and vitamins were not discussed in this brief review. However, this is an important area of research that is also crucial for future of the field and has been extensively reviewed elsewhere (Koduah et al., 2017; Layé, 2010) (see Fig. 2).

## Declaration of competing interest

The author declares no conflict of interest.

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