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Neuroinflammatory challenges compromise neuronal function in the aging brain: Postoperative cognitive delirium and Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease that targets memory and cognition, and is the most common form of dementia among the elderly. Although AD itself has been extensively studied, very little is known about early-stage preclinical events and/or mechanisms that may underlie AD pathogenesis. Since the majority of AD cases are sporadic in nature, advancing age remains the greatest known risk factor for AD. However, additional environmental and epigenetic factors are thought to accompany increasing age to play a significant role in the pathogenesis of AD. Postoperative cognitive delirium (POD) is a behavioral syndrome that primarily occurs in elderly patients following a surgical procedure or injury and is characterized by disruptions in cognition. Individuals that experience POD are at an increased risk for developing dementia and AD compared to normal aging individuals. One way in which cognitive function is affected in cases of POD is through activation of the inflammatory cascade following surgery or injury. There is compelling evidence that immune challenges (surgery and/or injury) associated with POD trigger the release of pro-inflammatory cytokines into both the periphery and central nervous system. Thus, it is possible that cognitive impairments following an inflammatory episode may lead to more severe forms of dementia and AD pathogenesis. Here we will discuss the inflammation associated with POD, and highlight the advantages of using POD as a model to study inflammation-evoked cognitive impairment. We will explore the possibility that advancing age and immune challenges may provide mechanistic evidence correlating early life POD with AD. We will review and propose neural mechanisms by which cognitive impairments occur in cases of POD, and discuss how POD may augment the onset of AD.

Keywords

Aging; Neuroinflammation; Postoperative cognitive delirium; Alzheimer's disease; BDNF

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1. Introduction

The aging population, individuals 65 years or older, represents 12.9% of the total US population; and it is estimated that by year 2030 this number will rise to 19% [1]. In the US, over 5 million aging individuals suffer from various forms and severities of age-related cognitive decline, dementia, or Alzheimer's disease (AD) [2]. Aging is a natural biological and physiological process that is accompanied by physical and mental changes. As one ages, an individual may experience a slow and steady decline in cognitive ability, including difficulty in learning and subtle transient loss of memory. Individuals who experience these mild, age-related impairments in cognition are more susceptible to dementias and neurodegenerative diseases later in life, including AD [2]. Although advanced aging is the greatest risk factor for dementia and AD in the elderly population, evidence now suggests that immunological mechanisms and neuroinflammation may play a significant role in determining preclinical factors that may lead to AD pathogenesis [3]. It is important to understand and determine the preclinical events and molecular mechanisms that may regulate the transitional state between age-related cognitive impairment and AD. We will discuss this topic in this review.

1.1. Alzheimer's disease

AD is the most common neurodegenerative disease and is the main cause of dementia in the elderly population. The primary clinical hallmarks of AD include loss of declarative memory and cognitive decline. In addition to behavioral symptomology, neuropathological biomarkers have also been identified in the AD brain. These include the production of neurofibrillary tangles (NFTs) by hyperphosphorylation of the tau protein, as well as the formation of senile plaques from the aggregation of the A β cleavage fragments (A β ₄₂) of the amyloid-precursor protein (APP) [4–7]. The presence of large amounts of aggregated A β ₄₂ plaques and neurofibrillary tangles have negative effects on the cholinergic systems within memory-related brain regions, including the temporal lobe and hippocampus [8,20]. Measuring these pathological markers of AD can provide preclinical insight, as well as diagnostic evaluation of AD pathology.

1.2. Delirium

Delirium is a neuropsychiatric behavioral syndrome that is characterized by sudden and transient disturbances in awareness, consciousness, and cognition [9]. Postoperative cognitive delirium (POD) is considered an age-related syndrome, primarily occurring in the elderly population (>65 years of age). Symptoms of POD include pronounced cognitive deficits that persist for long periods of time (up to several months post-operation) and are implicated in the development of long-term neurological disorders [10–12]. A number of clinical studies have found that the incidence of POD can depend heavily on the type of operation or medical procedure. For example, the highest incidence of POD is found to occur in patients with hip fractures (35–65%) [13], followed by surgery for atherosclerosis pathologies; including cardiac (37–52%) [14,15], peripheral vascular (30–48%) [16,17], and abdominal aortic aneurysm (33–54%) [16–19]. Major head and neck injury, as well as cataract surgery have a lower incidence of POD (17%) [20] and (4%) [21] respectively. There is no formalized medical definition for POD, rather POD falls under a category of

postoperative cognitive disorder that is characterized by heightened confusion, lack of awareness, and decline in memory and executive function in the brain [10,22]. There are no specific diagnostic criteria for POD; however, early studies of POD have defined it as a condition (post-operative) that produces significant and persistent changes in mental ability as assessed by low performance on neurocognitive tests [23]. As a result of these deficits, individuals that experience POD following surgical and/or medical procedures are at an increased risk for developing dementia and AD later in life [24].

Two hypotheses have emerged to explain the potentially causative role of POD in the development of AD. The first hypothesis suggests that anesthesia used during a medical procedure is a precipitating factor for *peri*-operative cognitive impairments, as well as AD pathogenesis. This hypothesis is supported by a number of studies that identified links between anesthetics and cognitive decline, memory impairments, and increases in AD-related biomarkers [25–27]. However, additional studies provide evidence that exposure to anesthesia has no effect on cognition or the expression of AD biomarkers [28,29]. The second hypothesis, and the one we will focus on in this review, proposes that declines in cognition occur as a result of neuroinflammatory cascades that are activated by the invasive nature of surgical procedures [30]. This hypothesis is driven by human and animal studies examining the peripheral and central inflammatory responses following surgical procedures and/or other immune challenges, and how these inflammatory-related mechanisms may disrupt cognition. The findings from these studies, reviewed in Cerjeria et al., 2010 suggest that increased inflammation associated with POD cases is localized to brain regions that are important for learning behavior and memory processes, thus increasing one's risk for developing AD [30]. However, the mechanistic link between POD-associated inflammation and AD is not fully understood. We will discuss both hypotheses and expand on the neuroinflammatory hypothesis in detail.

2. Postoperative cognitive delirium and Alzheimer's disease

The association between POD and AD suggests there may be a common event and/or mechanism that occurs with *peri*-operative procedures that further exacerbates the cognitive deficits associated with POD and eventually leads to AD.

2.1. Hypothesis 1: anesthesia

The first hypothesis suggests that cognitive dysfunction associated with POD occurs as a result of anesthetics used during a surgical operation, and this may be a precipitating factor to AD pathogenesis. Several studies have provided mechanistic links between anesthetics and AD. Exposure to anesthetics, including type, delivery, and duration is associated with cognitive decline, memory impairments, and increases in AD-related biomarkers [25–27]. For example, inhalation delivery of halothane and isoflurane enhance A β aggregation and the excitotoxic effects of A β peptides, whereas propofol and ethanol only increase A β aggregation at high doses [31]. Furthermore, *in vitro* and *in vivo* studies show that sevoflurane and isoflurane can increase A β aggregation and activate apoptotic cell-death pathways via caspase activation [32,33]. An additional link between anesthetics and AD is the ability for anesthetics to disrupt the cholinergic system and cholinergic

neurotransmission, as well as enhance hyperphosphorylation of tau protein [27,34,35]. It is thought that the combination of increased biomarkers of AD with decreased cholinergic activity in memory-related brain regions following anesthesia underlie *peri*-operative cognitive impairments and memory loss.

On the other hand, it is difficult to directly correlate anesthesia exposure to AD for a number of reasons. Anesthetics wear off over time, making it difficult to differentiate the long-term post-operative cognitive effects from other factors, such as inflammation. Furthermore, the underlying link between anesthesia and AD, based on the literature, seems to hinge on the fact that anesthetics affect AD biomarkers and the cholinergic system, with overlapping deficits in cognitive domains observed in cases of POD. This, in addition to contrasting data that indicates anesthetic exposure does not affect cognition suggests that additional factors that surround POD may be more significant.

There are studies suggesting that anesthetics do not influence cognitive function nor associate with AD pathology. Recent clinical studies have found that the incidence for dementia and AD is unchanged in patients with exposure to general anesthesia during surgery [28], with cognitive functions unaffected by anesthetics (sevoflurane) [36,37]. An additional study found that levels of AD biomarkers (tau and A β) were increased following surgical procedure, but were unaffected by anesthesia exposure alone [29]. Animal studies find that the anesthetic sevoflurane alone has no effect on contextual fear memory or synaptic plasticity/connectivity in the medial pre-frontal cortex, but in combination with a surgical procedure did impair memory and connectivity [38]. Thus, there are abundant studies both in support and in disagreement with this hypothesis with conflicting evidence across human and animal studies of anesthetics and surgery. These data suggest that more work needs to be done to differentiate the effects of general anesthetics *peri*-operatively, specifically with regards to cognition. To determine if there is an association between anesthesia and AD, further investigation into the effects of anesthetics on the cell biological and biochemical activity of both the tau and A β proteins would be needed.

2.2. Hypothesis 2: inflammation

A second proposed hypothesis, which will be the primary focus of this review, suggests cognitive decline and impaired memory (symptomology of POD) result from the activation of the immune response. The invasive nature of many surgical procedures activates an immune response and triggers the inflammatory cascade [30]. Once this cascade is triggered, resident microglia and monocytes then produce and release pro-inflammatory cytokines, including interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF α) in the peripheral and central nervous systems [30,39]. The activity of these pro-inflammatory cytokines is thought to provide a mechanistic link between cognitive impairments associated with POD and AD pathogenesis. By making pre-operative cognitive assessments clinicians can directly observe the development of POD post-operation, validating the link between cognitive impairments and surgical procedures. Using this assessment method a number of studies have identified a variety of medical and surgical procedures that trigger systemic inflammation and increase clinical cases of POD [30].

For decades it was unclear how an immune challenge or surgical procedure in the periphery can affect processes in the central nervous system (CNS). However, a wealth of evidence over the last two decades has demonstrated a strong communicative link between the peripheral nervous system (PNS) and CNS with regards to immune regulation and the inflammatory response [39–45]. Indeed, a number of studies have confirmed this, showing that peripheral immune challenges in humans (e.g. systemic infection, surgery, or injury) and rodents (e.g. *E. coli* or lipopolysaccharide injection) activate PNS and CNS immune cells and cause increased production of pro-inflammatory cytokines TNF α , interleukin-1 beta (IL-1 β), interleukin-8 (IL-8), and interleukin-6 (IL-6) in memory-related brain regions like hippocampus and cortex [30,40]. Moreover, increases in the expression of these proinflammatory cytokines are associated with cognitive decline, POD, and AD [41–48]. Several studies using human and animal models of AD have reported that immune challenges (causing inflammation) are strongly correlated with increases in hippocampal APP expression and A β ₄₂ production, heightened levels of proinflammatory cytokines in hippocampus, hyper-phosphorylation of tau protein, and significant cognitive impairments and memory loss [49–53]. How this occurs is not fully understood; however, having a better understanding of the inflammatory response as a whole (including immune challenges, cell types, and pro-inflammatory cytokines) may provide significant insight into cases of POD and AD pathogenesis in the elderly population. We will next discuss the inflammatory cascades, and the involvement of immune cell types and cytokines in cognitive impairment associated with POD and AD.

3. The inflammatory response

There are several potential pathways by which the peripheral immune system communicates with the brain: (1) passive diffusion of cytokines from the blood into the brain via leaky blood-brain barrier (BBB) [54,55], (2) carrier-mediated active transport of peripheral cytokines into the brain (intact BBB) [56–58], and (3) *de novo* cytokine production following activation of resident immune cells (microglia) in the brain via vagal afferents following peripheral immune signals [59–61]. The upregulation of pro-inflammatory cytokines in the brain is defined as neuroinflammation. In this section, we will explore the age-related differences of microglia and the inflammatory response to gain a better understanding of neuroinflammation in POD.

3.1. Aging: inflammation and microglia

Significant changes in the basal-state function of the innate immune system occur with normal aging. Of particular interest are microglia, which are the predominant immune cell in the brain, serving many functions. Microglia are known to play a central role in regulating neural processes necessary for learning, memory, and cognitive behaviors in both humans and rodents [62,63]. At the basal state microglia have the capacity to take on a number of immunophenotypes. But in the aging brain, the sensitized or primed state of microglia is more present and pronounced [64–66].

Microglia undergo functional and morphological changes that result in their transformation from a normal basal-state to a primed state. The immunophenotype of microglia is

characterized by the expression of major histocompatibility complex class II molecules (MHCII), B7 molecules, and the cluster of differentiation molecule 11b (CD11b) [40,67]. In the healthy young mammalian brain resident microglia are in a quiescent state, expressing low basal levels of MHCII and CD11b; whereas in the aging brain resident microglia express significantly higher levels of these molecules (characteristic of a primed state) [64–66,68–71]. These phenomena have been observed in the aged brain of a number of mammals, including humans, non-human primates, canines, and rodents [72]. The consequence of microglia being in a primed state is a reduced threshold of activation to elicit an inflammatory response. This significantly impacts both the severity and duration of the CNS inflammatory response [73]. As a result, activated microglia in the aging brain produce heightened levels of pro-inflammatory cytokines for an extended period of time, beyond that of the younger brain following immune challenge [74–79]. Fig. 1 illustrates the immunophenotype and activity of microglia in young and aged brain.

These data suggest the hypothesis that age-related changes of the inflammatory response occur at the level of the microglia, and that aging may change the overall functionality of resident microglia in the brain. It is possible that these changes in microglia, in combination with lingering cytokine expression, may impair neural processes in the brain that are necessary for cognition. By determining how aging alters the basal-state functionality of microglia and how this impairs neuronal processes, we may uncover the critical link between immune dysregulation and cognitive decline that is observed in POD and AD.

What is the best model to test the links between peripheral immune challenges, microglia, and cognitive function? Microglia activation in humans has been primarily assessed by measuring pro-inflammatory cytokines [30,80,81]. Animal studies have allowed us to determine microglia activation by measuring levels of pro-inflammatory cytokines following peripheral immune challenges. For example, aged rats produce a robust and exaggerated neuroinflammatory response following peripheral infection with bacteria or virus [74,75,77,82–86] or surgical procedure [78,87–89] when compared to younger counterparts and non-infected/surgically exposed controls. This exaggerated response includes increased levels of IL-1 β and TNF α in areas of the brain critical for learning and memory, such as the hippocampus. These increases are strongly associated with cognitive deficits and memory impairments [90–98]. Therefore, based on cytokine profiling, these rodent models of aging and peripheral immune challenge provide an accurate model of POD. These findings provide initial evidence that pro-inflammatory events alter hippocampal function in animal models. In conclusion, this model can help to distinguishing the individual and/or combined effects of aging, immune challenges, and neuroinflammation as precipitating factors of AD pathogenesis. Eventually, this model may allow researchers to elucidate the mechanistic links between POD and AD.

4. Cognition and neuroinflammation

An exaggerated neuroinflammatory response in the aging brain has significant consequences on cognition. Here, we will discuss how pro-inflammatory cytokines impact hippocampal processes. The hippocampus is a critical brain region for learning (contextual and spatial), navigation, and memory formation (episodic) [99–101]. Multiple forms of hippocampal

synaptic plasticity, including long-term potentiation (LTP) and long-term depression (LTD) are widely accepted representations of the cellular and molecular correlates underlying learning and memory-related processes [102–105]. These forms of hippocampal synaptic plasticity are regulated by a number of proteins and signaling pathways, including brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family of growth factors that is highly expressed in the hippocampus [106,107]. Aging alone can have a negative impact on hippocampal anatomy, biology, and physiology [108], and changes in hippocampal structure and function are thought to be responsible for normal age-related cognitive decline. A number of imaging studies in humans have shown that the structural integrity of the hippocampus becomes compromised as the brain ages, with specific changes occurring in hippocampal sub-regions dentate gyrus (DG) and CA3 [109,110]. Furthermore, memory-related processes that rely on the hippocampus for full expression, including several forms of synaptic plasticity, are shown to equally decline with age across multiple species [109,111]. These findings provide an important understanding of the cognitive decline that occurs during normal aging, however these are not pathological. Clinical disorders like POD and AD seem to have a strong inflammatory component that exacerbates the negative effects of aging and may drive the normal aging process into a pathological state [30,40].

The hippocampus seems to be uniquely sensitive to the proinflammatory cytokine IL-1 β , with the greatest effects of IL-1 β on hippocampal functions following peripheral immune challenges [40,112,113]. Although TNF α is also found to be elevated in hippocampus following peripheral challenges [114], and most proinflammatory cytokines can impair hippocampal synaptic plasticity [113], a link to peripheral immune challenges is few and modest compared to IL-1 β . Hippocampal vulnerability to neuroinflammation and pro-inflammatory cytokines has been found to occur for a number of reasons. The hippocampus has a dense microglia population [115,116], with hippocampal neurons (DG and pyramidal cell layer) and hippocampal microglia having a high constitutive expression of IL-1 receptors [117–121]. Furthermore, the inflammatory response within the hippocampus is elevated compared to other brain regions, with increases in expression and production rate of pro-inflammatory cytokines following a peripheral immune challenge [122]. Heightened levels of pro-inflammatory cytokines, particularly IL-1 β , in hippocampus are associated with significant impairments in memory behavior [90–98,123–125]. Moreover, a number of *in vivo* and *in vitro* electrophysiological studies have shown that IL-1 β in hippocampus blocks hippocampal synaptic plasticity, specifically LTP [113,126–135] and reduces BDNF protein levels and BDNF-dependent signaling at hippocampal synapses [136]. Thus, neuroinflammation following peripheral immune challenges elicit a robust inflammatory response in the hippocampus, and this impairs learning and memory related processes.

The neuroinflammatory response in the aging brain is exacerbated, with heightened levels of pro-inflammatory cytokines in the hippocampus beyond that of the young brain, and persisting for a longer period of time following peripheral infections [75,137–140]. Therefore, a decrease in cognitive function should be expected based on the evidence presented in previous sections. In cases of POD, levels of pro-inflammatory cytokines are also significantly increased in hippocampus following peripheral surgical procedures [30,138,141,142–145]. Animal studies identifying the effects of surgical procedures have

confirmed that deficits in learning and memory are associated with elevated levels of pro-inflammatory cytokines in hippocampus compared to young animals [138,144,146–149]. Biological and physiological mechanisms of the neuroinflammatory components underlying cognitive decline associated with POD and AD are unknown, however the role of pro-inflammatory cytokines in hippocampal function may provide an overlapping mechanism by which cognitive decline occurs in cases of POD that may manifest into AD. The following section will explore potential mechanisms that may link neuroinflammation to neuronal processes of the hippocampus.

5. Cognitive mechanisms targeted by inflammation

There are a number of key proteins and signaling pathways that regulate synaptic plasticity in the hippocampus [104,150]. Induction and facilitation of hippocampal LTP requires the synaptic activation of several post-synaptic membrane receptors, including N- methyl-D- aspartate (NMDA) receptors, metabotropic glutamate receptors (mGluRs), and tropomyosin receptor kinase B (TrkB) [104,151–153]. Additionally, activation of intracellular signaling pathways downstream of receptor activation is important to maintain plasticity and regulate cellular processes in the hippocampus. These signaling pathways include the calcium/ calmodulin-dependent protein kinase II (CamKII) [154,155], cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) [156], mitogen-activated protein kinase (MAPK/ERK) [157–159], phosphatidylinositol 3-kinase (PI3K) [160,161], and BDNF (a high-affinity ligand of TrkB) [162,163]. Rodent studies have found that levels of IL-1 β and the IL-1 receptor are enriched in hippocampal post-synaptic fractions, and that this has direct effects on NMDA receptor activity and downstream signaling [164,165]. Additionally, there is strong evidence that levels of BDNF, as well as cellular events downstream of BDNF activity and TrkB receptor activation are perturbed in the presence of IL-1 β *in vitro* and *in vivo* [136,166,167]. Heightened levels of IL-1 β not only perturb pro-plasticity/pro-cognitive pathways, they also influence intracellular signaling pathways that regulate neurodegeneration and apoptosis by increasing reactive oxygen species (ROS) in the hippocampus [133]. Specifically, studies have linked IL-1 β -dependent increases in ROS with increased activation of cell-death mediated signaling pathways p38/MAPK [133,134] and c-jun N-terminal Kinase (JNK) [133,168,169].

Thus far, we have discussed the aging and neuroinflammatory contribution to cognitive decline that occurs following peripheral immune challenges, as observed in human cases and animal models of POD. We have highlighted the inherent differences in basal-state microglia, the severity and degree of the neuroinflammatory response, and the role of pro-inflammatory cytokines (specifically IL-1 β) on neuronal function in the aging brain. These data support the proposal that IL-1 β -dependent regulation of intracellular neuronal pathways may underlie cognitive decline associated with POD and AD pathogenesis. Next, we will discuss a potential mechanistic link between the inflammatory profile of POD and that of AD.

6. Alzheimer's disease: cognition and neuroinflammation

As we have discussed in previous sections, neuroinflammation and immunological insults may play a significant role in determining preclinical factors that may lead to AD pathogenesis [3]. Therefore, POD provides a model that can help us understand the transition between inflammation-evoked cognitive decline in the aging population and AD pathogenesis [170]. The neuroinflammatory components and cognitive phenotypes surrounding POD and AD may help uncover this transitional state. Here we will discuss neuroinflammation and cognition in AD.

6.1. Neuroinflammation

There is a strong neuroinflammatory component associated with AD pathology and potential pathogenesis [3]. Both amyloid deposition and hyperphosphorylated tau lead to accumulation of complement, activation of microglial cells, and synthesis and production of pro-inflammatory cytokines [171–177]. Although these events are important characteristics of AD pathology, it is not known whether neuroinflammation plays a protective or harmful role in the AD brain. Microglia are the primary immune cells at the root of neuroinflammation in AD, and evidence suggests that the active microglia may serve a protective or harmful role in the brain [178]. As we discussed earlier, neuroinflammation associated with POD is triggered following microglia activation via foreign pathogen receptor interactions, leading to increases in proinflammatory cytokine expression [30]. In the AD brain, A β seems to be a key player in driving microglia activation and the neuroinflammatory response. Studies have shown that A β can directly activate microglia cells via interactions with surface receptors [179–183]. In addition, increased A β concentrations in transgenic mouse models of AD (TgAPPsw and PSAPP) [184] are associated with increased levels of pro-inflammatory cytokines. *In vitro* studies report increases in released IL-1 β from activated microglia following A β stimulation. IL-1 β and Caspase-1 (the enzyme that cleaves pro-IL-1 β into IL-1 β) is also increased in microglial cells surrounding A β plaques in human AD brain and in CSF of AD patients [185,186].

Conversely, activation of microglia and the neuroinflammatory response has also been suggested to be neuroprotective as a result of the phagocytic function of microglia cells. For example, increased expression of IL-1 β in the APP/PS1 transgenic mouse model of AD decreased A β plaque pathology [187,188], whereas expression of the anti-inflammatory cytokine IL-4 exacerbated A β deposition in hippocampus [189]. A recent study has found that administration of IL-33, a member of the IL-1 superfamily of cytokines, rescues AD pathology and cognitive decline in APP/PS1 transgenic mice by altering the immunophenotype of microglial cells to an anti-inflammatory state, thus reducing the synthesis and release of IL-1 β [190]. The conflicting findings regarding the neuroinflammatory benefits in AD have been borne out by a number of clinical trials showing that anti-inflammatory drugs taken by patients with AD produced insignificant and/or modest results [191–205]. It is possible that the time of administration of these anti-inflammatory drugs was not appropriate, and administration may have been too late to see any potential benefit. It is plausible that anti-inflammatory drugs may have a greater effect on cognitive protection if given pre-operatively. Thus, the question still remains whether

neuroinflammation plays a protective or harmful role in the AD brain. The effects, whether positive or negative, of microglia and pro-inflammatory cytokines may be dependent upon the pathological stage of the disease [3]. Determining the mechanisms underlying cognitive impairments associated with AD may uncover a time frame for when neuroinflammation contributes to pathogenesis.

6.2. Cognition

Biomarkers of AD have been strongly linked to neural dysfunction in the basal forebrain and hippocampus, causing deficits in synaptic plasticity, impaired synaptic function, and initiation of apoptotic cell death *in vivo* and *in vitro* [35,36,52,53,206–210]. It is thought that these biological and physiological impairments cause the cognitive decline and memory loss of AD. Human studies reveal that AD brains have fewer synapses overall compared to age-matched cognitively unimpaired controls [211], and this effect is particularly strong in the hippocampus [212,213]. Accumulation of A β is thought to be the root cause of synaptic changes and dysfunction [35], however mechanisms for which this occurs are not fully known. A number of studies have reported that A β directly affects hippocampal synaptic plasticity by impairing LTP [214,215]. Furthermore, a correlation between heightened levels of IL-1 β in the hippocampus with reductions in hippocampal LTP has been identified in transgenic mouse models of AD [216–218]. This reduction in LTP was restored when blocking IL-1 β signaling with the IL-1 receptor antagonist (IL-1RA) [219], suggesting IL-1 β specificity in AD-related impairments in LTP. Unfortunately, animal models of AD do not adequately model the natural history of the human disease, thus it is difficult to determine the start of microglial activation and cytokine production. Is neuroinflammation due to A β aggregation over time, or are the increased concentrations of A β late-stage initiating the neuroinflammatory cascade? In contrast, models of POD provide an opportunity to monitor and control peripheral immune challenges, and thus may provide greater insight into the neuroinflammatory contributions to changes in synaptic plasticity and synaptic processes. Using POD as a model of early-stage cognitive impairments following immune challenges researchers may find significant similarities and differences that can shed light on understanding the complexity of AD pathogenesis.

7. Conclusions and future directions

From these lines of work we have learned that peripheral immune challenges that include surgical procedures, medical conditions, injuries, and infections elicit an inflammatory response in the CNS. This neuroinflammatory response is exacerbated in the aging brain as a result of the immunophenotypic changes of resident microglia. We have established that increases in hippocampal levels of pro-inflammatory IL-1 β specifically targets synapses to impair synaptic plasticity, resulting in hippocampal dysfunction and cognitive decline. We discussed human studies of POD cases, and determined that neuroinflammation following peripheral challenges in the aging population can be modeled in animals to study the mechanisms of POD [40]. We propose that future studies utilizing models of POD can provide significant insight into the biological and physiological mechanisms underlying preclinical cognitive pathologies that can manifest into AD. It is appropriate to suggest that the aging process alone holds as the primary contributor to early-stage cognitive decline that

leads to more severe neuropathies. However, the literature reviewed in this special issue article suggests that aged brain vulnerability, in combination with neuroinflammatory episodes, contribute to the cognitive abnormalities of normal aging, POD, and neurodegenerative diseases.

An important direction of this work will be to determine if neuroinflammation in the AD brain is beneficial or harmful [220]. It is likely to be a little bit of both, like most complex neurological systems. Therefore, research in this area is inconclusive and there is a need to develop more effective models. It is proposed that cognitive decline following neuroinflammatory episodes surrounding POD have a negative effect on hippocampal processes. Moreover, it is possible that inflammation in AD serves as a protective mechanism to enhance clearance of A β deposits. It is plausible that neurodegeneration (synaptic failures and inefficiencies) can continue to occur while microglia are protecting against A β .

Another advance in this field would be to identify the time course that differentiates synaptic failure and A β deposition. One way to address this is to perform a time-course experiment using a model of POD to measure cognitive behaviors (learning and memory) and synaptic functions (plasticity and intracellular signaling pathways) at multiple time points after a peripheral immune challenge. Clinical studies in aging populations have measured biomarkers of AD in patients before and after surgery in an attempt to discern an association between POD and a heightened risk of AD pathogenesis. Results from these studies have yielded conflicting and inconsistent evidence, with levels of AD biomarker expression varying across pre- and post operative procedures [221–225]. Thus, measuring biomarkers of AD in aging individuals *peri*-operatively may not be a reliable indicator of one's increased risk for AD. Furthermore, animal models of POD would be required to accurately assess these biological mechanisms and physiological processes, due to the limitations of human studies.

A third future area of investigation would be to identify the hippocampal processes that involve BDNF. Several studies have shown that BDNF expression levels can decrease in models of POD and AD, with IL-1 β [40,135,166,136], A β [226–229], and tau [230] directly affecting BDNF-associated intracellular signaling pathways and synaptic plasticity. Clinical studies in patients with the BDNF Val66Met polymorphism find that cognitive impairments associated with changes in BDNF occur more in preclinical stages of AD and not in advanced stages of AD (defined by high A β deposits) [231–233]. Furthermore, the APP/PS1 transgenic mouse model of AD expresses high levels of A β plaques in hippocampus accompanied by significant memory impairments, and studies have linked these memory impairments with decreases in BDNF and perturbations in BDNF – TrkB signaling [234,235]. Changes in BDNF associated with POD are less understood. One human study found that levels of BDNF are unchanged in aged non-POD and POD groups [222]. Conversely, rodent studies have found that levels of BDNF, as well as BDNF-dependent signaling pathways are decreased in both young [141,236] and aged [237] animals following surgical procedures. Thus, decreases in BDNF seem to be prevalent in cases of POD and models of AD. Future studies may reveal BDNF to be a biomarker of preclinical AD pathogenesis.

Overall this literature suggests a potential therapeutic intervention for cognitive decline associated with neuroinflammation would be to increase the expression or activity of BDNF. BDNF, and other neurotrophic factors have been used in clinical trials to treat a variety of neurodegenerative disease, but progress has been slowed due to lack of BBB penetration and severe side effects [238]. We propose that the combination of low-dose BDNF treatment while suppressing *peri*-operative inflammation using anti-inflammatories may be a more effective and safer alternative therapeutic strategy.

Focusing on preventative targets and treatments for preclinical pathologies may overall be more beneficial, non-invasive, and most likely cost effective. Behavioral strategies and approaches, such as exercise and environmental enrichment can have preventative and therapeutic benefits on cognitive behaviors. Environmental enrichment, which includes physical exercise, has the capacity to increase cognitive functions of the hippocampus [239,240], increase levels of BDNF [241,242], suppress neuroinflammation [240], and protect against neurodegeneration associated with AD [243]. Moreover, environmental enrichment has been shown to enhance learning and memory behavior as well as increase BDNF-dependent signaling pathways, including TrkB phosphorylation and extracellular signal-regulated kinases (ERK) activation [244]. These data suggest that enrichment improves healthy cognitive aging, protects against hippocampal dysfunction and neuroinflammation (including POD), and may have additional neuroprotective and therapeutic effects for individuals suffering from neurodegenerative diseases. This behavioral therapeutic strategy would address the neuroinflammatory hypothesis of AD by targeting hippocampal functions/processes and neuroinflammatory components. Thus, additional research into the neuronal and glial mechanisms impacting cognition and AD is warranted.

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Highlights

- Neuroinflammation underlies cognitive decline in postoperative cognitive delirium and Alzheimer's disease.
- The susceptibility to neuroinflammatory challenges increases with age.
- Neuroinflammation is exaggerated in the aging brain.
- POD and AD pathogenesis have common immune links.
- POD serves as a model to study late-stage cognitive decline and AD.

Fig. 1.

The Inflammatory Response in Young and Aged Brain. (A) Microglia in the young brain are in a resting state. Following an immune challenge (surgical procedure, medical condition, and/or infection) resting microglia become primed and then activated. Once activated, microglia synthesize and release the pro-inflammatory cytokine IL 1 β which may target neuronal synapses in brain regions necessary for cognitive function. (B) Microglia in the aged brain differ from young in that they are in a basal primed state. Once activated, microglia produce an exaggerated inflammatory response characterized by significantly heightened levels of IL 1 β that may persist for longer periods of time. The effects of an exaggerated inflammatory response in the old brain may lead to more robust declines in cognition and increase the risk for AD.