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• REVIEW •
Special Focus on Brain Imaging and Addiction

Neuroimaging of inflammation in alcohol use disorder: a review

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Abstract Alcohol use disorder (AUD) is a global health concern associated with several comorbidities. Various health problems related to AUD, such as cognitive deficits, have been linked to neuroinflammation. Alcohol use has been associated with changes in neuroimmune activity, although current literature has yielded mixed results. For example, markers of gliosis, including translocator protein 18-kDa (TSPO), pro-inflammatory cytokines, glutamate (Glu), and myo-inositol (mI), are disrupted in the alcohol-dependent brain. Further, neuroinflammatory-related phenomena including membrane turnover, blood brain barrier (BBB) permeability, and adenosine release have also shown alterations in AUD. However, current literature remains inconclusive about the directionality of these changes. Both in vivo and in vitro studies have provided insight on the relationship between alcohol use and neuroinflammatory processes, suggesting considerable treatment potential for alcohol use disorder and its inflammatory comorbidities. Here, we review current neuroimaging literature assessing the impacts of alcohol use on neuroimmune activity in the brain.

Keywords acetate, adenosine, alcohol use disorder, blood brain barrier, choline, gliosis, glutamate, myo-inositol, neuroimaging, neuroinflammation

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1 Introduction

Alcohol use disorder (AUD) is a condition characterized by persistent and problematic alcohol use associated with clinically significant distress [1]. On a global scale, AUD affects millions and alcohol use is the seventh leading cause of death [2]. AUD-related neuroinflammation has a role in neurotoxic processes that contribute to a variety of health disruptions including cognitive impairment, which perpetuates the addiction cycle [3–9]. Treatment of neuroinflammation in AUD is therefore of interest and may have beneficial effects on craving, mood, and cognitive functioning [10, 11].

Chronic and acute alcohol consumption contribute to both peripheral and central inflammation [4]. For example, chronic alcohol use enhances gut leakiness, a phenomenon characterized by increased intestinal permeability and translocation of bacteria from the gut lumen into peripheral tissues [12]. This triggers a pro-inflammatory response [12–15]. Further, acute alcohol exposure increases glucocorticoid release [16], which primes inflammation, causing a greater inflammatory response the next time a response is elicited [17].

Recent reviews of neuroinflammation in substance use disorders [4, 5, 18] provide rich descriptions of the involvement of neuroimmune signaling in addiction. Here, we focus in-depth on in vivo neuroimaging

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Table 1 Direct and indirect indicators of neuroinflammation in AUD

Marker	Imaging method	Regions	Findings
Gliosis			
18-kDA	Human PET ([^{11}C]PBR28)	Averaged across regions; cerebellum; hippocampus^{ns}; striatum^{ns}	AUD < HV [21]
		Hippocampus	AUD < HV [22]
		Whole brain, GM, WM, hippocampus, and thalamus	AUD < HV$^{\#}$. neg corr. between cholesterol and PBR binding [23]
	Baboon PET ([^{18}F]DPA714)	Whole brain	Binge > non-binge; sustained TSPO increase after 7 to 12 months [20]
	Rat PET ([^{11}C]PBR28)	n/a	No significant differences [19]
Cytokines	DSC-MRI	Thalamus and frontal GM and WM	Alcohol-caused increase in CBF in social drinkers [24]
	DSC-MRI	Averaged across WM regions	Alcohol-caused increase in CBV in social drinkers [24]
Glutamate	MRS	Frontal WM	Glu neg corr. with drinking severity & "loss of control" [25]
		ACC	AUD < HV when presented with cues [26]
		Primary visual cortex	AUD < HV in early abstinence (Glx) [27]
		Bilateral medial frontal cortex	AUD < HV in early abstinence [28]
		ACC	AUD < HV in early abstinence [29]
		ACC	AUD > HV ([Glu] & [Glu]/[Cr]) [30, 31]
		Nucleus accumbens	AUD > HV [92]
Myo-inositol	MRS	Striatum	AUD > HV (in patients with HIV) [32]
		Parietal GM	Heavy drinkers > light drinkers [33]
		Averaged across parietal and frontal WM	AUD > HV [34]
		Right thalamus, ACC	AUD > HV [35]
Membrane Turnover			
Choline	MRS	Visual cortex	Increase during heavy drinking ([Cho]/[Cr]) [27]
		Parietal GM	Heavy drinkers > light drinkers [33]
		Cerebellum	AUD < HV, may or may not recover over time [36, 37]
		ACC	AUD < HV [30]
		Left prefrontal cortex	AUD < HV [38]
		Frontal WM, cerebellar cortex, and cerebellar vermis	AUD < HV, recovers after 3 months [39]
BBB Permeability			
Gadolinium-chelates	CE-MRI	Temporal cortex	Ethanol induced BBB degradation [40]
	Altered water distribution	Bilateral frontal and temporal WM;	AUD-C+AUD-R > HV [41]
		Bilateral parietal regions, fornix and thalamus	
Adenosine Release			
Acetate†	PET([^{11}C]Acetate)	Cerebellum and thalamus	Intoxication increases acetate uptake [42]
	ASL-MRI	Medial thalamus	Acetate increase in CBF [43, 44]
		Right orbitofrontal, medial prefrontal, and cingulate cortex, and hippocampus; superior/inferior frontal gyri and bilateral ACC	Alcohol increase in CBF [43, 44]

Note: ^{ns}: not significant; $^{\#}$: only in medium affinity binders; †: acetate metabolism by the brain that has been linked with acute and chronic alcohol consumption increases generation of adenosine and might contribute to neurotoxicity and neuroinflammation; ACC: anterior cingulate cortex; ASL-MRI: arterial spin labelling magnetic resonance imaging; CBF: cerebral blood flow; CBV: cerebral blood volume; CE-MRI: contrast enhanced magnetic resonance imaging; DSC-MRI: dynamic susceptibility contrast magnetic resonance imaging; GM: gray matter; MRS: magnetic resonance spectroscopy; PET: positron emission tomography; WM: white matter.

methods, such as positron emission tomography (PET) and magnetic resonance imaging and spectroscopy (MRI/MRS) techniques (Table 1 [19–44]) to assess the relationship between neuroinflammation and AUD.

2 Gliosis

2.1 Overview

Gliosis is a pro-inflammatory process that involves the excessive proliferation of glial cells, such as microglia and astrocytes, in response to central nervous system (CNS) damage [45–48]. Gliosis occurs in multiple steps [48], some of which have been associated with AUD.

Some of the first neuroimmune cells to migrate to the location of neural damage are microglia, the resident macrophages of the CNS [4, 49, 50]. Microglia can undergo several activational stages, including a pro-inflammatory (M1) or anti-inflammatory (M2) phase [51]. During the M1 state, pro-inflammatory molecules are released, including cytokines, glutamate (Glu), and reactive oxygen species [9, 52, 53]. Pro-inflammatory cytokines have been positively associated with alcohol craving and withdrawal in both alcohol-dependent rodents and humans. In rats, infusions of pro-inflammatory cytokine MCP-1 increased ethanol self-administration [30] and expression of several pro-inflammatory cytokines rose during the first 48 hours of alcohol withdrawal [54]. Further, lipopolysaccharide injections, which trigger cytokine release [55], and cytokine treatment both sensitized alcohol withdrawal-induced anxiety behaviors in rats [56]. In humans, various cytokines have been shown to positively correlate with craving and alcohol consumption [57, 58]. These findings suggest an involvement of neuroimmune molecules throughout various stages of the alcohol addiction cycle.

Following microgliosis, a variety of oligodendrocyte precursors, such as NG2-glia [59], migrate to the damaged region to begin remyelinating injured axons. Damage to white matter has been linked to AUD, indicating alcohol-induced damage (as reviewed by Harper [60] and Gallucci [61]). Moreover, increases in oligodendrocyte precursors have been associated with recent alcohol exposure and abstinence from chronic alcohol use, suggesting that alcohol-induced damage also elicits a reparative response [62, 63].

The final process is astrogliosis, the recruitment of astrocytes, which leads to the formation of scar tissue. Astroglial activity is key to the neuroinflammatory process: When activated, astroglia regulate neuroimmune responses to various stimuli, secreting cytokines and other pro-inflammatory molecules in a similar manner to activated microglia [64, 65]. Astrocyte activity has been linked to various stages of the alcohol addiction cycle [66, 67]. Further, compared to ethanol-naive rats, three weeks of abstinence in alcohol-dependent rats led to elevated astrocyte density in the nucleus accumbens core; controlled astroglial excitation of this region decreased motivation to self-administer alcohol in these abstinent rats compared to controls [68]. In humans, however, alcohol abstinence has been associated with decreases in astrocyte density in the dorsolateral prefrontal and orbitofrontal cortices as well as in the hippocampus [69–71]. By corroborating evidence of in vivo astrogliosis and microgliosis with evidence of other pro-inflammatory processes, we may better understand neuroinflammation in the alcohol-dependent brain.

2.2 Translocator protein 18 kDa

The translocator protein 18 kDa (TSPO) is a proposed biomarker of microglial activation. TSPO functions to maintain healthy cell function and is expressed on active microglia and other monocyte-derived cells [72]. Typically, TSPO levels are low; during injury and neurodegenerative events, however, activated microglia upregulates TSPO expression [72]. Thus, heightened levels of TSPO indicate neuroimmune activity. Radiotracers have been developed to measure TSPO levels in vitro to assess neuroinflammation in certain neurodegenerative conditions, including Alzheimer's disease [73]. More recently, brain autoradiography studies using TSPO tracers have been conducted in animal models of addiction. A study utilizing the TSPO radioligand [^{3}H]PK11195 in rats after a 4-day alcohol binge exposure showed higher binding in the hippocampus and entorhinal cortex in the binge group than in controls [74]. Further, Tyler et al. [19] observed higher binding of two different TSPO radioligands, [^{3}H]PK11195 and [^{3}H]PBR28, in the thalamus and hippocampus of rats exposed to chronic alcohol vapor (dependent rats) compared to controls, indicating increased TSPO expression after chronic exposure to alcohol. Despite elevated [^{3}H]PK11195 in the hippocampus, however, Marshall et al. [74] did not find evidence for fully activated microglia

(i.e., absence of OX-6 and ED-1 immunoreactive microglia and no increase in pro-inflammatory cytokines IL-6 or TNF-alpha). Marshall et al. [74] therefore suggested that the partial activation of microglia in binge drinking rats, as evidenced by elevated TSPO expression, may be a consequence of alcohol-induced neurodegeneration rather than the cause of it.

While these studies showed increased TSPO binding in vitro, results from in vivo PET studies are less clear. Prior to euthanasia, in the same rodent sample that showed increased binding of [^{3}H]PK11195 and [^{3}H]PBR28 by autoradiography, PET studies with [^{11}C]PBR28 did not show differences between dependent and non-dependent rats in vivo, suggesting possible interference in binding of [^{11}C]PBR28 to TSPO [19]. Another PET study that assessed TSPO levels with [^{18}F]DPA714 in adolescent baboons reported increased TSPO levels throughout the brain during acute binge alcohol exposure, with persistent elevation 7 to 12 months later, as compared to levels in a single control animal [20]. These contrasting findings could reflect species differences, diverse alcohol exposure histories, and the distinct methodologies (in vitro vs in vivo) and radiotracers used to measure TSPO and emphasize the need for continued investigation in this area of research.

Clinical PET studies assessing TSPO expression in AUD are also unclear. Unlike rodents or baboons, humans have differential binding affinity to [^{11}C]PBR28 depending on genotype [75]. Individuals homozygous for the TSPO rs6971 polymorphism have a high-affinity binding site for TSPO in their monocyte-derived cells, whereas individuals heterozygous for the polymorphism have both high-affinity and low-affinity TSPO binding sites, making them medium-affinity binders [75]. Individuals without the polymorphism only have low-affinity binding sites, thus, [^{11}C]PBR28 PET cannot reliably predict microglial activation in these individuals [75].

In three clinical PET studies, medium- and high-affinity TSPO binders were combined, while low-affinity binders were excluded. Hillmer et al. [21] and Kalk et al. [22] found that individuals with AUD had lower [^{11}C]PBR28 binding in their first few weeks of abstinence, relative to healthy controls; the authors concluded that long-term alcohol abuse may have led to downregulation of pro-inflammatory responses owing to chronic inflammation [21, 22]. In addition, Hillmer et al. [21] observed a lower peripheral pro-inflammatory cytokine response to lipopolysaccharide stimulation in patients with AUD compared to healthy volunteers, suggesting that AUD is associated with blunted immune activity in both the CNS and the periphery. A third study also observed lower [^{11}C]PBR28 binding in individuals with AUD compared to healthy controls; however, the effect was present only in medium, but not in high-affinity binders [23]. Kim et al. [23] explored whether the lower [^{11}C]PBR28 binding in AUD medium-affinity binders reflected competition of plasma cholesterol instead of downregulation of neuroimmune activity. In healthy cells, cholesterol binds to TSPO for transport during steroid synthesis, modifying the protein's structure [76, 77]. In heavy drinkers, plasma cholesterol levels tend to be higher than in controls; these higher levels may increase TSPO binding competition [78, 79]. Further, the rs6971 polymorphism also influences the cholesterol binding-domain of TSPO, such that cholesterol binding affinity is lowest in high-affinity radioligand binders and highest in low-affinity radioligand binders [80]. Plasma cholesterol levels in both AUD and healthy control groups were inversely correlated with [^{11}C]PBR28 binding in the brain [23], supporting a role of cholesterol competition in the downregulation of [^{11}C]PBR28 binding observed in AUD. Recently, the rs6971 polymorphism was also associated with alcohol withdrawal severity and with plasma cholesterol levels in AUD [81]. These findings highlight the need for further consideration of rs6971 and cholesterol when assessing TSPO binding in AUD.

To our knowledge, no other brain imaging studies have assessed TSPO binding in AUD. In the meantime, new TSPO radiotracers have been developed, such as [^{11}C]ER176, which binds to TSPO in all three affinity genotypes [82]. These radiotracers may provide additional information on microglial activation in AUD, as well as allow for continued investigations of second-generation TSPO radioligands on both pre-clinical and clinical scales.

2.3 Pro-inflammatory cytokines

Various AUD studies have assessed levels of both peripheral and central pro-inflammatory cytokines, which are released by microglia and astroglia, respectively, in response to damage [83–85]. Human studies in vivo have shown elevated levels of peripheral cytokines, such as IL-6, in people with AUD compared to controls, as well as other central cytokines such as IL-18, IL-1β [4,85–87]. In post-mortem brains of individuals previously diagnosed with AUD, multiple studies have demonstrated region-specific microglial markers of proinflammatory cytokine activity, such as toll-like receptor signaling that leads to NFkB transcription of proinflammatory cytokines [9,85]. More recent postmortem brain studies also identified elevation of TNFα, HMGB1, and IL-1β, which are markers for neuroinflammation [9,86]. Compared to the post-mortem brains of controls, the ventral tegmental area, substantia nigra, hippocampus, and amygdala of AUD brains featured an increased concentration of the cytokine MCP-1 [85]. Similarly, healthy volunteers' brains expressed the presence of MCP-1 following high dose alcohol exposure long after their blood alcohol level had cleared using multibead-based assay [88]. To our knowledge, however, no studies have assessed neuroinflammation and found noteworthy results regarding central pro-inflammatory cytokines in people with AUD using in vivo neuroimaging techniques. So far, researchers have utilized magnetic transfer resonance, an imaging method that is sensitive to water content and edema, to measure myelin content. This method has been useful for studying multiple sclerosis and traumatic brain injury and has successfully traced pathologic neuroinflammatory phenomena such as cytokine presence in clinical and preclinical studies [84, 89]. Therefore, magnetic transfer resonance may be a promising tool to study neuroinflammation in AUD in vivo.

Researchers have also identified cerebral blood flow (CBF) and cerebral blood volume (CBV) as methods to indirectly measure neuroinflammatory changes. Moreover, changes in CBF have been shown to correlate with the levels of multiple pro-inflammatory cytokines [90]. Specifically, in mice with repetitive mild traumatic brain injury, CBF was associated with upregulation of multiple pro-inflammatory cytokines such as RANTES and IL-17 [90]. These findings suggest that CBF and CBV, when coupled with peripheral markers of inflammation, might be used to assess neuroinflammation in AUD.

2.4 Glutamate

Glutamate (Glu), the most abundant excitatory neurotransmitter and an important molecule in cellular metabolism, has been linked to gliosis and has thus been considered a marker of neuroinflammation. It has been posited that glial cells exaggerate release and disrupt clearance of Glu during neuroinflammation, which contributes to the development of various mood disorders [91]. However, other studies suggest that disturbances in glutamatergic transmission can cause decreases in Glu concentrations in various brain regions implicated in reward networks, such as the anterior cingulate cortex (ACC), as a result of Glu clearing from those areas [26]. Glu has been measured via proton magnetic resonance spectroscopy (^{1}H-MRS) in various regions of the human brain [25, 27–29, 31, 32, 46, 92–98].

Glu and Glutamine (Gln) work in tandem to regulate neuronal energy metabolism and are difficult to measure separately with MRS owing to their overlapping contribution to a peak at 2.4 ppm; this combined peak is often referred to as "Glx" [95]. AUD disrupts the Glu-Gln cycle. One study measured an overall decrease in Glu and increase in Gln in the ACC of patients with AUD, relative to healthy controls, during a 2-day period of withdrawal [29], while another observed a similar decrease in the ACC in AUD during a 5 to 13-day period of withdrawal, which normalized 4 to 6 weeks later [28]. Further, another recent study showed a significant decrease in Glu concentration in the ACC of individuals with AUD compared to healthy controls when subjects were presented with alcohol cues [26]. This group also found a negative correlation between the number of heavy drinking days and Glu concentration in subjects with AUD, despite a lack of difference in baseline Glu levels between the groups [26]. Additionally, in heavy drinkers, dependence severity was negatively correlated with Glu concentration in frontal white matter; patients who reported a "loss of control" over drinking demonstrated significantly lower concentrations of Glu than those who did not [25]. In the primary visual cortex, the ratio of Glx to total creatine (Cr) was also shown to be lower in patients with AUD than in healthy controls after an average of 17.5 days of

abstinence [27]. Total Cr, which indicates cellular energy metabolite concentration, is commonly used as a reference peak (3.0 ppm) in MRS. However, studies have shown that it can be 2 to 3 times higher in glial cells compared to neurons and can increase during disease or in old age [47, 99, 100]. Therefore, if group differences in total Cr are present between AUD and controls, it may be beneficial to normalize the Glu signal to water rather than total Cr.

In contrast, some studies have found increases in both the absolute Glu concentration [31] and the ratio of Glu to Cr in the ACC of individuals with AUD during periods of acute withdrawal relative to healthy controls, which normalized after 2 weeks of abstinence [94]. Hermann et al. [31] additionally found that increases in the concentration of Glu correlated positively with breath alcohol levels, which also correlated positively with severity of AUD, percentage of heavy-drinking days, and benzodiazepine dosage during withdrawal. Additionally, Glu concentration was elevated in the nucleus accumbens of patients with AUD after 10 days of abstinence, and Glx concentration was positively correlated with measures of alcohol craving in both the nucleus accumbens and the ACC of patients with AUD [92]. Acamprosate, a medication that is typically used to reduce cravings and relapse, has been shown to decrease the Glu to Cr ratio in the ACC compared to a placebo during a 4-week AUD treatment program, consistent with the hypothesis that manipulation of Glu has therapeutic potential in AUD [97]. Indeed, administration of N-acetylcysteine, which restores glutamate homeostasis in the synapse, has been shown to protect against the neuroinflammatory changes from chronic alcohol exposure in rats [101]. These findings necessitate further exploration of cerebral Glu concentration in AUD, as manipulation may alleviate craving and neuroinflammation-related AUD comorbidities.

2.5 Myo-inositol

Another marker of gliosis is myo-inositol (mI), an organic osmolyte primarily localized in glial cells that is involved in glucose storage and volume regulation of primary astrocytes [32, 45–47, 102]. mI has been shown to accumulate in AUD in vivo, as well as to stabilize intracellular environments in vitro; it can be measured by MRS at a peak of 3.56 ppm [45, 95].

Gliosis has been correlated with elevated mI in certain inflammatory and infectious diseases of the CNS, including HIV and multiple sclerosis [35]. mI was elevated in the striata of patients with comorbid AUD and HIV compared to those with HIV alone, as well as compared to healthy controls, and higher levels of mI were positively correlated with the amount of alcohol consumed over the lifetime [32]. Many studies have shown higher mI in patients with AUD compared to healthy controls, although they vary in the duration of abstinence before measurement [32,34,35,46,103]. Heavy drinkers showed higher mI than light drinkers in parietal gray matter, which was associated with impaired working memory [33]. This difference was even greater between light drinkers and (more) dependent heavy drinkers, in populations older than 38 years, and with higher numbers of average monthly drinks consumed over the lifetime [33]. One study found greater parietal and frontal white matter mI (averaged) in 4-week detoxified participants with AUD compared to healthy controls [34]. The same group found higher mI in the right thalamus and ACC of 6-week detoxified patients with AUD compared to controls, and these elevated mI levels were also higher than those observed in patients with 1.7 years of abstinence on average [103]. In sum, these studies indicate that although mI is elevated during early abstinence in patients with AUD, this temporary elevation recovers during extended periods of abstinence presumably as neuroinflammation subsides.

3 Membrane turnover

3.1 Overview

The activation of microglia in neuroinflammation produces reactive oxygen species that can result in cellular membrane damage or altered membrane homeostasis [104]. Changes in membrane homeostasis can include increased membrane turnover in viral diseases, such as HIV [105, 106], HIV-related dis-

eases [107], or acute demyelination [108]. Significant changes in the concentration of choline-containing compounds are indicative of altered cell membrane synthesis and turnover; an increase in the concentration of these compounds can indicate cell membrane injury [105]. Preclinical studies indicate that membrane turnover, with respect to phosphatidylcholine, is higher in alcohol-tolerant rats, but decreases as tolerance progresses into dependence [109].

3.2 Choline-containing compounds

Choline-containing compounds (Cho), such as free choline, phosphocholine, and glycerophosphocholine, are found in white matter and can be measured with MRS at a peak of 3.2 ppm [32, 46]. Studies have shown that during periods of drinking, Cho concentration is increased in certain regions of the brain; one study found a significant increase in the ratio of Cho to Cr concentration in the visual cortex [27]. Additionally, a study comparing heavy and light drinkers found a significantly higher concentration of Cho in the parietal gray matter of non-abstinent binge drinkers than in non-binge drinkers [33]. This group also observed a positive correlation between average monthly drinks (consumed over the lifetime) and thalamic Cho concentration in non-abstinent heavy drinkers, suggesting that Cho concentration may also be elevated in this region during periods of heavy drinking [33].

While Cho levels in various brain regions may increase during periods of drinking [27,33], studies have shown lower Cho in various brain regions during early abstinence, which may be indicative of neuronal dysfunction and can recover to normal levels after longer periods of abstinence. Bendszus et al. [36] found that after only a few days of abstinence, the ratio of Cho to Cr in the cerebellum was lower in patients with AUD than healthy controls; after 5 weeks of abstinence, however, the Cho to Cr ratio increased such that there were no longer significant differences between the AUD and control groups [36]. A similar study also found a lower cerebellar Cho concentration in patients with AUD relative to healthy controls after 3 to 5 days of abstinence; however, in contrast to the previous findings, after 3 months of abstinence, Cho concentrations did not normalize to those of controls [37]. These studies suggest that although cerebellar Cho can decrease in AUD in early abstinence, whether it recovers during long-term abstinence is less clear. Cho concentrations were also significantly lower in the ACC of patients with AUD than in healthy controls after an average of 15.5 days of abstinence; this decrease was correlated with impairment of short-term memory in patients with AUD [94]. Further, the ratio of Cho to Cr was lower in the left prefrontal cortex of subjects with AUD compared to healthy controls after 2 weeks of abstinence; daily alcohol consumption was negatively associated with this ratio [38]. Cho concentrations also decreased significantly during early detoxification in patients with AUD (relative to healthy controls) in the frontal white matter, cerebellar cortex, and cerebellar vermis, but increased after 3 months; after 6 months, no additional significant increase was found [25]. It is therefore possible that Cho increases during acute exposure and decreases during chronic exposure and early detoxification in a similar manner to TSPO [20–23, 74], as the result of a competing endogenous process or a burnout effect. It appears that although Cho can recover over time, further research is required to investigate the impact of lifetime drinks, age, and comorbidities on the recovery of Cho levels during prolonged abstinence in patients with AUD.

4 Blood brain barrier permeability

4.1 Overview

Although abnormalities in blood brain barrier (BBB) permeability are not a direct indication of neuroinflammation, a barrier breakage almost invariably accompanies neuroinflammation [110]. The BBB acts as a tightly-controlled vascular membrane that is critical for the protection and delivery of nutrients to the brain. When it breaks down, both functions are compromised, and the draw of pro-inflammatory cytokines triggers an inflammatory response [110]. Specifically, the cytokines TNFα and IL-1β cross the BBB and may contribute to central effects [111, 112]. In the context of alcohol research, BBB disruption

reliably identifies areas associated with neuroinflammation owing to alcohol use along with the corroboration of other identifiers, such as proinflammatory cytokines and activated microglia [35, 110, 113]. It is important to note that BBB permeability alone is not a significant identifier of neuroinflammation, as it may signal other pathological phenomena such as stroke, trauma, or infection [113].

4.2 Gadolinium-chelates

BBB damage is most commonly analyzed using non-invasive contrast-enhanced MRI that utilizes contrast media with gadolinium [35, 114]. This method takes advantage of the gadolinium-chelates, which would not normally pass through an intact BBB [115]. Investigators have used this method to identify alcohol-induced protein tyrosine kinase signaling as a tracer for BBB degradation, which is a result of neuroinflammation from alcohol injury [40]. A dynamic contrast-enhanced curve MRI study also reported significantly elevated BBB permeability in the hippocampus of social drinkers [116]. More studies are necessary to elucidate the role of dynamic contrast-enhanced MRIs in analyzing neuroinflammation in AUD.

4.3 Altered water distribution

Changes in BBB permeability can also be detected by diffusion tensor imaging (DTI), which measures altered water distribution. Neuroinflammation causes an increase of water in brain tissue, which also increases its mean water diffusivity, a measure of total diffusivity within a voxel [117]. On a molecular level, BBB permeability variation results in changes in interstitial space composition, such as the onset of vasogenic edema and the leakage of macromolecules [118]. Altered water distribution is indicative of increased leakage, as more water moves through the damaged BBB and white matter in an anisotropic fashion [119]; this can be imaged by MRI using a diffusion tensor imaging sequence [41, 117, 119–122]. Researchers have analyzed white matter to locate abnormalities in subcortical areas associated with memory and sensory processing in AUD DTI-MRI using tract-based spatial statistics, a voxelwise statistics tool that analyzes the nonlinear transformation of individual participants' images on a mean fractional anisotropy skeleton [35, 41, 123, 124]. Participants with current AUD displayed abnormal diffusivity in fronto-temporal regions compared to healthy controls, indicating damage in these brain areas implicated in memory, attention, and impulsivity [41]. In addition, AUD participants with at least one year of remission exhibited damage in parietal regions critical to visuospatial and self-awareness processing [41]. These findings suggest that brain damage in AUD can be successfully captured by imaging water distribution abnormalities using DTI techniques that future studies, when combined with peripheral marker of inflammation, might be able to use to assess neuroinflammation with AUD.

In addition to these three methods, researchers have also analyzed permeability in vitro using paracellular markers such as [^{3}H]Inulin or propidium iodide [125]. Toborek et al. [126] sought to identify disruption in BBB permeability because it has previously been linked to HIV. They found that both HIV-1 gp120 and alcohol induced the formation of stress fibers, cytoplasmic filaments made up of actin that increase endothelial permeability [127], which was linked to increased BBB permeability [125]. Given the reliability of BBB permeability as a neuroinflammation marker, we recommend exploring its use in identifying neuroinflammation in people with AUD.

5 Adenosine release

5.1 Overview

Adenosine in the CNS functions as a neuromodulator that controls neuron excitability as well as the activity of microglia and astrocytes [128]. However, its modular role in neuroinflammation is complex owing to its ambiguity in either inhibiting or promoting neuroinflammation depending on the cell type and

interplay with other neurotransmitters [129–131]. The main factor influencing adenosine's functional ambiguity is the variance in the four metabotropic receptors: A_1, A_{2A}, A_{2B}, and A_3. All adenosine receptors are expressed in immunocompetent cells residing in the CNS and circulating in the periphery [132, 133].

Altered signaling in brain adenosine has been implicated in AUD: in cell cultures, acute exposure to alcohol inhibited adenosine reuptake via the adenosine transporter, ENT1, which led to increased extracellular concentrations of adenosine [134]. In contrast, chronic exposure to alcohol downregulated the expression of ENT1, decreasing adenosine concentrations [134]. Moreover, in vivo rodent studies have shown that adenosine is a key player in the behavioral effects of alcohol, including the promotion of sleep and the impairment of motor movements mediated by A_1 receptors [135–137]. Several PET radiotracers for adenosine A_1 and A_2 receptors have been developed [138–141]. Studies in healthy controls with the adenosine A_1 receptor PET ligand [^{18}F]CPFPX reported a 26% increase in receptor availability in several brain regions with ethanol infusion [142]. Therefore, future studies investigating adenosine and neuroinflammatory markers in the brain in AUD patients may yield promising results.

5.2 Acetate

Acetate, a metabolite of alcohol [128], is believed to contribute to alcohol induced neurotoxicity [141]. After alcohol is ingested, acetate becomes an energy source alongside ATP and acts as an agonist at G-protein coupled receptors in neurons [43, 131]. Acetate increases the generation of adenosine, a powerful vasodilator [143, 144]. Using PET and [$_{11}$C]Acetate, Volkow et al. [42] found that acute alcohol consumption increased acetate uptake in the human brain, whereas it decreased brain glucose metabolism. Arterial spin labeling sequencing with MRI, an alternative measure to trace the presence of acetate, and therefore adenosine and inflammation, has been used to track CBF regionally [43,44]. Alcohol researchers identified increased CBF in the medial thalamus, left parietal cortex, and hippocampus; these regions have been found to be affected by neuroinflammation in relation to acetate [43]. Another group using the same arterial spin labeling-MRI technique found five significant clusters, including the superior and inferior frontal gyri and bilateral ACC, that demonstrated increased CBF in participants with low reactivity to alcohol, a preemptive phenotype of AUD [44]. To the best of our knowledge, there are no reported studies that have investigated the association between brain acetate levels and metabolism and neuroinflammation in AUD. This highlights an area of potential growth for neuroinflammation research in the field of AUD.

6 Discussion

The relationship between alcohol and neuroinflammation is complex. Although there is agreement that alcohol exposure is pro-inflammatory, the neural correlates of neuroinflammation in AUD remain unclear. The current mixed findings highlight the necessity for more research on alcohol-related neuroinflammation so that ultimately, treatments for AUD that target the neuroimmune system can be developed.

6.1 Mechanisms of neuroinflammation

The mechanism by which alcohol acts to induce neuroinflammation must be further explored. While several studies link alcohol exposure to neuroinflammation, the type of exposure and time since exposure vary. Many animal studies assess models of acute binge drinking, while others focus on chronic alcohol use. Further, studies of abstinent individuals with AUD vary; some studies comprise individuals in their first few days of abstinence, while others include long-term abstinent patients. We suggest broadening current literature by designing studies that consider both acute and chronic patterns of alcohol use to understand whether the amount of exposure (by volume or duration) impacts how neuroinflammation and alcohol use interact. We also recommend longitudinal studies that follow abstinent patients long-term to determine whether healthy neuroimmune activity is recovered over time.

Further, the studies discussed do not address whether the neuroinflammation associated with alcohol use is solely mediated by peripheral inflammatory events (such as through increased gut-leakiness) or

if alcohol also immediately elicits neuroinflammation upon reaching the brain. Although changes in peripheral and central inflammation have been linked in populations with AUD [21], we suggest that more studies consider peripheral inflammation, including plasma measures of C-reactive protein and other inflammatory markers. A clearer link between peripheral inflammation and AUD would permit development of targeted treatments. For example, if the neuroinflammation elicited by alcohol exposure is primarily caused by initial peripheral inflammation, medications that pinpoint systemic inflammation may be feasible options, as side-effects caused by passage through the BBB [145] would not be a concern. These medications would also be useful in treating a variety of conditions comorbid with AUD that are also linked to inflammation, including heart disease, liver cirrhosis, and bone density deficits [146–149]. Also, clinical studies have rarely considered gender differences in neuroinflammatory responses to alcohol, despite preclinical evidence that sex is a variable that influences alcohol toxicity [150].

An additional mechanism by which alcohol may elicit neuroinflammation is via sleep disturbances. While the role of adenosine in neuroinflammation is unclear, it is known to be involved in sleep regulation [151–153]. AUD is associated with sleep disorders [154–158] and sleep deprivation appears to increase immune activity as measured by increased levels of plasma and brain pro-inflammatory cytokines [159–163]. Thus, it is possible that adenosine modulates neuroinflammation in AUD through sleep, but findings supporting a relationship between adenosine and sleep in AUD are limited. For example, in rats, acute ethanol-induced adenosine release in the basal forebrain has been associated with a decrease in wake-promoting neurons, suggesting adenosine might modulate the acute sleep-promoting effects of alcohol [163–168]. In another set of preclinical studies, sleep disruption was linked to higher levels of adenosine and increased ethanol self-administration [135, 169], and sleep restriction was associated with decreased ethanol sensitivity [135, 169]. Whether ethanol-induced changes in adenosine release are a cause or effect of sleep deprivation is unknown.

6.2 Corroboration between markers of neuroinflammation

Another critical limitation of current literature is the focus on a single marker (e.g., TSPO, Glu) as indicative of neuroinflammation. Neuroinflammation is a complex phenomenon; one marker does not confirm neuroimmune activity [113]. Consideration of multiple markers is necessary to infer neuroinflammation. Although many of the studies reviewed here only found significant changes in a single neurometabolite [26, 29, 31, 92], there is evidence across studies that the various neuroinflammatory markers seem to show AUD-related alterations that converge in specific brain regions. For instance, the ACC has been repeatedly implicated in AUD over several studies using different methodologies related to neuroinflammation. During withdrawal, ACC Glu decreases in patients with AUD at rest [28, 29] or when subjects were presented with alcohol cues [26], indicating Glu suppression in early abstinence. It appears that gliosis may have a coordinated impact on neurometabolite concentrations in patients with AUD, with mI concentration negatively correlating with Glu in both the visual cortex and the ACC [27, 94]. These studies, along with others, displayed a synchronized effect of gliosis and increased membrane turnover, perhaps indicating the ACC is an area of high neuroimmune activity [27, 33, 94].

More broadly, the ACC is a nexus for higher-level functions critical for AUD, including cognitive control and emotion regulation [170], as evidenced by its strong connections with both the limbic system and other prefrontal regions [171]. Patients with AUD consistently show functional and structural abnormalities the ACC. For example, lower left ACC volume in adolescence predicted alcohol use four years later [172] and in patients with AUD, abstinence from alcohol was linked to ACC volume increases [173]. Further, in a study comparing heavy social drinkers to dependent, non-abstinent drinkers, BOLD activity in the ACC was greater during a spatial working memory task [174] in the dependent group. These results likely provide valuable insight into neuroinflammatory processes in patients with AUD, since other studies [175, 176] have shown strong associations between these fMRI measures and markers of inflammation. However, future studies are needed to confirm whether ACC neuroinflammation is linked to these MRI findings in AUD.

The incorporation of additional indicators of neuroinflammation would also be helpful to corroborate

current findings. N-acetyl-aspartate (NAA), for example, is a marker of living, mature neurons which can be measured with ^{1}H-MRS [46]. Decreases in the concentration of NAA may be useful in the assessment of neuroinflammation in individuals with AUD, as alcohol-induced brain damage may initiate neuroinflammation. NAA MRS peaks have been used to indirectly measure the degree of neuronal loss in patients; compared to controls, studies have demonstrated decreased NAA in heavy drinkers, which was shown to recover during periods of abstinence [27, 33, 34, 36, 37, 46, 177, 178]. Further, PET imaging of the BBB in AUD may advance knowledge of neuroinflammation. [^{68}Ga]EDTA, for example, detects BBB permeability [179–182]. This tracer has been used in patients with multiple sclerosis [181], and has the potential to assess neuroinflammation in AUD. Further consideration of these molecules may provide helpful information for understanding the role of neuroinflammation in AUD and possible interventions.

6.3 Structural and functional MRI

Future studies should also consider brain structural changes associated with AUD as measured with MRI. AUD is associated with lower gray matter volume relative in matched controls in many brain regions [183,184]. There are several processes by which gray matter loss can occur, including healthy aging and sedentary lifestyle [185,186]. Neuroinflammation has been shown to contribute to neurodegeneration via activation of toll-like receptor 4 (TLR4), which is expressed in microglia [187, 188]. In patients with AUD, TLR4 methylation, a process which impedes TLR4 activity [189], was increased in regions where AUD-related gray matter loss has been the most pronounced, including the precuneus and inferior parietal cortex [190, 191]. This paradoxical finding hints at the possibility that chronic alcohol use induces TLR4 upregulation as a protective mechanism. It remains unclear whether TLR4 plays a causal role in gray matter depletion.

Functional MRI studies may also be useful for determining the role of neuroinflammation in AUD. AUD is associated with marked alterations in resting state connectivity [192–194], as well as increased neural responses to alcohol cues [137, 195]. Not much is known about the impact of neuroinflammation on BOLD response to cue reactivity and other tasks in AUD. One study in elderly healthy volunteers, however, did find a negative correlation between neural activation during a working memory task and plasma cytokine levels, suggesting a possible relationship between inflammation and task-related brain function [175]. Although functional connectivity in patients with Alzheimer's and other neurodegenerative disorders has been linked to changes in [^{11}C]PK11195 binding to TSPO [176], this association has not yet been studied in AUD. Studies that include both MRI and nuclear imaging targeting inflammatory markers are needed to determine the relationship between functional activity and neuroinflammation in individuals with AUD.

6.4 Treatment potential for AUD

Manipulation of neuroinflammation in animal models of AUD has promising results. For example, treatment with minocycline, a tetracycline antibiotic with inhibitory effects on microglia, reduced alcohol self-administration in rats [196, 197]. Anti-inflammatory indomethacin reduced both alcohol self-administration and alcohol-induced neurotoxicity in rodents, suggesting that targeting the neuroimmune system to treat AUD may impact the addiction cycle as well as the CNS damage associated with drinking [198]. Further, phosphodiesterase inhibitors such as ibudilast and rolipram have anti-inflammatory effects and reduced alcohol self-administration in rodents [199–201]. In clinical trials, ibudilast appears to reduce craving in individuals with AUD [202], but whether this would result in lower alcohol consumption long-term is still unknown. Finally, TLR4 inhibitors such as nalmefene and naltrexone have also been useful for decreasing alcohol administration in rodents [203, 204]. In humans, these medications have generally found success in reducing alcohol consumption [205–207]. Given the link between gray matter integrity and TLR4 [190,191], these drugs might also protect against cognitive impairments linked to gray matter reduction [208, 209]. These findings demonstrate the rich treatment potential that investigations into alcohol-related neuroinflammation offer.

In addition to medications, behavioral interventions show potential for treating neuroinflammation in AUD. Cognitive behavioral therapy, for example, has been effective in treating AUD [210], and decreasing systemic inflammation among individuals with depression [211]. Mindfulness meditation, a method which has recently gained traction for AUD treatment [212], has also been associated with anti-inflammatory effects in studies of stressed, but otherwise healthy adults [213–215]. Finally, among its variety of benefits, exercise is associated with improvements in peripheral inflammatory markers [216]. Although it has not been shown to reduce alcohol consumption, exercise reduced depression symptoms and, as expected, improved physical fitness in a study of individuals with AUD [217]. Thus, exercise may be useful in treating cognitive deficits and other processes associated with neuroimmune activity in AUD.

6.5 Summary

In sum, the current literature provides compelling but incomplete information on the relationship between AUD and neuroinflammation. The findings discussed are indicative of the great potential in targeting neuroimmune activity in AUD to treat symptoms of addiction (e.g., craving) and associated deficits such as cognitive impairment.

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