



Review

Chronic Neuroinflammation and Cognitive Decline in Patients with Cardiac Disease: Evidence, Relevance, and Therapeutic Implications

Jan Traub ^{1,2,*}, Anna Frey ^{1,2}  and Stefan Störk ^{1,2} ¹ Department of Internal Medicine I, University Hospital Würzburg, 97080 Würzburg, Germany² Department of Clinical Research & Epidemiology, Comprehensive Heart Failure Center, University and University Hospital Würzburg, 97078 Würzburg, Germany

* Correspondence: traub_j1@ukw.de; Tel.: +49-93120139216

Abstract: Acute and chronic cardiac disorders predispose to alterations in cognitive performance, ranging from mild cognitive impairment to overt dementia. Although this association is well-established, the factors inducing and accelerating cognitive decline beyond ageing and the intricate causal pathways and multilateral interdependencies involved remain poorly understood. Dysregulated and persistent inflammatory processes have been implicated as potentially causal mediators of the adverse consequences on brain function in patients with cardiac disease. Recent advances in positron emission tomography disclosed an enhanced level of neuroinflammation of cortical and subcortical brain regions as an important correlate of altered cognition in these patients. In preclinical and clinical investigations, the thereby involved domains and cell types of the brain are gradually better characterized. Microglia, resident myeloid cells of the central nervous system, appear to be of particular importance, as they are extremely sensitive to even subtle pathological alterations affecting their complex interplay with neighboring astrocytes, oligodendrocytes, infiltrating myeloid cells, and lymphocytes. Here, we review the current evidence linking cognitive impairment and chronic neuroinflammation in patients with various selected cardiac disorders including the aspect of chronic neuroinflammation as a potentially druggable target.

Keywords: neuroinflammation; cognitive impairment; dementia; myocardial infarction; heart failure; hypertension; coronary artery disease; atrial fibrillation; cardiac arrest; aortic valve stenosis



Citation: Traub, J.; Frey, A.; Störk, S. Chronic Neuroinflammation and Cognitive Decline in Patients with Cardiac Disease: Evidence, Relevance, and Therapeutic Implications. *Life* **2023**, *13*, 329. <https://doi.org/10.3390/life13020329>

Academic Editor: Chad R. Frasier

Received: 3 January 2023

Revised: 16 January 2023

Accepted: 18 January 2023

Published: 24 January 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Acute myocardial infarction (MI) is the leading cause of morbidity and mortality worldwide. It affects about 16 million patients every year [1] and predisposes not only to chronic heart failure (HF) [2], but also to an accelerated cognitive decline beyond ageing. Not only MI and HF, but also other common cardiac disorders such as hypertension, atrial fibrillation (AF) and coronary artery disease (CAD) markedly increase the risk for developing mild cognitive impairment (MCI), vascular cognitive impairment and dementia (VCID), and Alzheimer's dementia (AD) [3,4]. Due to the ageing population and an increase in the number of patients with cardiac diseases, these sequelae are of great relevance as they impact both morbidity and quality of life on the side of patients and their relatives, and healthcare costs on the side of society [5]. However, the pathophysiological links between cardiac disease, central nervous system (CNS) dysfunction and cognitive decline remain poorly understood. Shared risk factors such as hypertension, diabetes, obesity, arteriosclerosis, age, and genetic predisposition [6] might be involved, but there are also specific cardiac sequelae such as a decreased cerebral blood flow, neurohumoral activation, and systemic inflammation [7]. There is now compelling preclinical and clinical evidence that the latter might also induce or deteriorate chronic inflammatory responses of the central nervous tissue, which mediate pathophysiological processes leading to neurodegeneration [8]. Thus,

so-called ‘neuroinflammation’ might be partially responsible for cognitive decline after MI, but also in other cardiac disorders such as chronic HF [9]. The current review aims to summarize current knowledge on cognitive decline in cardiac disorders, introduce the concept of neuroinflammation, highlight its role and clinical relevance in cardiac disease, and discuss potential therapeutic options.

2. Cognitive Decline and Dementia in Common Cardiac Disorders

2.1. Myocardial Infarction and Coronary Artery Disease

There is now consolidated evidence for an accelerated cognitive decline after MI [3,4]. The Rotterdam Study reported on 4971 individuals in whom a prior history of MI was associated with worse cognitive performance, independent of age and education [10]. Further analysis revealed an increased risk of dementia and a higher degree of cerebral small vessel disease in people with unrecognized MI [11]. Likewise, the Bronx Aging Study studying 488 subjects observed a five-fold increased risk of developing dementia when patients with a history of MI were compared to those without [12]. Consistently, an accelerated cognitive decline was observed only after and not prior to the occurrence of MI in the English Longitudinal Study of Ageing with 7888 patients [13]. Recurrent non-ST elevation MI was independently associated with cognitive decline after one year of follow-up in the “Improve cardiovascular outcomes in high-risk older patients” (ICON-1) study in 211 patients [14]. A history of MI doubled the risk for MCI or probable dementia in the Women’s Health Initiative Memory study in 6455 cognitively intact, postmenopausal women [15]. Likewise, in the Italian Longitudinal Study of Aging, a history of MI was associated with an increased risk of progression from MCI to dementia among 2963 participants [16]. Interestingly, in a huge Danish nationwide population-based cohort study with 314,911 patients with MI and 1,573,193 matched comparison cohort members, MI predicted a greater risk for VCID, but not for AD [17].

Cognitive decline beyond ageing also affects people with CAD. In a small Californian study including 74 subjects, CAD was associated with a greater decline in global cognition, verbal memory, and executive function [18]. Zheng et al. found that the presence of atheromatosis in coronary vessels positively correlated with cognitive dysfunction [19]. The rate of memory decline among older adults with CAD seems to be similar between groups of patients undergoing coronary revascularization with coronary artery bypass grafting or percutaneous coronary intervention [20]. Of note, some data also point towards the reversibility of the process of cognitive decline, e.g., 43 patients with CAD who were treated with a statin and weekly in-hospital aerobic exercise for 5 months improved their Mini-Mental State Examination (MMSE) score [21]. In addition, lower cardiovascular health predicted late-life decline in cognitive function among high-risk CAD patients [22].

2.2. Heart Failure

Chronic HF is a complex clinical syndrome that often coexists with multiple comorbidities. MCI appears to be a particularly important condition in HF [7], although reports on its prevalence vary between 25% and 75% across population-based studies due to variation in definitions and diagnostic criteria [23–27]. Patients with HF typically exhibit MCI in the domains of memory, working memory, attention, processing speed, and executive function [25,28]. In patients with HF, MCI was shown to significantly increase the risk of hospitalization and mortality, and decrease quality of life [7]. Chronic HF is also associated with an increased risk of dementia and AD in older adults [29]. On the contrary, a Danish nationwide population-based cohort study found that chronic HF was associated with an increased risk of all-cause dementia, but not AD [30]. Thus, there is no consensus as to whether HF may also increase the risk of AD. Impaired cognition in people with chronic HF was reported to relate to hypertension, daytime sleepiness, stress, and poor quality of life [31]. In this regard, type 2 diabetes was shown to accelerate MCI and significantly reduce the executive ability of elderly patients with chronic HF [32]. In contrast to chronic

HF, MCI in acute HF remains frequently unrecognized, since there are still many unresolved issues regarding cognitive changes in patients hospitalized with acute HF [33].

2.3. Hypertension

Hypertension has been shown to be a risk factor for both AD and VCID, as indicated by several epidemiologic studies [34]. Cerebral infarcts, lacunae, and white matter changes are implicated in the pathogenesis of VCID, but may also favor the development of AD [35]. A recent investigation including 90 individuals found that hypertensive participants revealed more deficits in skills involving delayed recall and prefrontal-region skills [36]. Likewise, the greatest impact on cognitive function in those with hypertension appears to be on executive or frontal lobe function, similar to the area most damaged in vascular dementia [37]. In a large Chinese study with 2413 individuals, it was reported that hypertension diagnosed during mid-life was associated with worse cognition compared to that diagnosed in late life [38]. Managing and controlling blood pressure could thus preserve cognitive function, e.g., by reducing the risk of VCID or stroke [39].

2.4. Atrial Fibrillation

According to a recent meta-analysis including 2,415,356 individuals, AF is linked to an increased risk of incident dementia and cognitive decline [40] (random-effect hazard ratio 1.36). Further, prospective observational studies have shown that AF increased the risk of stroke, an important cause of cognitive impairment, although the association between both conditions may well be independent of stroke and other shared risk factors [41]. Along these lines, incidental AF was associated with an increased risk of both early and late-onset dementia, independent of the occurrence of clinical stroke [42]. Interestingly, the use of oral anticoagulants and successful catheter ablation were associated with a decreased risk of developing dementia [43]. In a post hoc sub analysis of the Systolic Blood Pressure Intervention (SPRINT) trial, processing speed was the most prominent cognitive domain affected by AF. Potentially, this property might help with screening for early signs of cognitive dysfunction [44]. Several markers indicative of atrial cardiomyopathy, a structural and functional disorder of the left atrium, such as increased brain natriuretic peptide and left atrial enlargement, were also associated with an increased risk for cognitive impairment [45].

2.5. Aortic Valve Stenosis

Comprehensive neurocognitive assessment unmasked advanced cognitive impairment in patients with severe aortic stenosis planned for transcatheter aortic valve replacement (TAVR) [46]. Interestingly, the mere presence of aortic valve calcification in computer tomography was not associated with cognitive impairment in any cognitive test, nor any measure of global cognition [47]. There is now also evidence that TAVR may improve cognitive functions that depend on cerebral perfusion, especially of the hippocampus in elderly patients with severe aortic stenosis [48]. Such preservation or improvement of cognition after TAVR is particularly encouraging, as this population is characterized by a rapidly declining cognitive trajectory set in motion by ageing [49].

2.6. Cardiac Arrest

After cardiac arrest, the initial survival of patients is limited by brain death and severe neurological damage, either mandatorily (in the case of brain death) or potentially (in the case of severe damage and corresponding presumed patient wish) [50]. Cognitive dysfunction, in particular memory problems, is frequent amongst survivors of out-of-hospital cardiac arrest [51], e.g., cognitive impairment four years after cardiac arrest was present in more than one-quarter of patients [52]. Cohort studies demonstrated a high prevalence (54.4%) of long-term cognitive deficits and functional limitations in cardiac arrest survivors [53], even in those with apparently favorable neurological recovery [54]. While early systematic testing of cognitive performance is recommended by the current post-resuscitation guidelines, such concepts are infrequently implemented [55].

3. Acute vs. Chronic Neuroinflammation

The CNS is considered an immunologically ‘privileged’ organ because peripheral leucocytes are blocked from entering by the blood–brain barrier. The term neuroinflammation refers to both acute and chronic inflammatory responses of the central nervous tissue. Neuroinflammation is central to the shared pathology of several acute and chronic brain diseases [56]. Acute neuroinflammation is usually caused by infection, trauma, stroke, or toxins, and characterized by platelet deposition, edema, and endothelial cell activation [57]. It includes the activation of resident microglia, resulting in a phagocytic phenotype and the release of cytokines and chemokines [58]. Acute neuroinflammation is typically short-lived and unlikely to be detrimental to long-term neuronal survival. Currently, it is believed that an acute neuroinflammatory response is beneficial to the CNS, since it tends to minimize further injury and contributes to the repair of damaged tissue [59].

In stark contrast, chronic neuroinflammation must be considered a long-standing and often self-perpetuating process after an initial injury or insult. It is characterized by persistent activation of microglia and results in sustained oxidative and nitrosative stress by resident glial cells [60]. It is often accompanied by a disrupted blood–brain barrier, which facilitates the infiltration of peripheral macrophages into the brain parenchyma, thus further perpetuating inflammation [61]. Chronic neuroinflammation may be caused by external (toxic metabolites, microbes, viruses, air pollution) or internal factors (ageing, autoimmunity), and is associated with neurodegenerative disorders [62]. Other than acute neuroinflammation, chronic neuroinflammation is typically detrimental and damaging to nervous tissues [59]. As the most abundant cell type within the CNS, resident microglia, which are part of the innate immune system, are responsible for immune scavenging, phagocytosis, antigen presentation, cytotoxicity, synaptic stripping, and the promotion of cell repair [63]. Therefore, microglia are currently regarded as the crucial point of convergence for multiple triggers eliciting an adaptive immune response [59]. Microglia undergo morphological, proliferative, and functional changes in response to the above-mentioned factors [9]. They can modify microglial cell-surface receptor expression, transforming the specific cell task from a monitoring role to one of protection and repair [58]. Secondly, astrocytes may become activated in response to signals produced by activated microglia, release various growth factors, and undergo morphological changes themselves [57]. In conclusion, whether neuroinflammation affects the brain in a beneficial or harmful way may depend critically on the duration of the inflammatory response and the immune cells involved [59].

4. Chronic Neuroinflammation in Neurodegenerative Disorders

Common neurodegenerative disorders such as AD, but also multiple sclerosis, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, and tauopathies, are associated with chronic neuroinflammation and elevated levels of cytokines [59,64]. In these conditions, it is thought that microglia (upon other) produce factors such as interleukin-1, tumor necrosis factor alpha and nitric peroxide that are toxic to neurons [64]. Neuropathological and neuroradiological studies indicate that neuroinflammatory responses precede the significant loss of neuronal populations [65], rendering neuroinflammation a potential therapeutic target.

In AD brains, microglia display an activated phenotype when surrounding amyloid plaques [66] and produce cytokines and other pro-inflammatory mediators [67]. Although it is clear that not all microglia activation is injurious to neurons, it is becoming widely accepted that a certain phenotype of neurotoxic microglia—e.g., when overexpressing mutant superoxide dismutase [68]—has a central role in the pathophysiology of AD [59]. Furthermore, the loss of microglial neuroprotective and phagocytic functions, as indicated by the dysfunctional clearance of amyloid plaques, and correlations between microglial activation and tau tangle spread demonstrate the critical involvement of malfunctioning microglia in driving tau propagation [69]. Recent data from brain imaging support the association of increased neuroinflammation during the progression of MCI and AD [70]. In

contrast to ‘classical’ AD, VCID is a heterogeneous brain disease, where chronic cerebral hypoperfusion and persistence of an ischemic and hypoxic micro-environment leads to neuroinflammation, oxidative stress, neurotrophic uncoupling, destruction of the blood–brain barrier, and eventually to cognitive dysfunction [71]. In several animal models of VCID, neuroinflammation caused by chronic cerebral hypoperfusion induced white matter damage, while microglia and astrocytes were activated [71,72].

Summing up, microglia are thought to act as critical sensors of a disturbed brain tissue homeostasis in neurodegenerative disease: their differential activation constitutes the pivotal point regulating neuroinflammation and inducing neurotoxicity and subsequent cognitive decline [73]. The emergence of novel techniques such as single-cell RNA sequencing revealed the heterogeneity of microglia, including the differentiation of microglia and CNS-associated macrophages [74].

Thus, phenotypical and functional changes to microglia and associated cells in cardiac disease may also precede or accelerate neurodegenerative processes, which may lead to higher rates of AD and VCID and accelerated cognitive decline in these patients. In the following, we summarize current evidence on neuroinflammatory modulations in cardiac disease.

5. Neuroinflammatory Sequelae of Cardiac Disorders

5.1. Myocardial Infarction and Coronary Artery Disease

Recently published positron emission tomography data were the first to image microglial activation early and late after MI in humans [75,76]. Here, increased signals of the mitochondrial translocator protein (TSPO), which is expressed on activated microglia, were seen in the cerebellum, temporal and frontobasal cortex, as well as the hypothalamus. The strategy to investigate neuroinflammation after MI is rooted in promising preclinical findings, which are summarized in the following.

Small animal studies used immunohistochemistry to detect regional phenotypical changes to microglia after MI: morphologically altered microglia after MI were observed in the rostral ventrolateral medulla (RVLM), the nucleus tractus solitarius (NTS), and the periaqueductal grey (PAG) in rats, which share important cardiovascular regulatory functions [77]. Concordantly, an increase in such activated microglia occurred in the hypothalamic paraventricular nucleus (PVN) 2 to 16 weeks after MI, but not earlier [78,79]. These studies suggest that the observed changes are correlates of an augmented sympathetic tone after MI.

However, murine (and human) TSPO imaging revealed elevated neuroinflammatory signals even beyond the aforementioned regions [75]. Along these lines, 48 h after MI, significant changes in specific microglia phenotypes in the PVN, thalamus, prefrontal cortex, and hippocampus were found through the immunofluorescence approach [80]. Two studies demonstrated increased microglial activity peaking at day 3 in the caudate putamen and hippocampus after 30 min ischemia/reperfusion injury [81,82]. Further supporting the idea of global chronic inflammation in the CNS, pro-inflammatory cytokine levels in the brain were elevated following MI [83], and an augmented cerebral TNF- α expression of microglia was seen in a murine study 6–8 weeks after cardiac ischemia.

Activation of microglia also triggers the subsequent activation of neighboring astrocytes [84]. Positron emission tomography with ^{11}C -methionine identified astroglial activation after permanent coronary artery ligation in mice [76]. These findings were paralleled by experiments, where astrocytes were activated in PVN with enhanced expression of cytokines and glial fibrillary acidic protein (GFAP) [85]. Five weeks after experimental MI, there was a sharp increase in GFAP-positive astrocytes in the hippocampus in rats [86].

Lastly, infiltrating monocyte and neutrophil abundance was also increased in the brain within the first day after MI and remained elevated for at least one week compared to controls [87]. As a possible mechanism, the skull bone marrow was found to contain direct vascular channels to the brain parenchyma, facilitating the migration of monocytes and

neutrophils, which are transcriptionally distinct from host microglia [88], into the brain parenchyma after CNS injury [89].

Lymphocytes are also likely involved in neuroinflammatory changes after MI. Recent studies suggested that CD4⁺ T lymphocytes exhibit biphasic kinetics post MI [90] with a rapid CD4⁺ T cell response at 3 days post-MI and a second phase of activation in chronic HF. Increased levels of pro-inflammatory markers after MI were shown to be associated with worse systolic function [91]. It has also been established that peripherally activated T cells are capable of adhering to and crossing the blood–brain barrier to enter the perivascular space [92]. Murine and human immunohistochemical analysis showed a crucial role of perivascular and parenchymal infiltrating CD4⁺ helper T cells, but not cytotoxic T cells (CD8⁺) or B cells (CD20⁺), in the neocortex, hippocampus, and striatum in neurodegenerative disease [93], with close proximity to activated astroglia, microgliosis, and expression of pro-inflammatory cytokines. Therefore, peripherally activated T cells may also trigger or even amplify neuroinflammation after MI.

5.2. Heart Failure

The above-mentioned long-lasting elevated TPSO signals after MI [75] suggest relevant global chronic neuroinflammation also in chronic (ischemic) HF. Animal models of HF demonstrated that the expression of inflammatory genes, such as Toll-like receptor-4 (TLR-4), tumor necrosis factor- α , and interleukin-6, were significantly upregulated in the cortex and hippocampus, particularly in mice [94]. Most preclinical studies in HF to date, however, focused on autonomic control areas of the CNS, as there is some evidence suggesting that it plays an important role in cardiac dysfunction in HF [95].

There are three primary brain nuclei involved in the regulation of sympathetic tone, i.e., NTS, PVN, and RVLM [96]. In fact, the chronic activation of RVLM astrocytes is associated with increased mortality in animals exhibiting HF with a reduced left ventricular ejection fraction [97]. Indeed, activated microglia have been observed in these key autonomic control areas in HF [98] and have been shown to co-localize with activated neurons in the PVN, RVLM, and NTS of post-MI rats [78]. There is evidence to suggest that this transition takes place in response to augmented astrocytic and neuronal activation [98]. Summing up, chronic HF appears to trigger both regional (i.e., autonomic control areas) and global (i.e., cortex, hippocampus) chronic phenotypical and functional inflammatory changes in resident cells within the CNS.

As discussed above, neuroinflammation in HF may also result from peripherally activated immune cells entering the CNS [92]. CD4⁺ T-lymphocytes are globally expanded and activated in chronic ischemic HF [99]. Furthermore, the expression of tumor necrosis factor- α and tumor necrosis factor receptor increased in HF-activated CD4⁺ T cells [100]. Activated T cells were not only shown to cross the blood–brain barrier, but also to induce its disruption and increase its permeability [101]. In summary, processes from within the CNS (in response to increased neuronal activation) and from the periphery (i.e., activated T cells) seem to be intricately involved in heart failure-related neuroinflammation.

5.3. Hypertension

Models of hypertension increased the number of activated microglia in the cortex and hippocampus of mice, upregulated triggering receptor expressed on myeloid cells 2 (TREM2) produced by microglia, and increased amyloid-beta deposition [102]. In mice with transverse aortic constriction, it was demonstrated that hypertension per se triggered neuroinflammation before amyloid-beta deposition occurred [103]. Damage to the cerebral microvasculature and the locally activated renin–angiotensin system might thus be a crucial mechanism linking hypertension to neuroinflammation and neurodegeneration [104]. In turn, overstimulation of the pro-inflammatory pathways within brain areas responsible for sympathetic outflow is widely acknowledged as a primary contributing factor to the establishment and maintenance of neurogenic hypertension [105]. In another study, aerobic

training regulated microglia activation and the production of pro-inflammatory cytokines in the presence of hypertension [106].

5.4. Atrial Fibrillation

Patients with AF exhibited elevated plasma concentrations of several inflammatory markers such as interleukin-1 β and tumor necrosis factor- α that have been related to the development of AD [107]. Besides the generation of microemboli occurring with AF, an alternative explanation for the development of dementia in AF may be thrombotic microinfarctions triggered by inflammatory processes [108].

5.5. Aortic Valve Stenosis

Little is known about neuroinflammation in patients with aortic valve stenosis or its effects on microglia and astrocytes. Here, (pre-)clinical studies are needed.

5.6. Cardiac Arrest

Extensive microglial activation and neurodegeneration in the *cornu ammonis* area 1 (CA1) and the dentate gyrus of the hippocampus are evident following brief asystolic cardiac arrest and are associated with severe neurological injury [109]. Another recent study in rats demonstrated that microglial pyroptosis mediated by the NLR family pyrin domain containing 3 (NLRP3) inflammasome appears to be critically involved in the pathogenesis of post-cardiac arrest brain injury [110].

6. Potential Biomarkers

As shown above and summarized in Table 1, the evidence for neuroinflammation in cardiac diseases remains predominantly rooted on complex experimental findings. Considerable inter-individual differences, but also elaborate experimental settings and/or cost-intensive imaging (i.e., positron emission imaging), constitute current barriers for the advancement of this important research area. Therefore, biomarkers of cognitive decline and neuroinflammation might help in identifying patients at risk: studies of cardiac biomarkers to date have mainly focused on the N-terminal pro-B-type natriuretic peptide (NT-proBNP), which is an established surrogate of the severity of cardiac wall stress and symptom burden in HF. Of note, both cross-sectionally measured NT-proBNP and changes in NT-proBNP over time were found to predict incident dementia [111]. Furthermore, higher NT-proBNP levels were inversely associated with MMSE scores [112]. Interestingly, the measurement of highly sensitive troponins should also be considered an early and sensitive biomarker of cytotoxic effects of ‘inflammageing’ mechanisms (a term used to describe the chronic inflammatory state typical of elderly individuals) on myocardial tissue, as well as the cognitive decline in older adults [113].

Table 1. Important preclinical and human studies on neuroinflammatory processes in cardiac diseases.

Cardiac Disease (Chapter in Article)	Evidence of (Chronic) Neuroinflammation	
	Preclinical Models	Human Studies
Myocardial infarction/coronary artery disease (5.1)	Microglial activation in the RVLM, NTS, PAG, and PVN [77–79] Phenotypic global changes to microglia [80–82] Astroglial activation [76,84,85] Monocyte and neutrophil abundance [87–89]	TSPO on microglia in the cerebellum, temporal and frontobasal cortex, and hypothalamus [75,76]

Table 1. Cont.

Cardiac Disease (Chapter in Article)	Evidence of (Chronic) Neuroinflammation	
	Preclinical Models	Human Studies
Heart failure (5.2)	Inflammatory genes in the cortex and hippocampus [94] Astrocyte activation in the RVLM [97] Microglia co-localization and activation in the PVN, RVLM, and NTS [98]	
Hypertension (5.3)	Activation and TREM2 production by microglia in the cortex and hippocampus [102] Neuroinflammation before amyloid-beta deposition [102,103] Pro-inflammatory pathways involved in sympathetic control [105]	
Atrial fibrillation (5.4)	Interleukin-1 β and tumor necrosis factor- α levels [107]	
Aortic valve stenosis (5.5)		
Cardiac arrest (5.6)	Microglial activation and neurodegeneration in the <i>cornu ammonis</i> area 1 [109] NLRP3 inflammasome [110]	

Neuroinflammatory serum and cerebrospinal fluid (CSF) biomarkers associated with either microglia (soluble TREM2, monocyte chemoattractant protein-1 (MCP-1), and chitinase-3-like protein 1 (CHI3L1)) or astroglia (e.g., CHI3L1) are currently extensively investigated in AD patients [114]. Hence, these markers may reflect the inflammatory mechanisms within the CNS coupled with the neuro-degenerative pathways. A recent meta-analysis reported higher concentrations of CHI3L1, TREM2, MCP-1, and transforming growth factor- β in the CSF of AD patients compared to controls [115]. Along these lines, elevated neuronal serum biomarkers such as neurofilament light chain, phosphorylated tau protein and GFAP are associated with cognitive decline in chronic HF [116,117]. The recently observed increase in serum GFAP after MI might reflect the abovedescribed astroglial activation [118]. However, more studies on the mentioned biomarkers will be needed to further evaluate their relevance and potential in this currently evolving field of research.

7. Therapeutic Implications

From neurological research, there is now a group of candidate drugs that aim to modulate the activation and functional states of microglia, thus exerting potentially protective effects against the neuroinflammation caused by cardiac disorders.

Angiotensin II, a major hormone peptide that binds to angiotensin II type 1 and type 2 receptors (AT1R and AT2R, respectively) expressed in neurons, microglia, and astrocytes, has pleiotropic roles in the brain, including the mediation of inflammation and neuronal cell injury [119]. Interestingly, two antagonists of AT1R used to treat hypertension and heart failure, candesartan (NCT02646982) and telmisartan (NCT02085265), are now in phase II clinical trials for AD [120]. As these agents are already widely in use in cardiac disease, they might already make an important contribution to limiting cognitive functions.

Minocycline, an antibiotic that can permeate the blood–brain barrier, exhibits anti-inflammatory and neuroprotective effects [121]. Minocycline inhibits interleukin-1 β , tumor necrosis factor, and interleukin-6 production by microglia in vitro, and suppresses microglial activation [122]. It also improves cognitive decline in AD transgenic mice [123]. However, preclinical or clinical data on the relevance of minocycline in cardiological diseases are missing.

In addition, pharmacological ubiquitin-specific protease 7 (USP7) inhibition attenuated microglia activation and associated neuron injury, thereby improving behavioral deficits in dementia and Parkinson's disease mouse models. Thereby, the inhibition of USP7 might provide an attractive future direction for cardiogenic neurodegenerative disease [124].

8. Conclusions

There is now compelling and growing evidence for temporally and regionally varying, heterogenic neuroinflammatory changes occurring in the CNS during the progression of multiple cardiac diseases (Figure 1). These conditions are associated with accelerated cognitive decline beyond ageing and a higher prevalence of dementia. Recent findings from neurodegenerative research consistently suggest that chronic neuroinflammation precedes and aggravates cognitive decline, which might therefore also apply in cardiac disease. However, further (pre-)clinical investigations will be needed to specifically prove and evaluate the relative influence of neuroinflammation on cognitive decline in cardiological patients. So far, it has not been clear if and how reported regional changes in specific nuclei trigger global neuroinflammation, which is thought to precede cognitive decline. Furthermore, standardization of cognitive testing and better standardization of test settings (e.g., in-hospital vs. outpatient testing) will be important factors to advance research. Beyond contemporary guideline-based treatment of cardiac disorders, potential therapeutic options may include anti-inflammatory treatments specific to the brain in order to prevent an accelerated cognitive decline in cardiac disease.

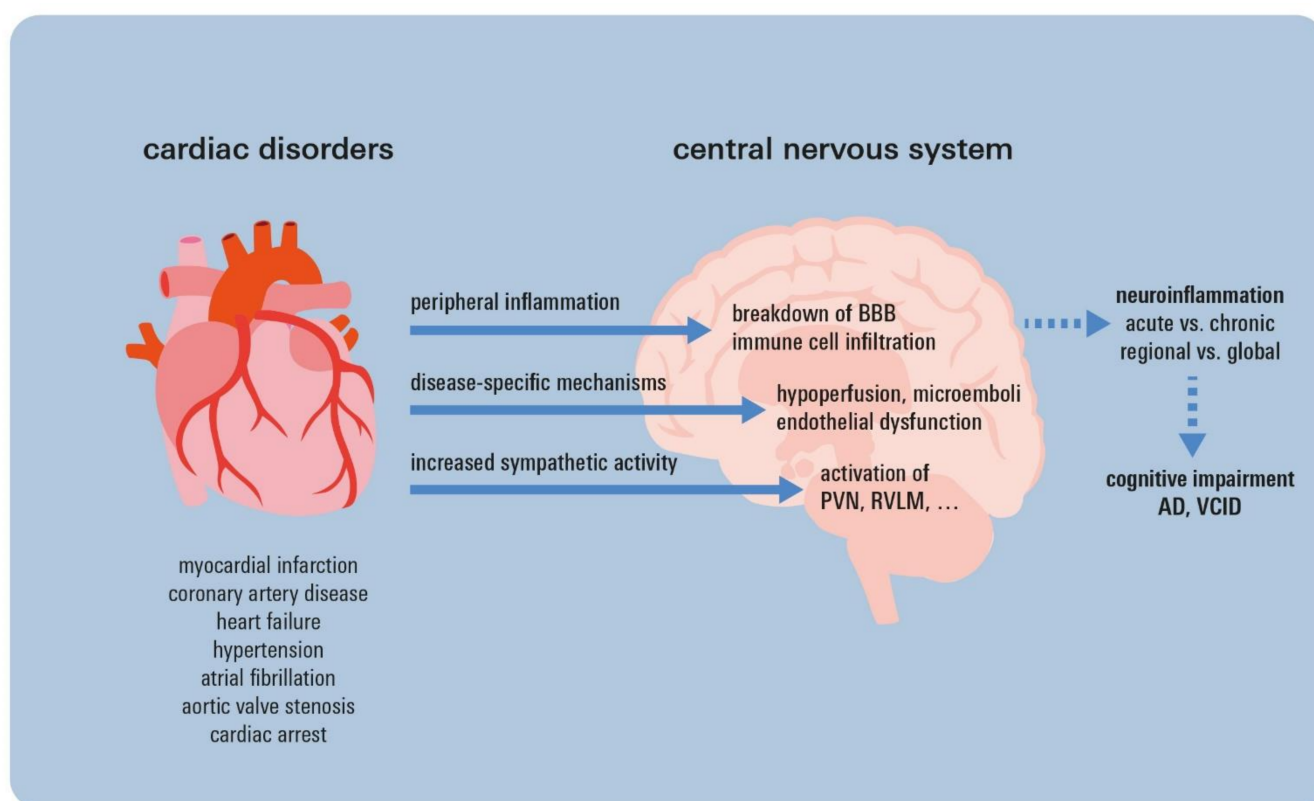


Figure 1. Current concept linking cardiac disorders, neuroinflammation, and cognitive impairment. For the displayed cardiac disorders, it has been shown that they can induce neuroinflammatory activation, thereby triggering cognitive impairment. Neuroinflammation may occur on both a regional and global level through (i) peripheral immune cell activation with subsequent CNS infiltration, (ii) disease-specific mechanisms, e.g., microemboli in atrial fibrillation, and (iii) over-activation of nuclei involved in sympathetic regulation. AD = Alzheimer's dementia; BBB = blood–brain barrier; PVN = paraventricular nucleus; RVLM = rostral ventrolateral medulla; VCID = vascular cognitive impairment and dementia.

Author Contributions: Conceptualization, S.S and J.T.; writing—original draft preparation, J.T.; writing—review and editing, J.T., S.S., A.F.; illustration, J.T.; supervision, S.S.; project administration, S.S., A.F. All authors have read and agreed to the published version of the manuscript.

Funding: The authors received funding from the Bundesministerium für Bildung und Forschung (01ES0816, 01ES01901, 01ES01902, 01EO1004), habilitation grant (AF), UNION-CVD Clinician Scientist Program grant (JT) by the Interdisciplinary Center of Clinical Research Würzburg (DFG project number 413657723) and from the German Research foundation (DFG project numbers 391580509; 453989101).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Disease, G.B.D.; Injury, I.; Prevalence, C. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990–2015: A systematic analysis for the Global Burden of Disease Study 2015. *Lancet* **2016**, *388*, 1545–1602. [[CrossRef](#)]
2. Kobayashi, M.; Voors, A.A.; Girerd, N.; Billotte, M.; Anker, S.D.; Cleland, J.G.; Lang, C.C.; Ng, L.L.; van Veldhuisen, D.J.; Dickstein, K.; et al. Heart failure etiologies and clinical factors precipitating for worsening heart failure: Findings from BIOSTAT-CHF. *Eur. J. Intern. Med.* **2020**, *71*, 62–69. [[CrossRef](#)]
3. Zhang, W.; Luo, P. Myocardial Infarction Predisposes Neurodegenerative Diseases. *J. Alzheimers Dis.* **2020**, *74*, 579–587. [[CrossRef](#)] [[PubMed](#)]
4. Wolters, F.J.; Segufa, R.A.; Darweesh, S.K.L.; Bos, D.; Ikram, M.A.; Sabayan, B.; Hofman, A.; Sedaghat, S. Coronary heart disease, heart failure, and the risk of dementia: A systematic review and meta-analysis. *Alzheimers Dement.* **2018**, *14*, 1493–1504. [[CrossRef](#)] [[PubMed](#)]
5. Zuidersma, M.; Thombs, B.D.; de Jonge, P. Onset and recurrence of depression as predictors of cardiovascular prognosis in depressed acute coronary syndrome patients: A systematic review. *Psychother. Psychosom.* **2011**, *80*, 227–237. [[CrossRef](#)] [[PubMed](#)]
6. Yusuf, S.; Hawken, S.; Ounpuu, S.; Dans, T.; Avezum, A.; Lanas, F.; McQueen, M.; Budaj, A.; Pais, P.; Varigos, J.; et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet* **2004**, *364*, 937–952. [[CrossRef](#)] [[PubMed](#)]
7. Yang, M.; Sun, D.; Wang, Y.; Yan, M.; Zheng, J.; Ren, J. Cognitive Impairment in Heart Failure: Landscape, Challenges, and Future Directions. *Front. Cardiovasc. Med.* **2021**, *8*, 831734. [[CrossRef](#)]
8. Frantz, S.; Hundertmark, M.J.; Schulz-Menger, J.; Bengel, F.M.; Bauersachs, J. Left ventricular remodelling post-myocardial infarction: Pathophysiology, imaging, and novel therapies. *Eur. Heart J.* **2022**, *43*, 2549–2561. [[CrossRef](#)]
9. Thorp, E.B.; Flanagan, M.E.; Popko, B.; DeBerge, M. Resolving inflammatory links between myocardial infarction and vascular dementia. *Semin. Immunol.* **2022**, *59*, 101600. [[CrossRef](#)]
10. Breteler, M.M.; Claus, J.J.; Grobbee, D.E.; Hofman, A. Cardiovascular disease and distribution of cognitive function in elderly people: The Rotterdam Study. *BMJ* **1994**, *308*, 1604–1608. [[CrossRef](#)]
11. Ikram, M.A.; van Oijen, M.; de Jong, F.J.; Kors, J.A.; Koudstaal, P.J.; Hofman, A.; Witteman, J.C.; Breteler, M.M. Unrecognized myocardial infarction in relation to risk of dementia and cerebral small vessel disease. *Stroke* **2008**, *39*, 1421–1426. [[CrossRef](#)]
12. Aronson, M.K.; Ooi, W.L.; Morgenstern, H.; Hafner, A.; Masur, D.; Crystal, H.; Frishman, W.H.; Fisher, D.; Katzman, R. Women, myocardial infarction, and dementia in the very old. *Neurology* **1990**, *40*, 1102–1106. [[CrossRef](#)]
13. Xie, W.; Zheng, F.; Yan, L.; Zhong, B. Cognitive Decline Before and After Incident Coronary Events. *J. Am. Coll. Cardiol.* **2019**, *73*, 3041–3050. [[CrossRef](#)]
14. Gu, S.Z.; Beska, B.; Chan, D.; Neely, D.; Batty, J.A.; Adams-Hall, J.; Mossop, H.; Qiu, W.; Kunadian, V. Cognitive Decline in Older Patients With Non- ST Elevation Acute Coronary Syndrome. *J. Am. Heart Assoc.* **2019**, *8*, e011218. [[CrossRef](#)] [[PubMed](#)]
15. Haring, B.; Leng, X.; Robinson, J.; Johnson, K.C.; Jackson, R.D.; Beyth, R.; Wactawski-Wende, J.; von Ballmoos, M.W.; Goveas, J.S.; Kuller, L.H.; et al. Cardiovascular disease and cognitive decline in postmenopausal women: Results from the Women’s Health Initiative Memory Study. *J. Am. Heart Assoc.* **2013**, *2*, e000369. [[CrossRef](#)] [[PubMed](#)]
16. Solfrizzi, V.; Panza, F.; Colacicco, A.M.; D’Introno, A.; Capurso, C.; Torres, F.; Grigoletto, F.; Maggi, S.; Del Parigi, A.; Reiman, E.M.; et al. Vascular risk factors, incidence of MCI, and rates of progression to dementia. *Neurology* **2004**, *63*, 1882–1891. [[CrossRef](#)] [[PubMed](#)]
17. Sundboll, J.; Horvath-Puho, E.; Adelborg, K.; Schmidt, M.; Pedersen, L.; Botker, H.E.; Henderson, V.W.; Sorensen, H.T. Higher Risk of Vascular Dementia in Myocardial Infarction Survivors. *Circulation* **2018**, *137*, 567–577. [[CrossRef](#)]

18. Zheng, L.; Mack, W.J.; Chui, H.C.; Heflin, L.; Mungas, D.; Reed, B.; DeCarli, C.; Weiner, M.W.; Kramer, J.H. Coronary artery disease is associated with cognitive decline independent of changes on magnetic resonance imaging in cognitively normal elderly adults. *J. Am. Geriatr. Soc.* **2012**, *60*, 499–504. [[CrossRef](#)]
19. Lima, L.M.; Carvalho, M.; Ferreira, C.N.; Fernandes, A.P.; Neto, C.P.; Garcia, J.C.; Reis, H.J.; Janka, Z.; Palotas, A.; Sousa, M. Atheromatosis extent in coronary artery disease is not correlated with apolipoprotein-E polymorphism and its plasma levels, but associated with cognitive decline. *Curr. Alzheimer Res.* **2010**, *7*, 556–563. [[CrossRef](#)]
20. Slawson, D.C. No Difference in Cognitive Decline in Older Patients with Coronary Artery Disease Undergoing CABG or PCI. *Am. Fam. Physician* **2021**, *104*, 422.
21. Toyama, K.; Sugiyama, S.; Oka, H.; Hamada, M.; Iwasaki, Y.; Horio, E.; Rokutanda, T.; Nakamura, S.; Spin, J.M.; Tsao, P.S.; et al. A Pilot Study: The Beneficial Effects of Combined Statin-exercise Therapy on Cognitive Function in Patients with Coronary Artery Disease and Mild Cognitive Decline. *Intern. Med.* **2017**, *56*, 641–649. [[CrossRef](#)]
22. Lutski, M.; Weinstein, G.; Goldbourt, U.; Tanne, D. Cardiovascular Health and Cognitive Decline 2 Decades Later in Men with Preexisting Coronary Artery Disease. *Am. J. Cardiol.* **2018**, *121*, 410–415. [[CrossRef](#)] [[PubMed](#)]
23. Zuccala, G.; Marzetti, E.; Cesari, M.; Lo Monaco, M.R.; Antonica, L.; Cocchi, A.; Carbonin, P.; Bernabei, R. Correlates of cognitive impairment among patients with heart failure: Results of a multicenter survey. *Am. J. Med.* **2005**, *118*, 496–502. [[CrossRef](#)] [[PubMed](#)]
24. Dong, Y.; Teo, S.Y.; Kang, K.; Tan, M.; Ling, L.H.; Yeo, P.S.D.; Sim, D.; Jaufeerally, F.; Leong, K.T.G.; Ong, H.Y.; et al. Cognitive impairment in Asian patients with heart failure: Prevalence, biomarkers, clinical correlates, and outcomes. *Eur. J. Heart Fail.* **2019**, *21*, 688–690. [[CrossRef](#)]
25. Frey, A.; Sell, R.; Homola, G.A.; Malsch, C.; Kraft, P.; Gunreben, I.; Morbach, C.; Alkonyi, B.; Schmid, E.; Colonna, I.; et al. Cognitive Deficits and Related Brain Lesions in Patients With Chronic Heart Failure. *JACC Heart Fail.* **2018**, *6*, 583–592. [[CrossRef](#)] [[PubMed](#)]
26. Festa, J.R.; Jia, X.; Cheung, K.; Marchidann, A.; Schmidt, M.; Shapiro, P.A.; Mancini, D.M.; Naka, Y.; Deng, M.; Lantz, E.R.; et al. Association of low ejection fraction with impaired verbal memory in older patients with heart failure. *Arch. Neurol.* **2011**, *68*, 1021–1026. [[CrossRef](#)] [[PubMed](#)]
27. Hajduk, A.M.; Kiefe, C.I.; Person, S.D.; Gore, J.G.; Saczynski, J.S. Cognitive change in heart failure: A systematic review. *Circ. Cardiovasc. Qual. Outcomes* **2013**, *6*, 451–460. [[CrossRef](#)] [[PubMed](#)]
28. Ampadu, J.; Morley, J.E. Heart failure and cognitive dysfunction. *Int. J. Cardiol.* **2015**, *178*, 12–23. [[CrossRef](#)]
29. Qiu, C.; Winblad, B.; Marengoni, A.; Klarin, I.; Fastbom, J.; Fratiglioni, L. Heart failure and risk of dementia and Alzheimer disease: A population-based cohort study. *Arch. Intern. Med.* **2006**, *166*, 1003–1008. [[CrossRef](#)]
30. Adelborg, K.; Horvath-Puho, E.; Ording, A.; Pedersen, L.; Sorensen, H.T.; Henderson, V.W. Heart failure and risk of dementia: A Danish nationwide population-based cohort study. *Eur. J. Heart Fail.* **2017**, *19*, 253–260. [[CrossRef](#)]
31. Geer, J.H.; Jeon, S.; O'Connell, M.; Linsky, S.; Conley, S.; Hollenbeak, C.S.; Jacoby, D.; Yaggi, H.K.; Redeker, N.S. Correlates of cognition among people with chronic heart failure and insomnia. *Sleep Breath*, 2022; *online ahead of print*. [[CrossRef](#)]
32. Liu, Y.; Meng, R.; Dong, J. Effect of Chronic Heart Failure Complicated with Type 2 Diabetes Mellitus on Cognitive Function in the Elderly. *Evid. Based Complement. Alternat. Med.* **2022**, 2022, 4841205. [[CrossRef](#)] [[PubMed](#)]
33. Ventoulis, I.; Arfaras-Melainis, A.; Parissis, J.; Polyzogopoulou, E. Cognitive Impairment in Acute Heart Failure: Narrative Review. *J. Cardiovasc. Dev. Dis.* **2021**, *8*, 184. [[CrossRef](#)] [[PubMed](#)]
34. Mansukhani, M.P.; Kolla, B.P.; Somers, V.K. Hypertension and Cognitive Decline: Implications of Obstructive Sleep Apnea. *Front. Cardiovasc. Med.* **2019**, *6*, 96. [[CrossRef](#)] [[PubMed](#)]
35. Hanon, O.; Seux, M.L.; Lenoir, H.; Rigaud, A.S.; Forette, F. Hypertension and dementia. *Curr. Cardiol. Rep.* **2003**, *5*, 435–440. [[CrossRef](#)]
36. Vicario, A.; Martinez, C.D.; Baretto, D.; Diaz Casale, A.; Nicolosi, L. Hypertension and cognitive decline: Impact on executive function. *J. Clin. Hypertens.* **2005**, *7*, 598–604. [[CrossRef](#)]
37. Cheon, E.J. Hypertension and cognitive dysfunction: A narrative review. *J. Yeungnam. Med. Sci.* 2022; *epub ahead of print*. [[CrossRef](#)]
38. Ding, L.; Zhu, X.; Xiong, Z.; Yang, F.; Zhang, X. The Association of Age at Diagnosis of Hypertension with Cognitive Decline: The China Health and Retirement Longitudinal Study (CHARLS). *J. Gen. Intern. Med.* 2022; *online ahead of print*. [[CrossRef](#)]
39. Turana, Y.; Tenglawan, J.; Chia, Y.C.; Hoshide, S.; Shin, J.; Chen, C.H.; Buranakitjaroen, P.; Naites, J.; Park, S.; Siddique, S.; et al. Hypertension and Dementia: A comprehensive review from the HOPE Asia Network. *J. Clin. Hypertens.* **2019**, *21*, 1091–1098. [[CrossRef](#)]
40. Islam, M.M.; Poly, T.N.; Walther, B.A.; Yang, H.C.; Wu, C.C.; Lin, M.C.; Chien, S.C.; Li, Y.C. Association Between Atrial Fibrillation and Dementia: A Meta-Analysis. *Front. Aging Neurosci.* **2019**, *11*, 305. [[CrossRef](#)]
41. Morales-Bacas, E.; Duque-Holguera, M.; Portilla-Cuenca, J.C.; Casado-Naranjo, I. Atrial fibrillation and cognitive impairment: A narrative review. *Rev. Neurol.* **2022**, *75*, 311–318. [[CrossRef](#)]
42. Kim, D.; Yang, P.S.; Joung, B. Prevention of Dementia in Patients with Atrial Fibrillation. *Korean Circ J* **2021**, *51*, 308–319. [[CrossRef](#)]
43. Kim, D.; Yang, P.S.; Sung, J.H.; Jang, E.; Yu, H.T.; Kim, T.H.; Uhm, J.S.; Kim, J.Y.; Pak, H.N.; Lee, M.H.; et al. Less dementia after catheter ablation for atrial fibrillation: A nationwide cohort study. *Eur. Heart J.* **2020**, *41*, 4483–4493. [[CrossRef](#)] [[PubMed](#)]

44. Zhao, M.; Jiang, C.; Lai, Y.; Wang, Y.; Li, S.; He, L.; Tang, R.; Sang, C.; Long, D.; Du, X.; et al. Association Between Atrial Fibrillation and Domain-Specific Cognitive Decline—Insights From the Systolic Blood Pressure Intervention Trial. *Circ. J.* **2022**, *87*, 20–26. [[CrossRef](#)]
45. Myers, S.J.; Jimenez-Ruiz, A.; Sposato, L.A.; Whitehead, S.N. Atrial cardiopathy and cognitive impairment. *Front. Aging Neurosci.* **2022**, *14*, 914360. [[CrossRef](#)] [[PubMed](#)]
46. Ndunda, P.M.; Vindhyal, M.R.; Muutu, T.M.; Fanari, Z. Clinical Outcomes of Sentinel Cerebral Protection System Use During Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. *Cardiovasc. Revasc. Med.* **2020**, *21*, 717–722. [[CrossRef](#)]
47. Wolters, F.J.; Bos, D.; Vernooij, M.W.; Franco, O.H.; Heart-Brain Connection collaborative research group; Hofman, A.; Koudstaal, P.J.; van der Lugt, A.; Ikram, M.A. Aortic Valve Calcification and the Risk of dementia: A Population-Based Study. *J. Alzheimers Dis.* **2017**, *55*, 893–897. [[CrossRef](#)] [[PubMed](#)]
48. Tsuchiya, S.; Matsumoto, Y.; Suzuki, H.; Takanami, K.; Kikuchi, Y.; Takahashi, J.; Miyata, S.; Tomita, N.; Kumagai, K.; Taki, Y.; et al. Transcatheter aortic valve implantation and cognitive function in elderly patients with severe aortic stenosis. *EuroIntervention* **2020**, *15*, e1580–e1587. [[CrossRef](#)] [[PubMed](#)]
49. Lai, K.S.; Herrmann, N.; Saleem, M.; Lancot, K.L. Cognitive Outcomes following Transcatheter Aortic Valve Implantation: A Systematic Review. *Cardiovasc. Psychiatry Neurol.* **2015**, *2015*, 209569. [[CrossRef](#)]
50. Volpp, K.G.; Abella, B.S. Improving Out-of-Hospital Cardiac Arrest Survival Rates-Optimization Given Constraints. *JAMA Cardiol* **2022**, *8*, 8–9. [[CrossRef](#)]
51. Moolaert, V.R.; Verbunt, J.A.; van Heugten, C.M.; Wade, D.T. Cognitive impairments in survivors of out-of-hospital cardiac arrest: A systematic review. *Resuscitation* **2009**, *80*, 297–305. [[CrossRef](#)]
52. Buanes, E.A.; Gramstad, A.; Sovig, K.K.; Hufthammer, K.O.; Flaatten, H.; Husby, T.; Langorgen, J.; Heltne, J.K. Cognitive function and health-related quality of life four years after cardiac arrest. *Resuscitation* **2015**, *89*, 13–18. [[CrossRef](#)]
53. Caro-Codon, J.; Rey, J.R.; Lopez-de-Sa, E.; Gonzalez Fernandez, O.; Rosillo, S.O.; Armada, E.; Iniesta, A.M.; Fernandez de Bobadilla, J.; Ruiz Cantador, J.; Rodriguez Sotelo, L.; et al. Long-term neurological outcomes in out-of-hospital cardiac arrest patients treated with targeted-temperature management. *Resuscitation* **2018**, *133*, 33–39. [[CrossRef](#)] [[PubMed](#)]
54. Byron-Alhassan, A.; Collins, B.; Bedard, M.; Quinlan, B.; Le May, M.; Duchesne, L.; Osborne, C.; Wells, G.; Smith, A.M.; Tulloch, H.E. Cognitive dysfunction after out-of-hospital cardiac arrest: Rate of impairment and clinical predictors. *Resuscitation* **2021**, *165*, 154–160. [[CrossRef](#)] [[PubMed](#)]
55. Orbo, M.; Aslaksen, P.M.; Larsby, K.; Norli, L.; Schafer, C.; Tande, P.M.; Vangberg, T.R.; Anke, A. Determinants of cognitive outcome in survivors of out-of-hospital cardiac arrest. *Resuscitation* **2014**, *85*, 1462–1468. [[CrossRef](#)] [[PubMed](#)]
56. Lyman, M.; Lloyd, D.G.; Ji, X.; Vizcaychipi, M.P.; Ma, D. Neuroinflammation: The role and consequences. *Neurosci. Res.* **2014**, *79*, 1–12. [[CrossRef](#)]
57. Mayer, C.L.; Huber, B.R.; Peskind, E. Traumatic brain injury, neuroinflammation, and post-traumatic headaches. *Headache* **2013**, *53*, 1523–1530. [[CrossRef](#)]
58. Tansey, M.G.; McCoy, M.K.; Frank-Cannon, T.C. Neuroinflammatory mechanisms in Parkinson’s disease: Potential environmental triggers, pathways, and targets for early therapeutic intervention. *Exp. Neurol.* **2007**, *208*, 1–25. [[CrossRef](#)]
59. Frank-Cannon, T.C.; Alto, L.T.; McAlpine, F.E.; Tansey, M.G. Does neuroinflammation fan the flame in neurodegenerative diseases? *Mol. Neurodegener.* **2009**, *4*, 47. [[CrossRef](#)]
60. DiSabato, D.J.; Quan, N.; Godbout, J.P. Neuroinflammation: The devil is in the details. *J. Neurochem.* **2016**, *139* (Suppl. S2), 136–153. [[CrossRef](#)]
61. Rivest, S. Regulation of innate immune responses in the brain. *Nat. Rev. Immunol.* **2009**, *9*, 429–439. [[CrossRef](#)]
62. Wang, M.; Pan, W.; Xu, Y.; Zhang, J.; Wan, J.; Jiang, H. Microglia-Mediated Neuroinflammation: A Potential Target for the Treatment of Cardiovascular Diseases. *J. Inflamm. Res.* **2022**, *15*, 3083–3094. [[CrossRef](#)]
63. Cheng, K.; Wang, J.; Chen, Q.; Zhao, G.; Pang, Y.; Xu, Y.; Ge, J.; Zhu, W. Inflammasome-mediated neurodegeneration following heart disease. *Ann. Transl. Med.* **2021**, *9*, 1560. [[CrossRef](#)] [[PubMed](#)]
64. Block, M.L.; Hong, J.S. Microglia and inflammation-mediated neurodegeneration: Multiple triggers with a common mechanism. *Prog. Neurobiol.* **2005**, *76*, 77–98. [[CrossRef](#)] [[PubMed](#)]
65. Mrazek, R.E.; Griffin, W.S. Glia and their cytokines in progression of neurodegeneration. *Neurobiol. Aging* **2005**, *26*, 349–354. [[CrossRef](#)]
66. McGeer, P.L.; Itagaki, S.; Tago, H.; McGeer, E.G. Reactive microglia in patients with senile dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR. *Neurosci. Lett.* **1987**, *79*, 195–200. [[CrossRef](#)] [[PubMed](#)]
67. Akiyama, H.; Barger, S.; Barnum, S.; Bradt, B.; Bauer, J.; Cole, G.M.; Cooper, N.R.; Eikelenboom, P.; Emmerling, M.; Fiebich, B.L.; et al. Inflammation and Alzheimer’s disease. *Neurobiol. Aging* **2000**, *21*, 383–421. [[CrossRef](#)] [[PubMed](#)]
68. Liao, B.; Zhao, W.; Beers, D.R.; Henkel, J.S.; Appel, S.H. Transformation from a neuroprotective to a neurotoxic microglial phenotype in a mouse model of ALS. *Exp. Neurol.* **2012**, *237*, 147–152. [[CrossRef](#)]
69. Ayyubova, G. Dysfunctional microglia and tau pathology in Alzheimer’s disease. *Rev. Neurosci.* **2022**; online ahead of print. [[CrossRef](#)]
70. Bradburn, S.; Murgatroyd, C.; Ray, N. Neuroinflammation in mild cognitive impairment and Alzheimer’s disease: A meta-analysis. *Ageing Res. Rev.* **2019**, *50*, 1–8. [[CrossRef](#)]

71. Tian, Z.; Ji, X.; Liu, J. Neuroinflammation in Vascular Cognitive Impairment and Dementia: Current Evidence, Advances, and Prospects. *Int. J. Mol. Sci.* **2022**, *23*, 6224. [[CrossRef](#)]
72. Simpson, J.E.; Fernando, M.S.; Clark, L.; Ince, P.G.; Matthews, F.; Forster, G.; O'Brien, J.T.; Barber, R.; Kalaria, R.N.; Brayne, C.; et al. White matter lesions in an unselected cohort of the elderly: Astrocytic, microglial and oligodendrocyte precursor cell responses. *Neuropathol. Appl. Neurobiol.* **2007**, *33*, 410–419. [[CrossRef](#)]
73. Chen, W.W.; Zhang, X.; Huang, W.J. Role of neuroinflammation in neurodegenerative diseases (Review). *Mol. Med. Rep.* **2016**, *13*, 3391–3396. [[CrossRef](#)]
74. Masuda, T.; Sankowski, R.; Staszewski, O.; Prinz, M. Microglia Heterogeneity in the Single-Cell Era. *Cell Rep.* **2020**, *30*, 1271–1281. [[CrossRef](#)] [[PubMed](#)]
75. Thackeray, J.T.; Hupe, H.C.; Wang, Y.; Bankstahl, J.P.; Berding, G.; Ross, T.L.; Bauersachs, J.; Wollert, K.C.; Bengel, F.M. Myocardial Inflammation Predicts Remodeling and Neuroinflammation After Myocardial Infarction. *J. Am. Coll. Cardiol.* **2018**, *71*, 263–275. [[CrossRef](#)]
76. Bascunana, P.; Hess, A.; Borchert, T.; Wang, Y.; Wollert, K.C.; Bengel, F.M.; Thackeray, J.T. (11)C-Methionine PET Identifies Astroglia Involvement in Heart-Brain Inflammation Networking After Acute Myocardial Infarction. *J. Nucl. Med.* **2020**, *61*, 977–980. [[CrossRef](#)] [[PubMed](#)]
77. Dworak, M.; Stebbing, M.; Kompa, A.R.; Rana, I.; Krum, H.; Badoer, E. Attenuation of microglial and neuronal activation in the brain by ICV minocycline following myocardial infarction. *Auton. Neurosci.* **2014**, *185*, 43–50. [[CrossRef](#)] [[PubMed](#)]
78. Rana, I.; Stebbing, M.; Kompa, A.; Kelly, D.J.; Krum, H.; Badoer, E. Microglia activation in the hypothalamic PVN following myocardial infarction. *Brain Res.* **2010**, *1326*, 96–104. [[CrossRef](#)]
79. Dworak, M.; Stebbing, M.; Kompa, A.R.; Rana, I.; Krum, H.; Badoer, E. Sustained activation of microglia in the hypothalamic PVN following myocardial infarction. *Auton. Neurosci.* **2012**, *169*, 70–76. [[CrossRef](#)]
80. Rinaldi, B.; Guida, F.; Furiano, A.; Donniacuo, M.; Luongo, L.; Gritti, G.; Urbanek, K.; Messina, G.; Maione, S.; Rossi, F.; et al. Effect of Prolonged Moderate Exercise on the Changes of Nonneuronal Cells in Early Myocardial Infarction. *Neural Plast.* **2015**, *2015*, 265967. [[CrossRef](#)]
81. Yuan, S.; Zhang, X.; Bo, Y.; Li, W.; Zhang, H.; Jiang, Q. The effects of electroacupuncture treatment on the postoperative cognitive function in aged rats with acute myocardial ischemia-reperfusion. *Brain Res.* **2014**, *1593*, 19–29. [[CrossRef](#)]
82. Frick, T.; Springe, D.; Grandgirard, D.; Leib, S.L.; Haenggi, M. An improved simple rat model for global cerebral ischaemia by induced cardiac arrest. *Neurol. Res.* **2016**, *38*, 373–380. [[CrossRef](#)]
83. Wang, H.W.; Ahmad, M.; Jadayel, R.; Najjar, F.; Lagace, D.; Leenen, F.H.H. Inhibition of inflammation by minocycline improves heart failure and depression-like behaviour in rats after myocardial infarction. *PLoS ONE* **2019**, *14*, e0217437. [[CrossRef](#)]
84. Liu, L.R.; Liu, J.C.; Bao, J.S.; Bai, Q.Q.; Wang, G.Q. Interaction of Microglia and Astrocytes in the Neurovascular Unit. *Front. Immunol.* **2020**, *11*, 1024. [[CrossRef](#)] [[PubMed](#)]
85. Chen, J.; Yin, D.; He, X.; Gao, M.; Choi, Y.; Luo, G.; Wang, H.; Qu, X. Modulation of activated astrocytes in the hypothalamus paraventricular nucleus to prevent ventricular arrhythmia complicating acute myocardial infarction. *Int. J. Cardiol.* **2020**, *308*, 33–41. [[CrossRef](#)] [[PubMed](#)]
86. Sun, N.; Mei, Y.; Hu, Z.; Xing, W.; Lv, K.; Hu, N.; Zhang, T.; Wang, D. Ghrelin attenuates depressive-like behavior, heart failure, and neuroinflammation in postmyocardial infarction rat model. *Eur. J. Pharmacol.* **2021**, *901*, 174096. [[CrossRef](#)] [[PubMed](#)]
87. Hoyer, F.F.; Naxerova, K.; Schloss, M.J.; Hulsmans, M.; Nair, A.V.; Dutta, P.; Calcagno, D.M.; Herisson, F.; Anzai, A.; Sun, Y.; et al. Tissue-Specific Macrophage Responses to Remote Injury Impact the Outcome of Subsequent Local Immune Challenge. *Immunity* **2019**, *51*, 899–914. [[CrossRef](#)] [[PubMed](#)]
88. Shemer, A.; Grozovski, J.; Tay, T.L.; Tao, J.; Volaski, A.; Suss, P.; Ardura-Fabregat, A.; Gross-Vered, M.; Kim, J.S.; David, E.; et al. Engrafted parenchymal brain macrophages differ from microglia in transcriptome, chromatin landscape and response to challenge. *Nat. Commun.* **2018**, *9*, 5206. [[CrossRef](#)] [[PubMed](#)]
89. Cugurra, A.; Mamuladze, T.; Rustenhoven, J.; Dykstra, T.; Beroshvili, G.; Greenberg, Z.J.; Baker, W.; Papadopoulos, Z.; Drieu, A.; Blackburn, S.; et al. Skull and vertebral bone marrow are myeloid cell reservoirs for the meninges and CNS parenchyma. *Science* **2021**, *373*, eabf7844. [[CrossRef](#)]
90. Kumar, V.; Prabhu, S.D.; Bansal, S.S. CD4(+) T-lymphocytes exhibit biphasic kinetics post-myocardial infarction. *Front. Cardiovasc. Med.* **2022**, *9*, 992653. [[CrossRef](#)]
91. Traub, J.; Schurmann, P.; Schmitt, D.; Gassenmaier, T.; Fette, G.; Frantz, S.; Stork, S.; Beyersdorf, N.; Boivin-Jahns, V.; Jahns, R.; et al. Features of metabolic syndrome and inflammation independently affect left ventricular function early after first myocardial infarction. *Int. J. Cardiol.* **2023**, *370*, 43–50. [[CrossRef](#)]
92. Goverman, J. Autoimmune T cell responses in the central nervous system. *Nat. Rev. Immunol.* **2009**, *9*, 393–407. [[CrossRef](#)]
93. Iba, M.; Kim, C.; Sallin, M.; Kwon, S.; Verma, A.; Overk, C.; Rissman, R.A.; Sen, R.; Sen, J.M.; Masliah, E. Neuroinflammation is associated with infiltration of T cells in Lewy body disease and alpha-synuclein transgenic models. *J. Neuroinflammation.* **2020**, *17*, 214. [[CrossRef](#)]
94. Hong, X.; Bu, L.; Wang, Y.; Xu, J.; Wu, J.; Huang, Y.; Liu, J.; Suo, H.; Yang, L.; Shi, Y.; et al. Increases in the risk of cognitive impairment and alterations of cerebral beta-amyloid metabolism in mouse model of heart failure. *PLoS ONE* **2013**, *8*, e63829. [[CrossRef](#)]

95. Guggilam, A.; Patel, K.P.; Haque, M.; Ebenezer, P.J.; Kapusta, D.R.; Francis, J. Cytokine blockade attenuates sympathoexcitation in heart failure: Cross-talk between nNOS, AT-1R and cytokines in the hypothalamic paraventricular nucleus. *Eur. J. Heart Fail.* **2008**, *10*, 625–634. [[CrossRef](#)] [[PubMed](#)]
96. Diaz, H.S.; Toledo, C.; Andrade, D.C.; Marcus, N.J.; Del Rio, R. Neuroinflammation in heart failure: New insights for an old disease. *J. Physiol.* **2020**, *598*, 33–59. [[CrossRef](#)]
97. Isegawa, K.; Hirooka, Y.; Katsuki, M.; Kishi, T.; Sunagawa, K. Angiotensin II type 1 receptor expression in astrocytes is upregulated leading to increased mortality in mice with myocardial infarction-induced heart failure. *Am. J. Physiol. Heart Circ. Physiol.* **2014**, *307*, H1448–H1455. [[CrossRef](#)] [[PubMed](#)]
98. Kapoor, K.; Bhandare, A.M.; Nedoboy, P.E.; Mohammed, S.; Farnham, M.M.; Pilowsky, P.M. Dynamic changes in the relationship of microglia to cardiovascular neurons in response to increases and decreases in blood pressure. *Neuroscience* **2016**, *329*, 12–29. [[CrossRef](#)] [[PubMed](#)]
99. Bansal, S.S.; Ismahil, M.A.; Goel, M.; Patel, B.; Hamid, T.; Rokosh, G.; Prabhu, S.D. Activated T Lymphocytes are Essential Drivers of Pathological Remodeling in Ischemic Heart Failure. *Circ. Heart Fail.* **2017**, *10*, e003688. [[CrossRef](#)] [[PubMed](#)]
100. Kumar, V.; Rosenzweig, R.; Asalla, S.; Nehra, S.; Prabhu, S.D.; Bansal, S.S. TNFR1 Contributes to Activation-Induced Cell Death of Pathological CD4(+) T Lymphocytes During Ischemic Heart Failure. *JACC Basic Transl. Sci.* **2022**, *7*, 1038–1049. [[CrossRef](#)] [[PubMed](#)]
101. Westland, K.W.; Pollard, J.D.; Sander, S.; Bonner, J.G.; Linington, C.; McLeod, J.G. Activated non-neural specific T cells open the blood-brain barrier to circulating antibodies. *Brain* **1999**, *122*, 1283–1291. [[CrossRef](#)] [[PubMed](#)]
102. Xu, X.; Du, L.; Jiang, J.; Yang, M.; Wang, Z.; Wang, Y.; Tang, T.; Fu, X.; Hao, J. Microglial TREM2 Mitigates Inflammatory Responses and Neuronal Apoptosis in Angiotensin II-Induced Hypertension in Middle-Aged Mice. *Front. Aging Neurosci.* **2021**, *13*, 716917. [[CrossRef](#)]
103. Carnevale, D.; Mascio, G.; Ajmone-Cat, M.A.; D’Andrea, I.; Cifelli, G.; Madonna, M.; Coccozza, G.; Frati, A.; Carullo, P.; Carnevale, L.; et al. Role of neuroinflammation in hypertension-induced brain amyloid pathology. *Neurobiol. Aging* **2012**, *33*, 205.e19–205.e29. [[CrossRef](#)]
104. Bajwa, E.; Klegeris, A. Neuroinflammation as a mechanism linking hypertension with the increased risk of Alzheimer’s disease. *Neural. Regen. Res.* **2022**, *17*, 2342–2346. [[CrossRef](#)]
105. Mowry, F.E.; Biancardi, V.C. Neuroinflammation in hypertension: The renin-angiotensin system versus pro-resolution pathways. *Pharmacol. Res.* **2019**, *144*, 279–291. [[CrossRef](#)] [[PubMed](#)]
106. Masson, G.S.; Nair, A.R.; Silva Soares, P.P.; Michelini, L.C.; Francis, J. Aerobic training normalizes autonomic dysfunction, HMGB1 content, microglia activation and inflammation in hypothalamic paraventricular nucleus of SHR. *Am. J. Physiol. Heart Circ. Physiol.* **2015**, *309*, H1115–H1122. [[CrossRef](#)] [[PubMed](#)]
107. Lappegard, K.T.; Pop-Purceanu, M.; van Heerde, W.; Sexton, J.; Tendolkar, I.; Pop, G. Improved neurocognitive functions correlate with reduced inflammatory burden in atrial fibrillation patients treated with intensive cholesterol lowering therapy. *J. Neuroinflamm.* **2013**, *10*, 78. [[CrossRef](#)] [[PubMed](#)]
108. Van Kuilenburg, J.; Lappegard, K.T.; Sexton, J.; Plesiewicz, I.; Lap, P.; Bouwels, L.; Sprong, T.; Mollnes, T.E.; Verheugt, F.; van Heerde, W.L.; et al. Persisting thrombin activity in elderly patients with atrial fibrillation on oral anticoagulation is decreased by anti-inflammatory therapy with intensive cholesterol-lowering treatment. *J. Clin. Lipidol.* **2011**, *5*, 273–280. [[CrossRef](#)] [[PubMed](#)]
109. Ousta, A.; Piao, L.; Fang, Y.H.; Vera, A.; Nallamothe, T.; Garcia, A.J., 3rd; Sharp, W.W. Microglial Activation and Neurological Outcomes in a Murine Model of Cardiac Arrest. *Neurocrit. Care* **2022**, *36*, 61–70. [[CrossRef](#)] [[PubMed](#)]
110. Chang, Y.; Zhu, J.; Wang, D.; Li, H.; He, Y.; Liu, K.; Wang, X.; Peng, Y.; Pan, S.; Huang, K. NLRP3 inflammasome-mediated microglial pyroptosis is critically involved in the development of post-cardiac arrest brain injury. *J. Neuroinflamm.* **2020**, *17*, 219. [[CrossRef](#)]
111. Ostovaneh, M.R.; Moazzami, K.; Yoneyama, K.; Venkatesh, B.A.; Heckbert, S.R.; Wu, C.O.; Shea, S.; Post, W.S.; Fitzpatrick, A.L.; Burke, G.L.; et al. Change in NT-proBNP (N-Terminal Pro-B-Type Natriuretic Peptide) Level and Risk of Dementia in Multi-Ethnic Study of Atherosclerosis (MESA). *Hypertension* **2020**, *75*, 316–323. [[CrossRef](#)] [[PubMed](#)]
112. Van Vliet, P.; Sabayan, B.; Wijsman, L.W.; Poortvliet, R.K.; Mooijaart, S.P.; de Ruijter, W.; Gussekloo, J.; de Craen, A.J.; Westendorp, R.G. NT-proBNP, blood pressure, and cognitive decline in the oldest old: The Leiden 85-plus Study. *Neurology* **2014**, *83*, 1192–1199. [[CrossRef](#)] [[PubMed](#)]
113. Perrone, M.A.; Aimo, A.; Bernardini, S.; Clerico, A. Inflammageing and Cardiovascular System: Focus on Cardiokines and Cardiac-Specific Biomarkers. *Int. J. Mol. Sci.* **2023**, *24*, 844. [[CrossRef](#)]
114. Hampel, H.; Caraci, F.; Cuello, A.C.; Caruso, G.; Nistico, R.; Corbo, M.; Baldacci, F.; Toschi, N.; Garaci, F.; Chiesa, P.A.; et al. A Path Toward Precision Medicine for Neuroinflammatory Mechanisms in Alzheimer’s Disease. *Front. Immunol.* **2020**, *11*, 456. [[CrossRef](#)] [[PubMed](#)]
115. Su, C.; Zhao, K.; Xia, H.; Xu, Y. Peripheral inflammatory biomarkers in Alzheimer’s disease and mild cognitive impairment: A systematic review and meta-analysis. *Psychogeriatrics* **2019**, *19*, 300–309. [[CrossRef](#)] [[PubMed](#)]
116. Traub, J.; Otto, M.; Sell, R.; Gopfert, D.; Homola, G.; Steinacker, P.; Oeckl, P.; Morbach, C.; Frantz, S.; Pham, M.; et al. Serum phosphorylated tau protein 181 and neurofilament light chain in cognitively impaired heart failure patients. *Alzheimers Res. Ther.* **2022**, *14*, 149. [[CrossRef](#)] [[PubMed](#)]

117. Traub, J.; Otto, M.; Sell, R.; Homola, G.A.; Steinacker, P.; Oeckl, P.; Morbach, C.; Frantz, S.; Pham, M.; Stork, S.; et al. Serum glial fibrillary acidic protein indicates memory impairment in patients with chronic heart failure. *ESC Heart Fail.* **2022**, *9*, 2626–2634. [[CrossRef](#)] [[PubMed](#)]
118. Traub, J.; Grondy, K.; Gassenmaier, T.; Schmitt, D.; Fette, G.; Frantz, S.; Boivin-Jahns, V.; Jahns, R.; Stork, S.; Stoll, G.; et al. Sustained Increase in Serum Glial Fibrillary Acidic Protein after First ST-Elevation Myocardial Infarction. *Int. J. Mol. Sci.* **2022**, *23*, 10304. [[CrossRef](#)] [[PubMed](#)]
119. Jackson, L.; Eldahshan, W.; Fagan, S.C.; Ergul, A. Within the Brain: The Renin Angiotensin System. *Int. J. Mol. Sci.* **2018**, *19*, 876. [[CrossRef](#)] [[PubMed](#)]
120. Fu, W.Y.; Wang, X.; Ip, N.Y. Targeting Neuroinflammation as a Therapeutic Strategy for Alzheimer’s Disease: Mechanisms, Drug Candidates, and New Opportunities. *ACS Chem. Neurosci.* **2019**, *10*, 872–879. [[CrossRef](#)] [[PubMed](#)]
121. Budni, J.; Garcez, M.L.; de Medeiros, J.; Cassaro, E.; Bellettini-Santos, T.; Mina, F.; Quevedo, J. The Anti-Inflammatory Role of Minocycline in Alzheimer’s Disease. *Curr. Alzheimer Res.* **2016**, *13*, 1319–1329. [[CrossRef](#)]
122. Seabrook, T.J.; Jiang, L.; Maier, M.; Lemere, C.A. Minocycline affects microglia activation, Abeta deposition, and behavior in APP-tg mice. *Glia* **2006**, *53*, 776–782. [[CrossRef](#)]
123. Choi, Y.; Kim, H.S.; Shin, K.Y.; Kim, E.M.; Kim, M.; Kim, H.S.; Park, C.H.; Jeong, Y.H.; Yoo, J.; Lee, J.P.; et al. Minocycline attenuates neuronal cell death and improves cognitive impairment in Alzheimer’s disease models. *Neuropsychopharmacology* **2007**, *32*, 2393–2404. [[CrossRef](#)] [[PubMed](#)]
124. Zhang, X.W.; Feng, N.; Liu, Y.C.; Guo, Q.; Wang, J.K.; Bai, Y.Z.; Ye, X.M.; Yang, Z.; Yang, H.; Liu, Y.; et al. Neuroinflammation inhibition by small-molecule targeting USP7 noncatalytic domain for neurodegenerative disease therapy. *Sci. Adv.* **2022**, *8*, eabo0789. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.