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Review Article

Sex, sepsis and the brain: defining the role of sexual dimorphism on neurocognitive outcomes after infection

Valerie E. Polcz[1], Evan L. Barrios[1], Benjamin Chapin[2], Catherine C. Price[3], Ravinder Nagpal[4], Paramita Chakrabarty[5], Gemma Casadesus[6], Thomas Foster[5], Lyle L. Moldawer[1] and Philip A. Efron[1]

[1]Department of Surgery and Sepsis and Critical Illness Research Center, University of Florida College of Medicine, Gainesville, Florida, U.S.A.; [2]Department of Neurology, University of Florida College of Medicine, Gainesville, Florida, U.S.A.; [3]Department of Clinical and Health Psychology, University of Florida College of Public Health and Health Professions, Gainesville, Florida, U.S.A.; [4]Florida State University College of Health and Human Sciences, Tallahassee, Florida, U.S.A.; [5]Department of Neuroscience, University of Florida College of Medicine, Gainesville, Florida, U.S.A.; [6]Department of Pharmacology and Therapeutics, University of Florida College of Medicine, Gainesville, Florida, U.S.A.

Correspondence: Philip Efron (philip.efron@surgery.ufl.edu)

Sexual dimorphisms exist in multiple domains, from learning and memory to neurocognitive disease, and even in the immune system. Male sex has been associated with increased susceptibility to infection, as well as increased risk of adverse outcomes. Sepsis remains a major source of morbidity and mortality globally, and over half of septic patients admitted to intensive care are believed to suffer some degree of sepsis-associated encephalopathy (SAE). In the short term, SAE is associated with an increased risk of in-hospital mortality, and in the long term, has the potential for significant impairment of cognition, memory, and acceleration of neurocognitive disease. Despite increasing information regarding sexual dimorphism in neurologic and immunologic systems, research into these dimorphisms in sepsis-associated encephalopathy remains critically understudied. In this narrative review, we discuss how sex has been associated with brain morphology, chemistry, and disease, sexual dimorphism in immunity, and existing research into the effects of sex on SAE.

Introduction

Sepsis remains a major cause of morbidity and mortality globally, with over half of septic patients in ICU care believed to experience sepsis-associated encephalopathy (SAE) [1]. Neuroinflammation is a response to infection. Even after acute recovery from illness, patients may be susceptible to long-term neurocognitive changes. Given the increase of Alzheimer's disease and related disorders in the community [2], the potential impact of sepsis on neurocognitive recovery has garnered interest in the scientific community. To date, there remain few studies prospectively following adults with sepsis for neurocognitive changes and the pathways for long-term downstream effects are unclear [3,4].

Similarly, awareness of sexual dimorphism and its impact on human physiology is increasing but remains understudied. Less than 10% of published immunology articles report data stratified by sex [5]. Sex differences may be secondary to a variety of biological and environmental factors, hormones, chromosomal differences, or both [6]. Hormonal differences vary based on the stage of the estrous/menstrual cycle, while chromosomal differences are related to differential gene expression [6]. Understanding baseline dimorphism in the immune system may improve sepsis research.

This narrative review will discuss sex-specific differences in human and rodent brain structure and function over time, sexual dimorphism and the immune system, and sepsis responses that may alter cognition. Consideration for dimorphism in sepsis and associated neurological behaviors will foster specific therapeutic and/or preventative strategies.

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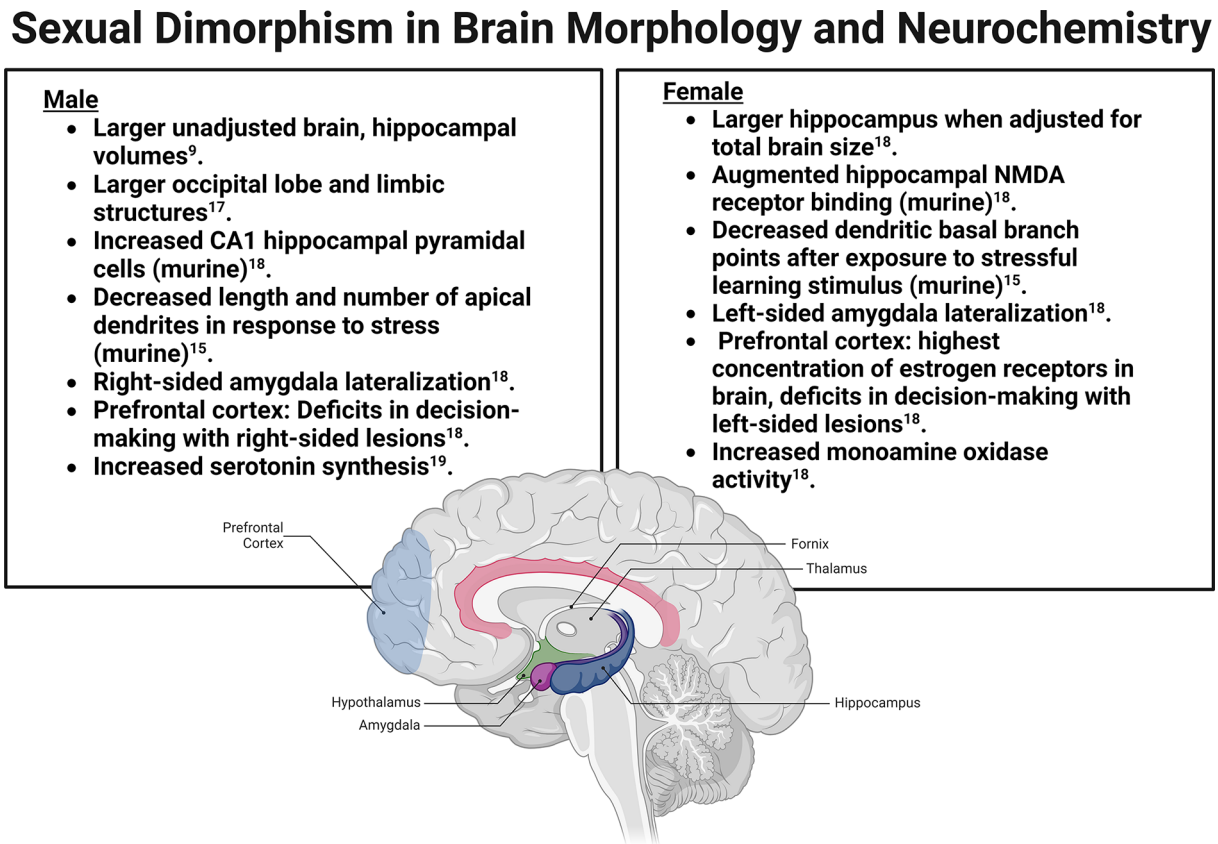

Figure 1. Sexual dimorphism in brain morphology and neurochemistry.

Several sex-dependent differences in lateralization, brain structure, function, and even neurotransmitter synthesis and concentrations exist between males and females, as depicted here.

Sexual dimorphism and the brain

Sex, brain morphology, and neurotransmission

Sexual dimorphism in brain morphology has been shown in both human as well as animal models, which persist throughout development [7,8] (Figure 1). Other structures in the brain may exhibit sexual dimorphism. In humans, some research suggests amygdalae are larger in males compared with females [17], and, with respect to memory formation, dimorphism exists such that emotional memories in the female amygdalae involve the left side (visually predominant, positive and negative emotions), but involve the right side in males (negative emotional responses) [18]. The prefrontal cortices express a high concentration of estrogen receptors which may lead to differences in decision-making between the two sexes, including the finding that human males take more risks compared with females [19,20]. Structural neuroimaging research suggests human males have decreased levels of overall cortical thickness, as well as an increase in the rate of cortical thickness decline [21], and females more white matter volume [22,23]. Further research is necessary to uncover the mechanisms behind these identified dimorphisms.

Murine animal model research suggests that the hippocampi are not only a fundamental hub of learning and memory formation but also one of the main regions affected in SAE. Within this model, the hippocampi contain different densities of androgen and estrogen receptors, which are based on location, phase of the estrous cycle, and age in Sprague Dawley rats [9]. Previous research in both animals and humans demonstrates that high and prolonged levels of glucocorticoids, released during periods of physiological and psychological stress, reduce associative learning, spatial memory, and hippocampal atrophy [10–13]. Relatively greater intralobular and intrahemispheric connectivity in male rodent brains allows faster communication from posterior to frontal regions, connecting perception to action. Relatively greater interhemispheric connectivity in females theoretically supports integration of the analytical and sequential reasoning of the left hemisphere with the spatial and intuitive processing of information in the right hemisphere [8]. On a cellular level, male mice are shown to have increased dendritic intersections in granule neurons;

however, female mice have greater branch points and primary dendrites with more dendritic spines in Sprague Dawley and Long-Evans hooded rats [14–16]. These structural differences contribute to practical differences in learning between reproductive-aged males and females, which will be discussed later in the review.

Sex differences in mammals have also been observed in neurotransmitter systems including adrenergic, serotonergic, cholinergic, corticosterone, benzodiazepine, and cholecystokinin [17]; these factors are largely related to episodic memory [18]. Some research suggests males synthesize more serotonin compared with females, which could impact disease states associated with serotonin dysfunction [19]. This can contribute to differences in the learning process, as seen during stress and the subsequent impact on conditioning (enhanced in males but inhibited in females) [20]. This association between dimorphic responses to stress is largely related to sex hormones [21].

Sex and the blood–brain barrier

The blood–brain barrier (BBB) is a critical physical and chemical barrier that serves as a gateway to the CNS for critical influx of nutrients, toxin removal, ion, and molecular exchange, in addition to carefully controlled communication with, and attenuation by peripheral chemical and immune signaling. This communication is essential to allow the CNS to adapt to various physiologic and pathologic states, such as the combined behavioral and physiologic changes seen in sickness behavior in response to overwhelming infection [22]. Structurally, the BBB is a complex interface involving a densely knit extracellular glycocalyx secreted by endothelial cells, which are tightly associated with pericytes and astrocytes [23]. Tight junction (TJ) proteins between endothelial cells also comprise an essential regulatory component of the BBB [24]. While usually tightly controlled, the permeability of the BBB can be compromised with exposure to inflammatory mediators in severe infection and SAE, through a combination of direct and indirect mechanisms [25].

While dimorphic structural and neurochemical differences have previously been described in both human and animal studies, emerging evidence from both human and animal studies on aging, cognitive decline, neurodegenerative and psychiatric diseases suggests that BBB permeability may also be influenced by sex hormones. Several *in vitro* and human imaging studies have supported that female sex may be associated with increased BBB integrity when compared with male counterparts, through a combination of hormonal, molecular, and transcriptional mechanisms [26–28]. As increased BBB permeability is believed to be one of the key pathophysiological underpinnings of SAE, these findings may have broader implications for sexual dimorphism in this disease process, although further research is critical to test and validate this association.

Sexual dimorphism in aging and neurocognitive decline

Female and male neurological systems may use different predominant mechanisms for memory retention [29]. Although controversial, some research suggests males have enhanced visuospatial abilities [21,30,31], while females have strengths in verbal memory overall [32,33]. These sex-related advantages may change with menopause, specifically initial learning and later self-recall, thereby supporting the concept that estrogen is important for memory formation [34,35]. Earlier age of menopause associates with higher risk of cognitive decline secondary to loss of estrogen production, and it is controversial whether hormone replacement therapy decreases this risk in menopausal women [36]. Research in animal models of menopause and epidemiological data has suggested that exogenous estrogen administration is most effective when started at the time of oophorectomy, however, with regards to cognition, in humans this link is less strong [37]. This is likely due to the involvement of other reproductive hormones including menopausal rises in gonadotropins whose receptors are also expressed centrally and are known to regulate cognition (reviewed in: [38,39] and recently published in [40]. As estradiol withdrawal progresses, genes that normally respond to estradiol undergo epigenetic regulation (primarily methylation), which may decrease transcription and mute downstream effects [41].

In healthy older adults, research reports a smaller impact of sex on age-related cognitive decline [42]. However, sexual dimorphism may also lead to differential responses (and susceptibilities) to some neurodegenerative diseases. Alzheimer's disease (AD) is the most common neurodegenerative disease and affects females more than males, even when controlling for age (given that females live longer, on average) [36,43,44]. In the hippocampi during AD, females experience relatively greater changes in hippocampal volume and amyloid level, whereas males experience a greater increase in white matter hyperintensities [9,45]. APOE-epsilon4 is the strongest genetic risk factor for the development of sporadic AD [46,47] and affects females significantly more than males (particularly at younger ages) [48]. APOE4 dysregulates neuronal and glial homeostasis, along with disrupting neural networks and mitochondrial function [49]. This results in significantly reduced brain volume in APOE3/4 heterozygotes, leading to worsened memory, potentially related to tau pathology [46,50]. Female APOE3/4 heterozygotes have an odds ratio of 4 (compared with

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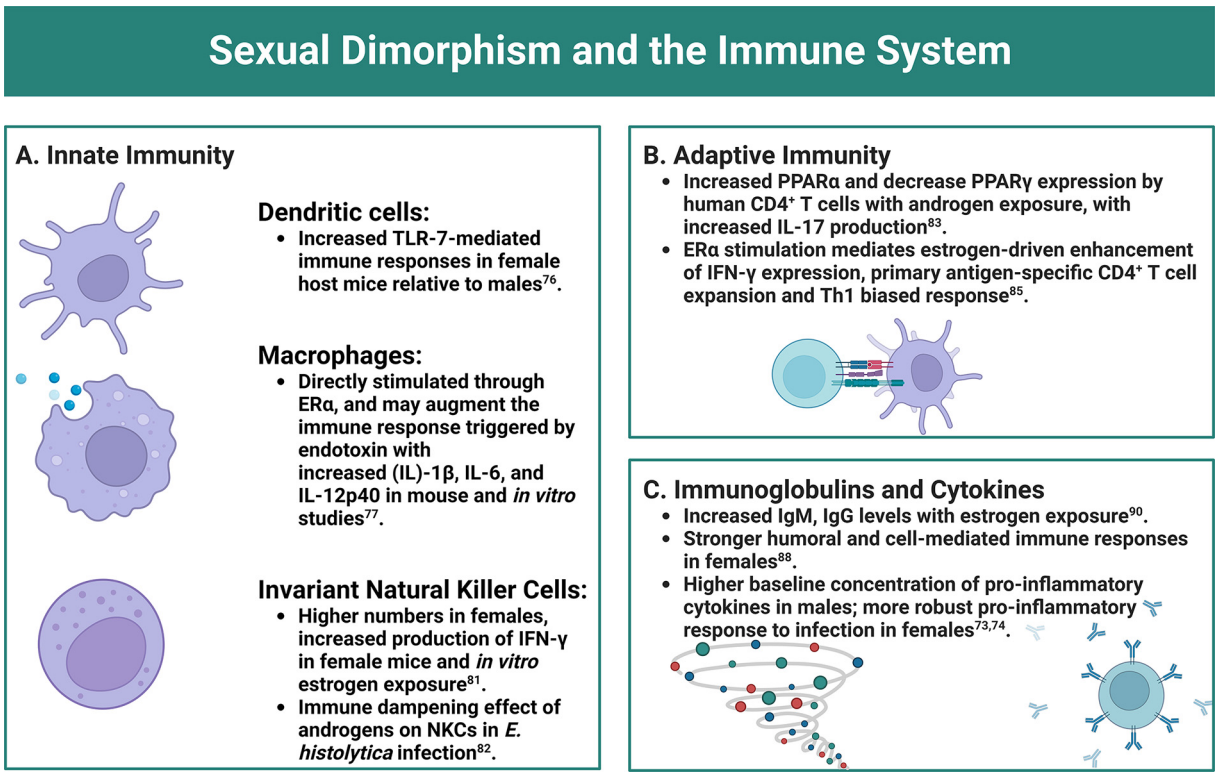

Figure 2. Sexual dimorphism and the immune system.

Males are more prone to infections from a variety of pathogens and have a tendency for more severe infections compared with females in epidemiological studies; by contrast, females' more robust immune response may contribute to the increased prevalence of autoimmune diseases seen in this group. Key distinctions in sex-hormone mediated innate immunity (**A**), adaptive (**B**) immunity and both immunoglobulin and cytokine production (**C**) are believed to drive these differences.

1 in men) of developing AD, and the risk of AD in homozygous APOE 4/4 is also higher in females compared to males [51]. APOE2 is neuroprotective, but only in women, and may be mediated by a differential lipid expression and biomarkers [52,53]. Lastly, differences in comorbid disease incidence and prevalence may also lead to increased disparity in neurocognitive decline based on sex. For instance, depression is also associated with increased risk of AD development, and females have been reported to be twice as likely to develop depression compared to males, which may also contribute to sexual dimorphism in the differential response to neurodegenerative disease [54].

Sexual dimorphism and the immune system

Some research suggests females exhibit stronger responses to pathogens in both innate and adaptive immunity compared with males, which aids in recovery from illness as well as improved vaccine efficacy [55]. However, these enhanced immune responses predispose females to increased risk of autoimmune diseases [56]. Although differences between males and females are becoming increasingly recognized, the mechanisms underlying these distinctions are incompletely characterized. What is clear is the interconnectedness between the influence of sex chromosomes and sex hormones on many aspects of the immune system, including immune cell quantity and function, as well as circulating cytokines (Figure 2).

'*Inflammaging*' occurs in mammals and consists of neuroinflammation associated with aging [57,58]. Inflammasomes can be activated by increased reactive oxygen species. This activates cytokine expression which augments the aging process via inhibition of autophagy through immune cell senescence [57,59]. Immunosenescence develops earlier in males than females [60]; however, the rate of immunosenescense after menopause is greater in females than similar-aged males [61]. This suggests the involvement of sex hormones in the neuroinflammatory process during aging. Sex hormones are one component of sexual dimorphism which impacts the immune system.

Innate immunity

Differences exist in the innate immune system with respect to sex, and products of both sex chromosomes (evidenced by higher susceptibility to infection in males throughout their lifespan) and sex hormones (via direct interactions with androgen receptors on immune cells) contribute to these differences [62]. Females have better outcomes after trauma and sepsis; however, the mechanisms behind these outcomes are poorly understood [63]. Males are consequently more susceptible to many bacterial, viral, fungal, and parasitic agents [64]. Differences in immune response between sexes may be related to sex hormones, chromosomal differences, microchimerism, and environmental factors [65].

Considering sex hormones and chromosomal differences, estradiol has been shown to augment proinflammatory immune responses via both adaptive and innate immune activation, whereas androgens have been shown to generally induce a more immune-dampening effect [66]. This is consistent with an increased incidence of autoimmune diseases seen in females [63], as the female immune system is reacting towards self and foreign 'antigens'. In the brain, estrogen acts on microglia, which serve as macrophages and regulate cytokine release in the brain [67]. Female sex hormones function agonistically by binding to genes like MyD88, IFR7, and Toll-like receptors (TLRs) involved in innate immunity [62]. The TLR7 gene is found on the X chromosome, and is expressed in higher levels in females [68], which contributes to higher levels of interferon production in females [69]. X-linked mosaicism may lead to an enhanced diversity of gene expression which may translate to a more robust immune system [66]. The X chromosome contains many genes involved innate and adaptive immunity, and failure of inactivation of one of the X chromosomes in cells may similarly contribute to the female immune response, increasing their vulnerability to autoimmune diseases such as systemic lupus erythematosus (SLE) [70].

Major histocompatibility complex (MHC) I functions to present and detect viral antigens and is found universally in the brain. This related pathway increases with age, but more so in female compared to male mice [71]. Antigen presenting cells also possess increased MHC Class II in females [72]. Baseline serum cytokine concentrations of IL-1β, IL-6, TNF-α, and C-reactive protein (CRP) have been shown to be higher in males, corresponding to testosterone level and male sex [73]. In addition, the production of immunosuppressive cytokines, such as IL-10, are also increased in males and correlated with androgen concentration [74]. Furthermore, the production of proinflammatory cytokines in response to pathogenic stimulus is more robust in females than males, as will be discussed below.

Sex influences multiple cell types within the immune system, and result in unique transcriptomics between the sexes [75]. Plasmacytoid dendritic cells, important innate immune cells involved in recognizing and responding to viral pathogens, show enhanced production of antiviral and immunostimulatory cytokines with exposure to estrogen [76]. In mice, estrogen was also found to stimulate macrophages and enhance their response to bacterial antigens via increased production of cytokines such as IL-1β, IL-6 and IL-12p40 [77], while testosterone has been shown to have a dampening effect [78]. Phagocytic activity of antigen-presenting cells is also enhanced in females [79]. Neutrophils in males display decreased maturity compared with females [61]. Male monocytes produced increased cytokines when stimulated compared with females [62]. Sexual dimorphism is present in nearly all aspects of the immune system, although further research needs to be conducted to validate early research and elucidate mechanisms behind these differences. Increased reporting of data by sex in the scientific community will contribute to the understanding of this important topic.

Adaptive immunity

Multiple facets of adaptive immunity differ between males and females. Natural killer cells occur in higher frequency in females [80], and estrogen exposure is essential to their stimulation and immune-enhancing properties in mice [81]. Testosterone, on the other hand, has the potential to decrease the response of natural killer cells to infection [82]. The Th1 phenotype produces cytokines and drives the inflammatory response to infection. Males have a propensity for Th2 and Treg responses, where females exhibit for a bias toward Th1 responses [83,84]. In mice, estrogen aids in the Th1 response, and leads to $CD4^+$ T cell expansion [85]. Males have higher levels of $CD8^+$ T cells [86]; however, females have greater cytotoxic activity [87]. T cells are also more sensitive to activation in females [87]. Estrogen also has a differential impact on B-cell gene expression, which culminates in a higher relative number of B cells and a greater antibody response to infection [88]. Overall, estrogen negatively affects lymphopoiesis, but increases synthesis of immunoglobulins in mature B cells, and can lead to the increased risk of antibody production against self-antigens [89–91]. Aging particularly affects the B cell population of men, with a transition towards an innate immune response that is not seen in the same magnitude as women [92]. Differences in the development of the immune system based on sex leads to a varied pathogenic response.

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Sepsis and neurocognition: sepsis-associated encephalopathy

Dysregulation of systemic immunity, both acute and chronic, can exacerbate cognitive decline. In healthy individuals, the metabolic, behavioral, and immunologic changes in response to infection and inflammation are typically transient. However, the cumulative effects of chronic stress, including antigenic stress, are believed to induce lasting phenotypic changes, with increasingly pervasive effects of such stressors on the body, and nervous system [93,94]. Increased basal levels of proinflammatory markers seen in aging and their altered profiles in neurocognitive disorders further support this, although a causal association between chronic inflammatory conditions and neurodegenerative disease progression has been challenging to establish [95]. In the case of acute and subacute inflammation, as seen in systemic infection, the mechanisms through which immune dysregulation exerts deleterious neurological effects are now becoming clearer. Furthermore, the dysregulation of typical neuroendocrine immune networks, and even, potentially, the gut–microbiome–brain axis, leads to a vicious cycle of further systemic immune dysregulation, gut dysbiosis, exacerbation of neuroinflammation, and ischemic injury, which represent characteristic features of SAE [96,97].

Epidemiology

SAE is clinically characterized by global cognitive dysfunction due to overwhelming infection not involving the CNS, and is the leading cause of ICU encephalopathy worldwide, with a reported incidence ranging from less than 10 to up to 70% in septic patients [98,99]. True characterization of disease prevalence is challenging, given a lack of standardized diagnostic criteria for SAE, discrepancies in timing of symptom onset in the clinical course, and heterogeneity of populations studied [98,100]. Its diagnosis is associated with increased risk of mortality, up to 70% in severe cases [98]. Age, history of neurocognitive disorders, renal/hepatic dysfunction and sepsis severity are considered risk factors and can exacerbate the lasting adverse neurological and psychiatric effects seen with SAE [99,101–103]. While very few studies have evaluated associations with infectious source, there are limited data to suggest increased incidence of SAE secondary to biliary and gastrointestinal pathogens, such as *Staphylococcus aureus*, *Enterococcus feacium*, *Acinetobacter*, *Pseudomonas aeruginosa,* and *Stenotrophomonas maltophilia* [104].

Pathophysiology

The underlying mechanisms of brain injury in SAE are both multifactorial and interconnected, characterized broadly by BBB hyperpermeability, altered cerebral perfusion and ischemia, dysregulation of neurotransmission, and increased CNS inflammation characterized by chronic microglial and astrocytic activation [99,105–107]. Postmortem studies of human brain pathology after sepsis demonstrate broader morphologic and histologic changes characterized by cerebral edema, hemorrhagic/ischemic injury, hypoxia, increased apoptosis, necrosis, and axonal injury [106]. Much of what is known regarding disease pathophysiology, however, is derived from animal models of bacterial sepsis.

The BBB plays a crucial role in maintaining CNS homeostasis, by protecting against unwanted exposure to inflammatory mediators, neurotoxins, and infiltration by peripheral leukocytes or pathogens [107]. It has been demonstrated that the post-sepsis cytokine storm, as well as exposure to pathogen and damage-associated molecular patterns (PAMPs and DAMPs), can affect the BBB and its permeability through direct contact and stimulation of CNS inflammatory cells (reviewed in [105,107]). As early as 24 h after exposure to endotoxin, down-regulation of TJ proteins leads to alterations in BBB permeability in key territories of the brain (reviewed in: [107]). Consequently, increased exposure to noxious free radicals and inflammatory cytokines leads to neurologic insult, reduced perfusion and cerebral edema (reviewed in [107]). These adverse effects appear to be attenuated, at least in the early stages of bacterial sepsis models, by microglial cell activation, infiltration across the BBB, and microglial claudin-5 expression, which attenuate the increased endothelial permeability seen in murine sepsis models [108]. In later stages, however, continued pathogenic exposure induces a phagocytic microglial phenotype that compromises BBB permeability [108]. This has been shown by a reduction of sphingolipid concentrations, key mediators of endothelial barrier maintenance, in murine bacterial sepsis models, while *in vitro* treatment with sphingosine-1-phosphate (S1P) has also been shown to tighten endothelial cell junctions in a dose-dependent fashion (reviewed in [108]). Endothelial cell mitochondrial dysfunction also contributes to the pathologic changes to the BBB in SAE, with increased cytochrome *C* release (a pro-apoptotic signaling protein) and mitochondrial fission [109,110]. These effects are believed to be mediated in large part by the dynamin-related protein 1 (Drp1), a protein involved in mitochondrial fission, and inhibition with peptide inhibitor P110 has been shown not only to reduce rates of mitochondrial fission but also to reduce secretion of proinflammatory cytokines into the CNS and prevented down-regulation of TJ proteins [110,111].

Dysregulated cytokine production and cytokine *'storming'*, as is seen in sepsis, can lead to CNS injury and contribute to SAE through direct and indirect mechanisms [105]. Direct extravasation into the CNS via a hyperpermeable BBB leads to diffusion of proinflammatory signaling proteins that are recognized by the native cytokine receptors present on microglia, astrocytes and neurons in key parts of the brain such as the hypothalamus and pituitary, limbic, noradrenergic and vasopressinergic systems (reviewed in [105]). Direct stimulation of glial cells within the CNS also results in cytokine and chemokine release, leading to CNS inflammation, worsening of BBB permeability, and recruitment of peripheral immune cells [105]. Excessive cytokine production can also indirectly influence CNS function without crossing the BBB by affecting its permeability and secretions, via afferent nerve stimulation and effects on periventricular organ function [112].

Direct autonomic stimulation by sepsis-induced peripheral infectious stimuli (e.g., bacterial, fungal, viral, and LPS) can also lead to cytokine signal transmission to the brain and may form a direct link between the peripheral immune system and the CNS [96,105]. This link, and that of the microbiome–gut–brain axis (MGBA), while typically essential for homeostatic brain function, cognition and memory under normal conditions, can lead to a feedback loop that promotes dysregulation of all three systems in a septic state [96,97,113,114].

Physiologic immune signaling is an integral component of normal neural function and plays a role in normal synaptic functioning and pruning, memory modulation, and maintenance of both neurologic and peripheral immune homeostasis [113]. Microglial synaptic pruning has been shown to rely on both chemokine and complement system components, and physiologic levels of inflammatory markers including TNFα and IL-1β have been shown to play important roles in hippocampal long-term potentiation (Reviewed in: [113]). Similarly, the CNS has been shown to play a crucial role in maintaining peripheral immune homeostasis, and its dysregulation in sepsis has been shown to affect vastly diverse cell lineages in both adaptive and innate arms of the immune system (reviewed in [96]). The mechanisms by which the CNS exerts this peripheral effect, and is in turn affected, occur via sympathetic, parasympathetic, and hypothalamic–pituitary–adrenal (HPA) axis signaling.

The cholinergic anti-inflammatory pathway (CAP) is one example of this. Activation of the CAP through peripheral vagal or α7 nicotinic acetylcholine receptors (α7nAchRs) helps to modulate an anti-inflammatory immune response and has been shown to alleviate end-organ dysfunction and improve survival in animal models (reviewed in: [96]). Increased cholinergic neuron apoptosis seen in sepsis models further points to a potential role of these pathways in contributing to both peripheral immune and CNS dysfunction and may have a role in SAE disease progression (reviewed in: [96]). Similarly, the HPA axis is known to have strong immunomodulatory effects, and deficiency or dysregulation of this system, as can be seen in the relative adrenal insufficiency that often accompanies sepsis, can contribute to clinical deterioration in these patients [115].

Autonomic and HPA dysfunction in sepsis have effects not only on peripheral immunity, but also the MGBA, with multiple proposed pathways of communication that have only recently come under investigation [97]. Under normal conditions, autonomic and neuroendocrine signaling (via the HPA axis) result in enteric nervous system stimulation and modulation of gastrointestinal motility and acidity, optimizing the landscape for resident immune and enteric cells, and by extension maintaining a healthy gut microbiome (reviewed in [97]). A gut microbiome in homeostasis secretes anti-inflammatory metabolites, such as short-chain fatty acids (SCFAs), critical for maintenance of the MGBA as well as the BBB [116,117]. Microbes themselves are capable of local neurotransmitter synthesis (such as dopamine, noradrenaline, and GABA) and neuroactive metabolite production, which can directly influence the CNS [118]. In sepsis, gut dysbiosis results from disruption of normal homeostatic systems and exogenous alteration of the microbiome via antibiotic administration, and increased gut permeability can lead to increased systemic release of endotoxin and worsen systemic inflammatory responses [97]. Moreover, excess production of GABA by a pathologic microbiome could potentially contribute to the progression of altered mental status. Additionally, reduced SCFA production limits the ability of the gut to maintain CNS homeostasis, thus potentially worsening SAE outcome [97]. While investigations into the mechanisms by which the MGBA impairment contributes to SAE development and progression are still under study, early evidence suggests that intestinal epithelial cell (IEC) exosome release during sepsis may also contribute to SAE and cognitive dysfunction, via IL-1β mediated pathways leading to hippocampal neuron apoptosis. Furthermore, early animal models show a potential beneficial effect of fecal transplantation on reversing these effects and may represent a promising adjunctive therapy that warrants future study [114]. There is a lack of understanding as to the relationship of sexual dimorphism in peripheral and central immune system crosstalk, and more mechanistic research could open up avenues for understanding the relative vulnerabilities of elderly populations to cognitive decline.

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Presentation of SAE and long-term sequelae

The diagnosis of SAE is one of exclusion, given the parallels in clinical presentation, functional measurements and imaging that can be seen secondary to effects of medications, primary CNS infections, cerebral ischemia and other causes of severe systemic inflammatory response (SIRS) [98]. Clinically, presentations may range from mild cognitive impairment, delirium, more severe encephalopathy or even coma, and up to 70% of severe cases may present with concurrent neuromyopathy [98]. The acute phase of the disease is most often characterized by symptoms of delirium, such as reduced focus, increased agitation, derangement of the sleep-wake cycle, and hallucination, but more significant alterations in consciousness can be seen [99]. In a septic patient presenting with acute mental status change, no widely accepted imaging or laboratory markers have been shown to be specific for SAE, and the diagnosis is primarily clinical. CT and MRI imaging is often nonspecific, although cerebral edema, ischemic lesions and signs of posterior reversible encephalopathy (PRES) can sometimes be observed [98,99]. EEG may demonstrate abnormalities, such as the presence of theta and delta waves, periodic or rhythmic discharges, or even seizure activity [99]. Although the true incidence of these findings in SAE is unclear and they are nonspecific to the disease, the severity of EEG abnormalities may indicate disease severity in SAE patients [99]. Several CSF and serum biomarkers have also been proposed for diagnosis; however, none are clearly superior in their discrimination of SAE [98,99].

Patients with known neurocognitive disorders, including dementia, may have worse short-term outcomes with increased risk of in-hospital mortality, acceleration of their neurological disease, and sustained decreases in cognitive function as a result of chronic inflammation or infection-related hospitalizations, potentially via sustained pathologic activation of microglial cells [89,96,97,113,116]. For septic patients who do survive to hospital discharge, the development of acute SAE (from the onset of sepsis to hospital discharge) has the potential to contribute to enduring changes in cognition and memory that may persist for years after hospital discharge ([119]; reviewed in [99,120]). Sepsis has, in fact, been associated with more than a ten percent increase in prevalence of moderate to severe chronic cognitive impairment, affecting domains such as executive function, working and processing memory, and new functional limitations that persisted for almost a decade in a long-term prospective study by Iwashyna et al. [119,121]. Severe infection may also increase rates of age-related cognitive decline [122,123] with associated brain changes in human studies [94], and may contribute to long-lasting psychiatric disturbance as well, with increased incidence of depression, anxiety, and PTSD (reviewed in [98,99]. Several risk factors have been shown to be associated with greater degrees of lasting cognitive impairment, including delay in antibiotic therapy, length of delirium, mechanical ventilation and hospitalization, underlying medical comorbidities and sepsis severity [119,124–127].

SAE treatment options

Given the potential for lasting morbidity in sepsis survivors, finding therapeutic modalities to prevent or treat SAE is highly appealing. Several therapeutic candidates have undergone testing in animal models of sepsis and SAE and may provide future opportunities for treatment. Select adrenergic agonists, glutamate inhibitors, ascorbate, caspase-1, KAT 5, and ferroptosis inhibitors have all shown encouraging effects in reversing cognitive deficits, cerebral edema and inflammation in animal models of SAE [128–134]. However, human trials remain necessary to determine the reproducibility of these initial findings.

Unfortunately, while many treatment strategies have been tested, currently, there is no widely accepted pharmacologic treatment of SAE shown to provide significant benefit in management of either acute or chronic sequelae of the disease in human studies. Early detection, appropriate identification and prompt treatment of sources of infection, and supportive care are mainstays of therapy. Non-pharmacologic delirium prevention measures, including frequent reorientation, maintenance of sleep/wake cycles, and early mobilization are important adjuncts in delirium management [135]. Dexmedetomidine has also shown promise in improving symptoms of delirium in septic patients with SAE. Consistent with this, septic animals treated with dexmedetomidine demonstrate improvement in memory and learning tasks, and reduced BBB permeability and neuroinflammation, possibly through astrocyte $\alpha 2$ adrenergic receptor stimulation [136]. Additional human studies utilizing sub-group analysis of septic versus non-septic patients in the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial also showed improvement in outcomes, with increased ventilator-free days, increased delirium-free days, reduced daily risk of delirium, and improved mortality compared with lorazepam-based sedation [137]. Prospective investigation is currently underway testing the efficacy of dexmedetomidine in SAE through the Adjunctive Sedation with Dexmedetomidine for the Prevention of Severe Inflammation and Septic Encephalopathy (ADVISE) trial. Probiotic administration or fecal microbiome transplantation may also warrant future human trials as an adjunct to aid in reducing severity and improving recovery from SAE, and may show dimorphic treatment effectiveness based on sex, given the significant differences in gut dysbiosis and recovery based on sex in animal sepsis models [97,114,138].

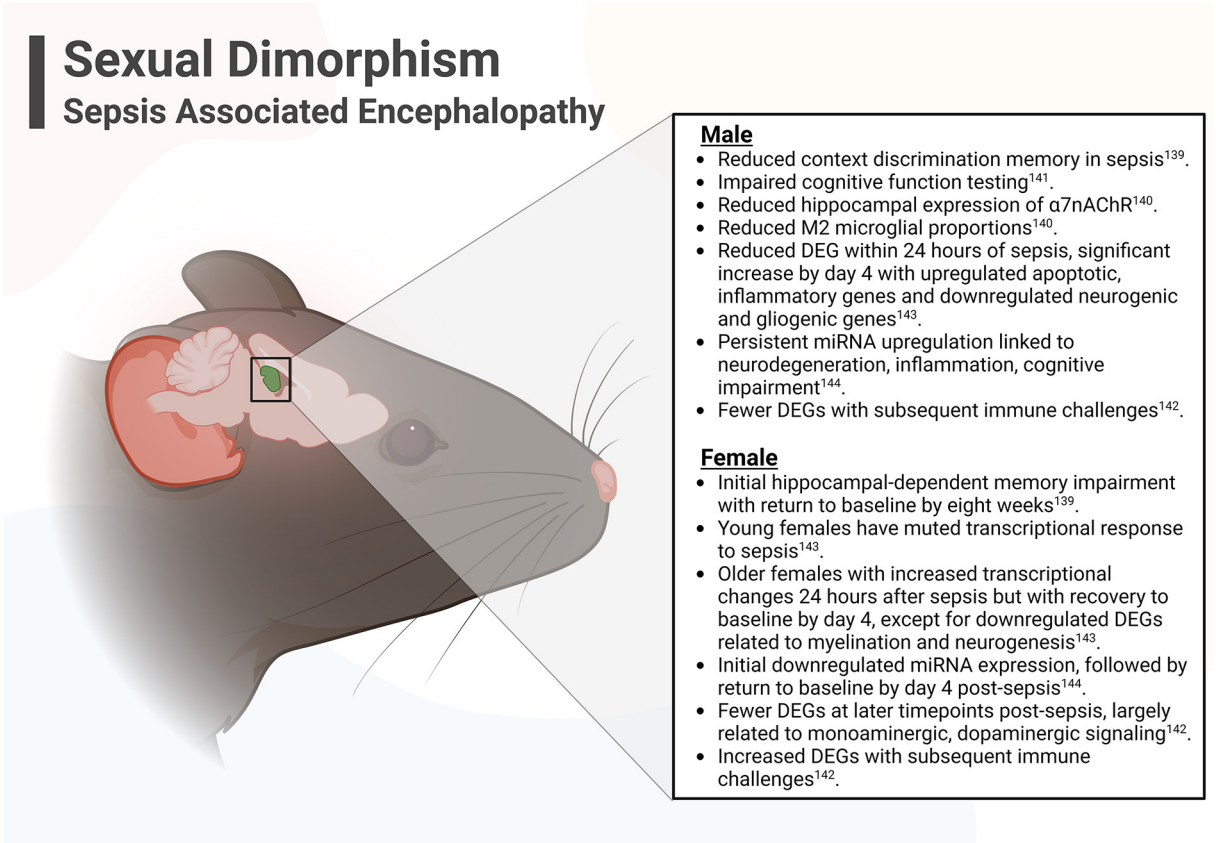

Figure 3. Sexual dimorphism in sepsis-associated encephalopathy.
While studies in humans are lacking, animal models of sepsis-associated encephalopathy show key differences in hippocampal microglial cell activation, differential gene expression (DEGs), and microRNA (miRNA) production.

While human data is lacking, treatment with fecal microbiome transplantation and vagal nerve stimulation have shown potential in reducing inflammation and improving the neurocognitive deficits seen in SAE animal models (reviewed in [97]).

Sexual dimorphism in SAE

While both human and animal investigations of SAE have grown substantially in the last decade, our understanding of the dimorphic effects of sex on pathophysiology, disease severity, treatment efficacy, and long-term outcomes still remain understudied. The significant number of studies on SAE designed with both age- and sex-matching points to an understanding, albeit implicit, of the vital influence these two factors have on the disease process; however, the paucity of data elucidating the exact ways in which sex influences sepsis-induced encephalopathy points to an urgent need for further research, particularly considering concerns regarding worse outcomes associated with male sex in preliminary studies [101].

While investigations are few and exclusively limited to animal models, recent studies begin to describe the key areas in which the effects of peripheral immune dysregulation and chronic inflammation on the brain are potentiated by sex (Figure 3). In a rat model of context discrimination memory, for instance, McNaughton et al sought to elucidate whether sex-specific differences in hippocampus-dependent memory tasks could be seen in septic Sprague–Dawley rats, and if these differences, if any, could be ameliorated by IL-1β inhibitors [139]. They found that peripheral immune activation via endotoxin administration led to impairment in context discrimination memory in male, but not female rats, with differential expression of *ccl1*, *cd70*, *il3*, *ppbp*, and *xcl1* between males and females that was not rescued by IL-1β receptor antagonists [139]. In an independent study using the cecal ligation and puncture (CLP) model, cognitive function in male mice was found to be persistently impaired, with reduced hippocampal expression of the

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α7 nicotinic acetyl cholinergic receptor (α7nAChR), a key component of the CAP in modulating anti-inflammatory immune response, with concurrent reduction in M2 microglial proportions compared with females [140].

Sex-specific differences in hippocampal gene expression and cytokine production have been demonstrated with sub-threshold immune activation in C57BL/6N mice [141,142]. These findings have been seen in mice treated with both endotoxin and poly I:C administration [141,142]. In these experiments,both sexes exhibited deficits persisting up to 8 weeks after immune stimulus. However, male mice were found to have cognitive and memory deficits that persisted for several months following challenge with bacterial and viral mimetics, suggesting increased duration and severity of cognitive impairment based on sex [141].

Single cell RNA sequencing of hippocampal neurons after immune challenges shows similar sex-specific differential gene and microRNA (miRNA) expression, at both early and late time points, and in response to both acute and subchronic immune activation [142–144]. In C57BL/6 mice undergoing CLP with restraint stress, differentially expressed genes (DEGs) were fewest in old males compared with young male and old/young female mice one day after septic challenge, with significant changes noted by day 4 in this age group, suggesting either a delayed response, or potential diminished recovery [143]. These older male mice showed up-regulation of genes related to apoptosis and inflammatory response, with down-regulated DEGs related to neurogenesis and gliogenesis [143]. Young female mice, by contrast, had a relatively muted transcriptional response to sepsis when compared to male and female counterparts, and while older females had robust changes in transcription 24 h after sepsis, most DEGs reversed to baseline expression by day 4, except for persistently down-regulated DEGs related to myelination and neurogenesis [143]. Similar studies evaluating miRNA expression in the same mouse sepsis model demonstrated initial decrease, followed by similar return to baseline of miRNA expression in young females by day 4 compared with other counterparts [144]. By contrast, old males showed persistent miRNA up-regulation at both early and late timepoints linked to neurodegeneration, inflammation and cognitive impairment [144].

Similar studies evaluating sub-threshold immune activation in C57BL/6N mouse models of bacterial and viral infection demonstrated sex-specific DEGs with persistent up-regulation of immune genes, and downregulation of neuroplasticity-related genes in male mice. These changes in DEG pattern were found to persist for months after immune insult [142]. Fewer DEGs were found at later timepoints in female mice, consistent with arapid recovery seen in other mouse models, and were largely related to monoaminergic and dopaminergic signaling [142]. Interestingly, when challenged again with LPS injection at a later timepoint, the mice showed sex-dependent DEG, with only 58 DEGs in males, versus 432 in females, suggesting long-lasting, sex-specific changes in hippocampal gene expression and responsiveness to infectious stimuli with female sex [142]. Administration of poly I:C resulted in similar sickness behavior in both sexes, with acutely increased proinflammatory cytokines in the hippocampus, though only male C57Bl/6N mice specifically up-regulated IFNα and IFNγ in response to viral mimetic, indicating sex-specific differences in hippocampal response to immunestimulation [145].

The sex-specific responses to bacterial or viral agonist-induced systemic inflammation can be exacerbated by age (as described previously), as well as presence of prior neurocognitive dysfunction. LPS stimulation in murine models of AD has shown sexual dimorphism in the metabolomic response to systemic inflammation as well, with sex-specific metabolic changes [146]. For instance, APPswe/PS1dE9 female mice were relatively prone to anti-inflammatory downregulation of methylglyoxal and methionine metabolism, and increased cytokine production, compared to male mice. On the other hand, the male mice exhibited down-regulation of proinflammatory pyruvate and methionine metabolism, suggesting increased resilience and protective response to infectious stimuli in female versus male mice [146].

The exact reasons for these sexual dimorphisms in cytokine production, gene expression, and persistent cognitive dysfunction in animal models of SAE are not yet clear. Several metabolic and systemic factors such as presence of steroid hormones, sex chromosome-related gene expression, differential cell death and immune pathways, and sex-specific microRNAs may contribute to the outcomes [147–149]. It is also possible that dimorphism in the gut–brain axis, believed to contribute indirectly to SAE, may play a role, as male C57BL/6 CLP mice show persistent decrease in alpha and beta microbiome diversity up to 2 weeks after induction of sepsis compared with controls, whereas female sex was associated with a recovery to non-septic baseline within 2 weeks following sepsis [138].

Conclusion/future directions

An aging population and increasing numbers of sepsis survivors necessitates a better understanding of the epidemiology, pathophysiology and effects of sepsis on brain organ dysfunction in the elderly. The prevalence of SAE in this elderly population and the potential for significant, long-term morbidity underscore a need for better characterization of the mechanisms underlying these cognitive changes, in the hopes of more effective and uniformly accepted

treatment modalities. Given the significant sexual dimorphisms seen not only in the immune system, but also in brain structure and function, it is critical to have a clear understanding of how sex may influence SAE pathogenesis, disease progression and sex-specific resilience, to devise a personalized therapeutic approach that maximizes successful treatment of all patients.

Data Availability

As a narrative review, all supporting data is included within the references of the main article, and no additional data sharing is applicable to the manuscript.

Competing Interests

The authors declare that there are no competing interests associated with the manuscript.

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CRediT Author Contribution

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Abbreviations

α7nAChR, α7 nicotinic acetyl cholinergic receptor; BBB, blood–brain barrier; CAP, cholinergic anti-inflammatory pathway; CNS, central nervous system; CLP, cecal ligation and puncture; CSF, cerebrospinal fluid; Drp1, dynamin-related protein 1; GABA, γ-Aminobutyric acid; LPS, lipopolysaccharide; MHC, major histocompatibility complex; PRES, posterior reversible encephalopathy; PTSD, post-traumatic stress disorder; SAE, sepsis-associated encephalopathy; SCFA, short-chain fatty acid.

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