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Review

Complement therapeutics in neurodegenerative diseases☆

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ABSTRACT

Neurodegenerative diseases (NDDs) such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis pose considerable therapeutic challenges, not only due to their complex pathophysiology, but also because any effective drug must be capable of penetrating the brain. Inflammation is a key feature of NDDs. Increasingly, the complement system, long studied in the context of host defence, has emerged as a central player in the brain, with roles extending far beyond its classical immune functions. Complement contributes to synaptic pruning and immune surveillance, but when dysregulated, it can drive chronic inflammation, synapse loss, and neurodegeneration. Complement is also implicated in neurodevelopmental and neuropsychiatric diseases, including schizophrenia and mood disorders, where overactivation of the cascade impacts brain maturation and circuit stability. In this review, we take a broad view of roles of the complement system in both health and disease in the central nervous system (CNS). We summarise key mechanisms through which complement contributes to pathology, discuss emerging therapeutic strategies, and consider major hurdles in CNS drug development, including brain delivery and the need for patient stratification. As our understanding of the pathological roles of the complement system in the brain advances, it is becoming clear that complement therapeutics may offer a novel approach in slowing neurodegeneration, and in addressing a broader spectrum of disorders affecting the brain.

1. Introduction

1.1. Introduction to the complement system

Complement is an ancient part of the innate immune system, with evolutionary origins dating back ~700 million years, long predating the evolution of the adaptive immune system. An ancestral complement system persists in early metazoans such as cnidarians comprising a C3-like opsonin and activation proteases including Factor B (FB)-like and MASP-like enzymes (Nonaka, 2014; Elvington et al., 2016). Complement in mammals consists of >40 plasma and cell-bound proteins, receptors and regulators collectively accounting for ~5% of total plasma protein content (Zelek et al., 2019a, 2019b). The system serves as a powerful tool for combating bacterial and viral infections (Heesterbeek et al., 2018; Agrawal et al., 2020); however, when dysregulated, it can drive pathology in various diseases (Ricklin and Lambris, 2013), including rheumatoid arthritis (RA), age-related macular degeneration (AMD), Alzheimer's disease, (AD) and many more including neurodegenerative diseases (NDDs; Fig. 1). In the brain, as in other organs, complement plays a key role in development, immune surveillance, cellular signalling networks impacting neuronal survival, metabolism, and facilitating rapid clearance of dead cells and debris (Parker et al., 2022; Bohlson and Tenner, 2023; Daskoulidou et al., 2025; Nimmo et al., 2024).

It is now very clear that C1q and C3 are critical for synaptic pruning during early development, a tightly regulated process essential for neural circuit refinement. However, dysregulation of this process has been implicated in neuropsychiatric disorders as well as pathological synapse loss in ageing and neurodegeneration. While complement protein entry from the bloodstream is tightly regulated by the blood brain barrier (BBB) in a healthy state (Barnum, 1995), some complement proteins can be produced locally in the CNS. Since both brain and systemic inflammation are linked to neurodegeneration, disruptions in complement activity outside the brain must also be considered as contributing to the progression of NDDs (Perry and Teeling, 2013; Tejera et al., 2019).

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1.2. The complement activation pathways, regulators and receptors.

Complement activation is triggered by binding of the initiating proteins to pathogens, damaged cells, or abnormal self-surfaces. These initiate enzymatic cascades in the three activation pathways: the classical pathway (CP), the lectin pathway (LP), and the alternative pathway (AP). The CP is activated when the pattern recognition molecule (PRM) C1q in the C1 complex binds to antibody-antigen complexes, misfolded proteins (e.g. beta-sheet amyloid-beta (Aβ) fibrils, hyperphosphorylated tau (p-tau), α Synuclein (αSyn), TDP-43)), or apoptotic cells, tagging them for clearance (Fig. 2). The diverse PRMs of the LP bind microbial carbohydrates. For both classical and lectin pathways, PRM-associated proteases (C1r/s for CP, MASPs for LP) are activated and sequentially cleave components C4 and C2. C4 cleavage exposes a highly reactive yet ephemeral thioester in the C4b fragment that covalently links to hydroxyl or amino groups on the activation surface. Immobilised C4b then

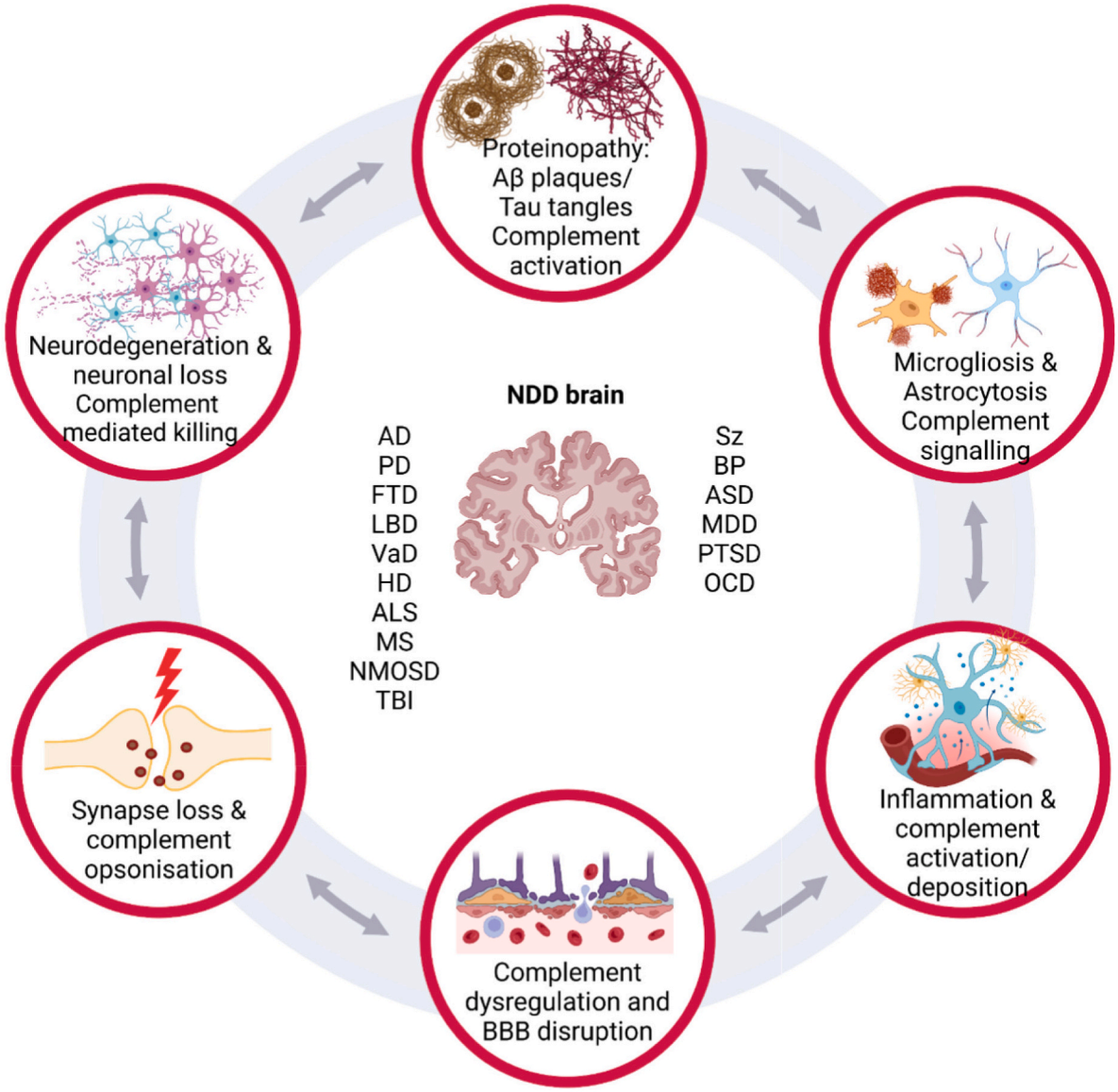


Fig. 1. Pathological cycle of complement-mediated neurodegeneration. A key pathological process and list of neurodegenerative diseases (NDDs) and neuropsychiatric diseases (NPDs) in which complement is implicated. The accumulation of amyloid-β (Aβ) plaques and tau tangles initiates complement activation, leading to chronic neuroinflammation. Microglia and astrocytes, responding to complement signalling (e.g. CR1, CR3, Ca5R), further amplify inflammatory cascades, resulting in excessive C1q, C3, and C5b-9 (membrane attack complex, MAC) deposition on glial cells and synapses. This complement-driven inflammation contributes to blood-brain barrier (BBB) dysfunction, increasing vascular permeability and allowing peripheral immune components to infiltrate the central nervous system (CNS). As a result, synaptic loss occurs through complement opsonisation, where C1q and C3 tag synapses for elimination by microglia, a mechanism defined in Alzheimer's (AD), and Schizophrenia (Sz). Persistent complement activation exacerbates neuronal loss through direct MAC-lytic properties and release of C3a, C5a anaphylatoxins. This self-perpetuating cycle of complement overactivation, neuroinflammation, synaptic elimination, BBB disruption, and neuronal injury is a central mechanism underlying neurodegenerative, neuroinflammatory, and neuropsychiatric diseases, including AD, PD, HD, MS, ALS, FTD, LBD, VaD, PDD, NMO, GBS, Sz, MDD, BD, ASD, and PTSD. *Abbreviations:* Aβ, amyloid-β; AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ASD, autism spectrum disorder; BBB, blood-brain barrier; BD, bipolar disorder; CNS, central nervous FTD, frontotemporal dementia; system; GBS, Guillain-Barré syndrome; HD, Huntington's disease; MDD, major depressive disorder; MS, multiple sclerosis; LBD, Lewy body dementia; VaD, vascular dementia; MAC, membrane attack complex; NMOSD, neuromyelitis optica spectrum disorder; PD, Parkinson's disease; PTSD, post-traumatic stress disorder; TBI, traumatic brain injury; schizophrenia (Sz); NDDs, neurodegenerative diseases. Figure created with BioRender (BioRender.com).

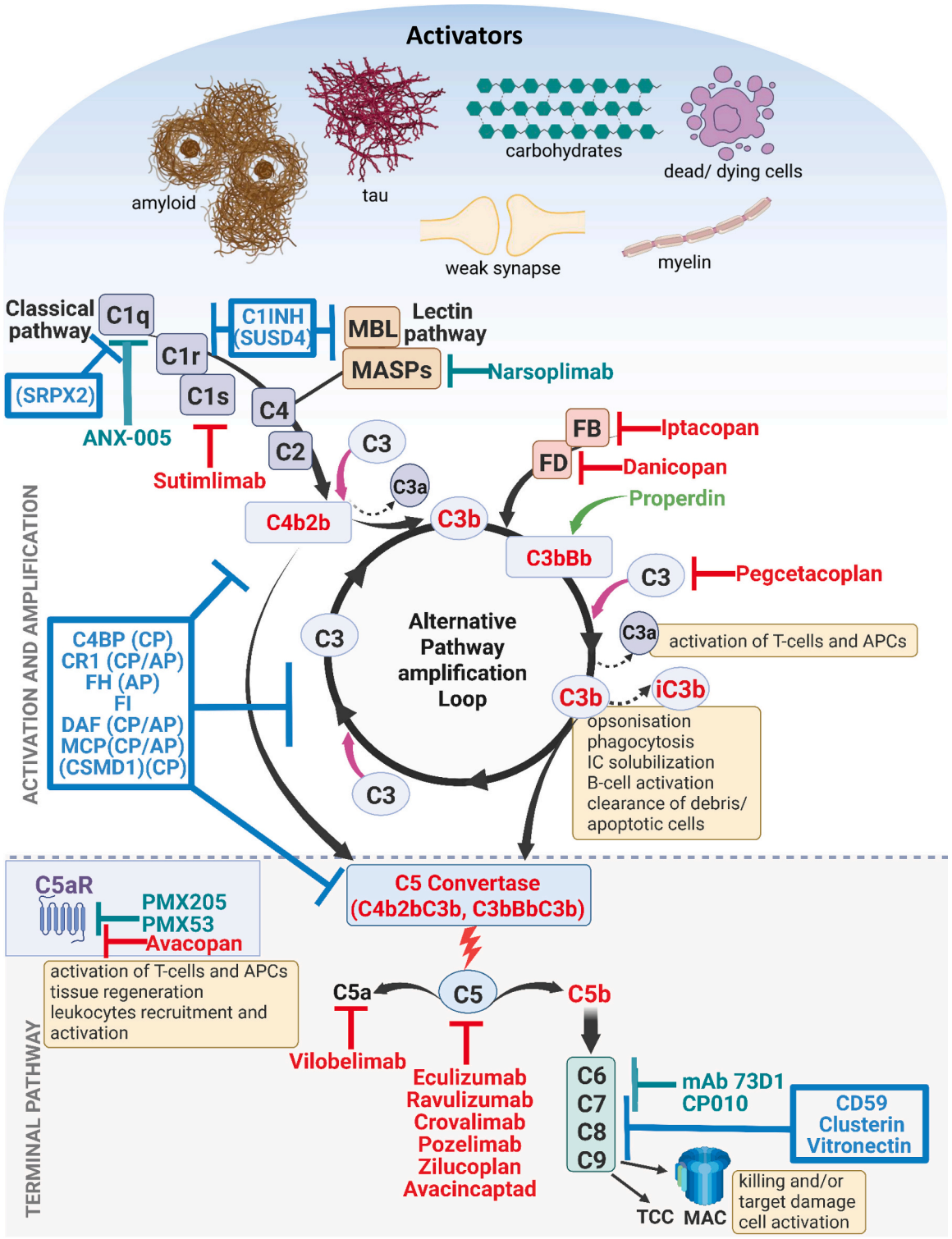


Fig. 2. The complement cascade and complement drugs in clinics. The complement system is activated via the classical (CP), lectin (LP), and alternative pathway (AP; also known as alternative loop), converging at C3 cleavage to amplify the response and drive downstream effector functions. The CP is initiated by C1q binding to immune complexes, leading to C1r/C1s activation and cleavage of C4 and C2 to form the C3 convertase (C4b2b; historical C4b2a). The LP is activated by mannose-binding lectin (MBL) or ficolins, which recruit MASPs (Mannan-binding lectin-associated serine proteases) to cleave C4 and C2. The AP is a feedback loop where C3b binds factor B (FB), which is cleaved by factor D (FD) to form C3bBb, amplifying complement activation. C3 convertases cleave C3 into C3b and C3a, where C3b functions as an opsonin and contributes to C5 convertase formation (C4b2aC3b or C3bBbC3b). The C5 convertase cleaves C5 into C5a and C5b, initiating the terminal pathway (TP), leading to membrane attack complex (MAC) formation via Cb6, C7, C8 and C9. The lytic pore formed kills cells by lysis. C5a is a potent inflammatory mediator that binds C5aR1 to drive immune cell recruitment. FDA-approved complement inhibitors are highlighted in red, targeting C1s (sutimlimab), C3 (pegcetacoplan), FB (iptacopan), FD (danicopan), C5 (eculizumab, ravulizumab, zilucoplan, avacincaptad, crovalimab, pozelimab), C5a (vilobelimab), and C5aR1 (avacopan). In the CNS, preclinical and clinical-stage inhibitors are also shown in green, targeting different complement components, including C1q (ANX-005), MASP-2 (narsoplimab), MAC formation (mAb 73D1, CP010), and C5aR1 (PMX205, PMX53). Putative complement regulators shown in green are enclosed in brackets. Figure created with BioRender (BioRender.com).

binds C2 and presents it for cleavage to generate a protease complex on the target surface, the CP/LP C3-convertase C4b2b (historically known as C4b2a). This in turn binds and cleaves many copies of the protein C3, releasing the small anaphylactic fragment C3a and exposing a thioester in the large C3b fragment that enables C3b to covalently link (as with C4b) to surface hydroxyl or amino groups to coat the activating surface, a process termed opsonisation. To trigger the AP, C3b binds the protease FB, enabling cleavage of FB by the enzyme FD to generate the AP C3-convertase (C3bBb) which cleaves more C3 into C3b and C3a, feeding the amplification loop for C3b deposition. High C3b density on the activating surface modifies substrate selectivity of the convertases enabling cleavage of C5 by enzymes now termed C5 convertases (C4b2bC3b; C3bBbC3b), yielding C5a, a potent pro-inflammatory mediator that recruits immune cells and amplifies inflammation, and C5b, which serves as the nidus for the assembly of the membrane attack complex (MAC). Unlike C3b and C4b, C5b does not covalently bind to surfaces but instead associates with C6 and C7 to form a membrane-associated complex that recruits C8 and multiple copies of C9 to assemble the lytic MAC pore (Fig. 2). In addition to lysing membranes, MAC interaction with host cells is highly pro-inflammatory, resulting in activation of the NLRP3 inflammasome, triggering the release of pro-inflammatory cytokines and fuelling the inflammatory cascade (Morgan, 2015; Triantafilou et al., 2013; Towner et al., 2016).

The complement cascade is precisely regulated at several key checkpoints along its progression. C1 inhibitor (C1-inh) is a well-characterised inhibitor of both the CP and LP by targeting activated C1r and C1s, as well as MASP-1 and MASP-2 (Noris and Remuzzi, 2013). Complement receptor 1 (CR1) plays a dual regulatory role by facilitating the clearance of opsonised debris and immune complexes while also accelerating the decay of C3 and C5 convertases. These convertases are also downregulated on membranes by the action of decay-accelerating factor (DAF; CD55) and membrane cofactor protein (MCP; CD46). DAF promotes the dissociation (decay) of C3/C5 convertases, while MCP acts a cofactor for factor I (FI)-mediated cleavage of C3b and C4b to iC3b and iC4b which can no longer participate as C3 or C5 convertases. In the fluid-phase, C4BP and FH regulate convertases in the CP and AP respectively. Properdin is the only positive regulator of the cascade, stabilising the C3bBb complex to prolong its activity. CD59, Clusterin (Clu), and Vitronectin are negative regulators of MAC formation on membranes and in fluid phase respectively, preventing polymerisation of C9 and MAC assembly (Bajic et al., 2015).

Fragments of complement proteins generated during activation have important roles in cell signalling. C3a and C5a exert diverse immunomodulatory effects through their respective receptors C3aR, C5aR1, and C5aR2, influencing both inflammation and protection (Klos et al., 2009). Traditionally, C3a has been considered as a powerful inflammatory mediator enhancing the expression of proinflammatory cytokines (IL-1β, and TNFα) and promoting T cell responses and proliferation through Treg suppression (Banda et al., 2012; Coulthard and Woodruff, 2015). However, recent reports have challenged this strict pro-inflammatory classification, revealing anti-inflammatory and neuroprotective roles of C3a (Pozo-Rodrigálvarez et al., 2021a, 2021b; Stokowska et al., 2023; Brennan et al., 2019). By contrast, C5a is a potent pro-inflammatory effector through interaction with C5aR1 that amplifies T cell proliferation, neutrophil recruitment, and cytokine upregulation, making it a key driver of inflammatory responses (Wang et al., 2015; Miyabe et al., 2017; Li et al., 2019; Mastellos et al., 2024). Though less well studied, C5aR2 is considered to be anti-inflammatory even beyond acting as a scavenger for C5a (Li et al., 2021a, 2021b; Biggins et al., 2017).

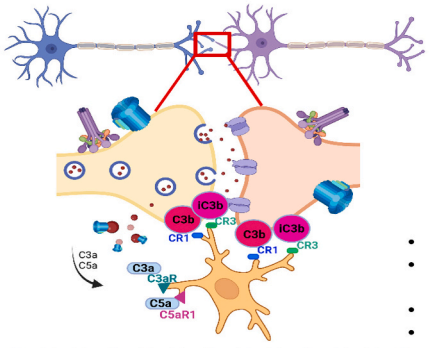
1.3. NDDs and complement system involvement.

Despite the clear roles of complement in immunosurveillance in other organs, less is known about roles of complement in brain homeostasis. Of the complement pathways, the CP is most prominently implicated in brain function and pathology. Synapse elimination mediated by C1 binding to synapses triggering C3b/C4b deposition for opsonisation is crucial in neurodevelopment and is also implicated in the excessive synaptic pruning observed in AD and other NDDs (reviewed in Tenner et al., 2018; Bohlson and Tenner, 2023; Nimmo et al., 2024). C3b/iC3b interaction with microglial complement receptors 1 (CR1; CD35), 3 (CR3; CD11b/CD18) and 4 (CR4; CD11c/CD18) enable phagocytic elimination of synapses and debris. The gene encoding *CR1* has been identified as one of the top five genetic risk factors for AD (Karch and Goate, 2015; Daskoulidou et al., 2023) highlighting its potential involvement in pathology. In AD, CP activation is evident, while amplification via the alternative pathway also contributes to chronic inflammation (Morgan, 2015). The anaphylatoxins C3a and C5a play important roles in microglia function. Effects of C3a in the brain are highly context-dependent and influenced by environment, adjacent cells and their receptor expression (Coulthard and Woodruff, 2015). C5a, a robust amplifier of inflammation in the brain, has been implicated in microglial activation, BBB disruption, and neuronal damage, (Fig. 1, Fig. 3, Woodruff et al., 2010). In ALS, complement activation involves both CP and AP, with elevated C5 activation fragments linked to disease progression (Woodruff et al., 2008; Paganoni et al., 2025). Together, C3a and C5a represent key complement-derived signals that shape neuroimmune interactions. MAC also contributes to synapse loss by causing microlysis at the synapse (Carpanini et al., 2022) (Fig. 3A). Clu (Apolipoprotein J), a fluid-phase MAC negative regulator, binds MAC precursor complexes (C5b-7, C5b-8), preventing MAC assembly (Morgan et al., 2017). The gene encoding *CLU* has also been identified as a top genetic risk factor for AD with Clu implicated in amyloid clearance and aggregation (Foster et al., 2019; Milinkeviciute and Green, 2023). SRPX2 (Sushi Repeat-Containing Protein X-Linked 2), and SUSD2/4 (Sushi Domain-Containing proteins 2 and 4) are brain-expressed putative complement regulators. Knockout of the latter in mice caused impaired cognition and excessive synaptic pruning with synaptic deposition of C1q and C3 (Baum et al., 2024), while mutations in *SRPX2* are linked to dyspraxia and epilepsy, suggesting a role in neurodevelopment (Roll et al., 2006; Cong et al., 2020; González-Calvo et al., 2022). Genetic studies have also linked variants in the brain-expressed complement regulator CSMD1 to an increased risk of schizophrenia (Sz), where complement-driven synaptic pruning is apparent (Donohoe et al., 2013). In Sz, elevated complement expression in the brain and altered systemic markers in plasma have been reported (Kopczynska et al., 2019; Mongan et al., 2020; Druart et al., 2021; Gracias et al., 2022). Notably, C4A isotype overexpression has been linked to excessive synapse elimination during adolescence, a critical period for neural circuit refinement that may contribute to disease onset (Yilmaz et al., 2021). In HD, evidence suggests CP involvement, with elevated C1q and downstream components in affected brain regions and CSF (Dalrymple et al., 2007; NCT04514367). Complement dysregulation for many years was considered as secondary consequence of neurodegeneration. However, it is now recognised as a primary driver of NDDs and an emerging mechanism in neuropsychiatric diseases (NPDs) (Fig. 1). While the CP in the brain has received most attention, the contributions of the other pathways: LP, AP, and TP is poorly understood. Further research is needed to delineate how these pathways operate, particularly in the contexts of brain development, healthy ageing, and neurodegeneration.

1.4. Beyond immunity: the emerging roles of intracellular complement.

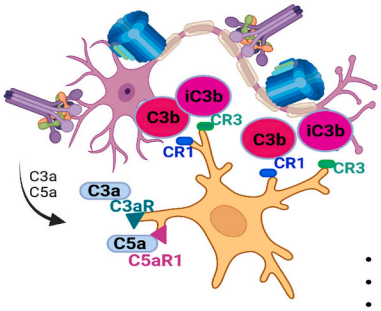
While traditionally considered as an extracellular immune system, recent reports suggest complement also has intracellular functions. These studies describe intracellular cleavage of C3 and C5, generating active fragments with potential non-canonical roles. For instance, cathepsin L-mediated cleavage of C3 within T cell organelles produce C3a-like and C3b-like products that may interact with complement receptors (O'Brien et al., 2023). The precise roles of intracellular complement and how important they are for regulating cells is unknown although a recent review has summarised potential roles in regulating

A: Synapse loss (complement activation on synapses)



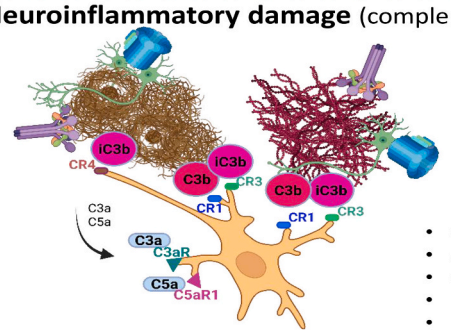
- C1q tagging low activity or damaged synapses
- C3b/iC3b – tagging synapses for removal by microglia via CR3, and/or CR1, CR4
- C3a/ C5a release
- MAC mediated synaptic microlysis

B: Gliopathy (complement activation on glial cells)



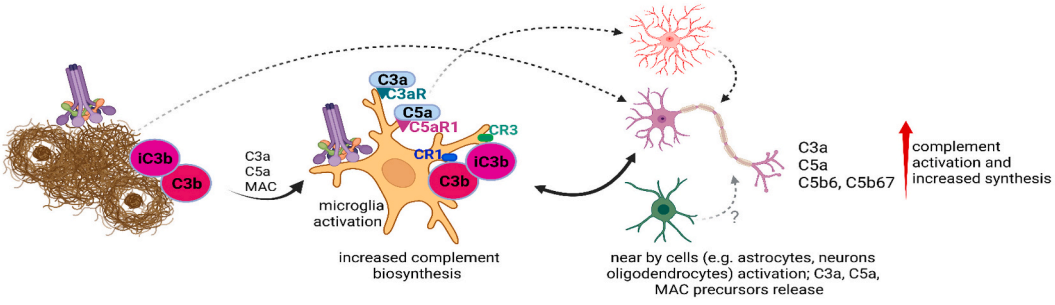
- Complement activation generated C3a and C5a
- Induction of microglial disease enhancing genes/pathways
- MAC mediated NLRP3 inflammasome activation
- Generation of neurotoxic mediators

C: Neuroinflammatory damage (complement activation by neuroaggregates)



- C3b/iC3b - excessive undesirable opsonisation
- activating microglia via CR3, and/or CR1, CR4
- C3a/ C5a release
- Damage to adjacent cells including neurons
- MAC mediated lysis/ NLRP3 inflammasome activation

D: Cross-cellular damage (activated complement facilitates cross talk with neurons and glia)



- Complement biosynthesis increases
- Increased generation of C3a, C5a, and MAC precursors (C5b6, C5b67) mediating bystander lysis

(caption on next page)

Fig. 3. Complement-mediated neurodegeneration: Synapse Elimination, Inflammation, and Cell Dysfunction. A; In the healthy brain, complement helps eliminate excess synapses during development. However, in neurodegenerative conditions, aberrant C1q and C3b deposition on synapses leads to excessive phagocytosis by microglia likely via CR1 and CR3. Upon activation of the terminal pathway MAC formation on synaptic membranes and synaptic vesicles occurs, causing structural damage and further driving synaptic dysfunction.
B/C; Complement activates by binding to misfolded neuroaggregates (Aβ, tau, αSyn, TDP-43) triggering microglial reactivity. C3b/iC3b opsonisation enhance the clearance of both damaged and functionally intact neuronal structures, propagating a feedforward cycle of neuroinflammation. MAC formation on glial cells leads to cytotoxicity and neuronal death but also release of NLRP3 inflammasome amplifying inflammatory responses exacerbating gliosis, oxidative stress, and neuronal dysfunction. Further amplifying neuroinflammation, C3a and C5a anaphylatoxins are released, acting on their respective receptors (C3aR, C5aR1) to drive microglial activation and inflammatory cytokine production. **D;** Accumulation of neurotoxic aggregates (e.g. Aβ, tau, αSyn, TDP-43) likely accelerates disease progression by driving excessive complement activation. Plaques and pathological inclusions become coated with complement proteins; C3b/iC3b and MAC. As complement expression increases, MAC precursors (C5b-7, C5b-8) can embed into the membranes of adjacent neurons and glial cells, predisposing them to terminal MAC assembly and lysis. The complement activation leads to release of C3a and C5a anaphylatoxins, binding to their respective receptors (C3aR, C5aR1) on microglia and astrocytes, further amplifying pro-inflammatory signalling activating the cytokine storm. This persistent activation induces a phenotypic shift in subsets of astrocytes and microglia from a homeostatic to a reactive, neurotoxic state, exacerbating synaptic loss and neuronal damage. NLRP3 inflammasome activation triggered in microglia and astrocytes, promoting the release of IL-1β and other pro-inflammatory mediators, reinforcing a self-destructing mechanism. Figure created with BioRender (BioRender.com).

metabolism, mitochondrial function, and stress responses (Negro-Demontel et al., 2024). Notably, whether intracellular complement expression occurs within specific brain cell compartments has not been explored, leaving a critical gap in our understanding of potential intracellular roles of complement in neurodegeneration and neuroinflammation.

1.5. Context and overview.

The below reviewed lines of evidence demonstrate that complement dysregulation drives key pathological processes in the brain, including synaptic loss, myelin degradation, neuroinflammation, and neuronal death, that contribute to the progression of NDDs (Singhrao et al., 1999; Fagan et al., 2017; Loeffler et al., 2006; Britschgi et al., 2012; Ingram et al., 2012; Hakobyan et al., 2016; Wu et al., 2019a, 2019b; Werneburg et al., 2020; Bellenguez et al., 2022; Naskar et al., 2022; van der Ende et al., 2022; Wilton et al., 2023; Yu et al., 2023a, 2023b; Kodosaki et al., 2024). Emerging evidence implicates complement dysregulation in diverse neuropsychiatric and neurodevelopmental disorders (Hovhannisyan et al., 2010; Rooryck et al., 2011; Lin et al., 2016; Gorelik et al., 2017; Fegan Sasaguri et al., 2017; Trubetskoy et al., 2022; Sekar et al., 2016; Cao et al., 2023; D'Acquisto et al., 2023; Lee et al., 2024; Sun et al., 2024; Gallwitz et al., 2024). In the NDDs, misfolded proteins, such as Aβ, tau, α Synuclein (αSyn), TDP-43, likely trigger complement activation, recruiting and activating microglia that exacerbate synaptic loss and chronic inflammation, leading to neuronal death and BBB disruption, further propagating neuroinflammatory damage (Fig. 2, Fig. 3) (Eikelenboom and Stam, 1982; Fatoba et al., 2022). In this review we will provide a comprehensive overview of complement dysregulation in neurodegeneration, and the potential for using complement-targeting drugs, summarising:

- Animal models used to study neurodegenerative diseases and complement system (Section 2)
- Complement biosynthesis in the brain (Section 3).
- The roles of the complement system in homeostasis and neurodevelopment (Section 4)
- Mechanistic pathways through which complement contributes to neurodegeneration (Section 5),
- Therapeutic approaches targeting complement in NNDs (Sections 6–7).

2. Animal models used to study neurodegenerative diseases and complement system.

Patient-derived iPSC cells can now be differentiated to various cell types, often retaining disease and age-related changes (Guttikonda et al., 2021; McQuade and Blurton-Jones, 2022; Sun et al., 2023; Minhas et al., 2024). This enables defined biochemical and molecular comparisons between controls and affected cells. However, many critical phenotypic and functional parameters such as cognitive behavior and motor skills require *in vivo* animal models. Transgenic mice have been, by far, the most widely used animal models to study neurodegenerative diseases. Initially combined with genetic knockouts of various complement components, receptors and regulators (such as C1q, C3, C4, CR3, C5aR1, C6), substantial evidence for roles for complement in disease progression accumulated, some of which is more fully described below. In the last 10-15 years, technical advances have enabled the construction of "knock-in" mice with humanized proteins expressed under endogenous promoters, and thus produced under physiologic regulation ((Sasaguri et al., 2017; Oblak et al., 2020; Carpanini et al., 2022), avoiding overexpression and induction of synthesis in inappropriate cell types or in a sex-linked manner due to the differential induction of the artificial promoter (such a Thy-1 in the commonly used 5xFAD mice). Furthermore, CRISPR technology has also enabled the generation of animals with disease associated allelic variants identified in human GWAS studies that can access effects on pathological and importantly functional changes of those variants. A 2024 comprehensive review of common models of Alzheimer's disease provides a summary of the pros and cons of many of these models, including some comparisons of molecular signatures from these models with those obtained from human AD brain (Zhong et al., 2024). [Newer models of late onset Alzheimer disease can be obtained from Jackson Laboratories and are free of any intellectual property constraints (Oblak et al., 2020; Xia et al., 2022). Information and initial omics characterization of a number of these new models can be found at the MODEL-AD portal (https://www.model-ad.org).] Now conditional- and even cell type specific- deletion of complement genes in these mouse models is adding valuable insights into the functional pathways induced by specific complement components and activities *in vivo,* avoiding the inherent caveats of complement deficiency during development (Fonseca et al., 2017; Batista et al., 2024; Schulz and Trendelenburg, 2022; Scott-Hewitt et al., 2024). In addition, overexpression of complement regulatory proteins (CD55, CD59; Morgan et al., 2006) and treatment with candidate complement inhibitors (Wang et al., 2020; Mallah et al., 2021) to study therapeutic potential are critical preclinical studies to facilitate the translation from laboratory-based biochemical and molecular mechanisms to clinical trials for vulnerable patient populations.

As will be noted below, there are established rodent and non-human primate models for other NDD in which contributions of complement have been investigated. Rodent models include MPTP-induced, 6-OHDA-induced, and α-syn transgenic models for Parkinson's disease (PD), the Huntington's disease (HD) models R6/2 and Q175 (Wilton et al., 2023; Creus-Muncunill et al., 2024), and SOD1 and TDP-43 transgenic mice for amyotrophic lateral sclerosis (ALS; Lee et al., 2017; Lee et al., 2018) and multiple models of tauopathy (Dejanovic et al., 2018; Litvinchuk et al., 2018; Wu et al., 2019a, 2019b; Audrain et al., 2019).

In non-human primates, models include MPTP-induced PD in monkeys and AD in marmosets and macaques (Depboylu et al., 2011; Datta et al., 2020; Sukoff-Rizzo et al., 2023). While these later are closer to human physiology and behavior, they require much longer study times due to lifespan. Nevertheless, they represent an investment to identify primate-specific etiologies in these complex disorders. All of these models, even though they do not fully replicate human pathologies and dysfunction, help investigate disease mechanisms, test potential therapies, assess biomarker identification and understand the role of the complement system in neurodegeneration.

3. Complement biosynthesis in the brain.

As focus expands beyond complement activities in blood, reports of complement biosynthesis in tissues have increased rapidly (Song et al., 1998; Peake et al., 1999; Springall et al., 2001). New RNA-sequencing technologies have enabled definitive identification of the sources of complement in tissues, beyond the liver and myeloid compartments, including brain. The integrity of the BBB and the tightly controlled component specific synthesis in the brain enables selective control of specific complement-mediated functions "as needed". As during development (Jeanes et al., 2015), in postnatal and adult brain synthesis of individual complement components is under distinct transcriptional control influenced by various inflammatory stimuli, cytokines (e.g., IL-1β, TNF-α, IFN-γ), age, and pathological conditions (e.g., infection, injury, NDDs) (Tenner and Petrisko, 2025). The early upregulation of C1q in response to injury promotes the clearance of cellular debris and apoptotic cells while avoiding downstream induction of inflammation. As neuronal injury or insult increases, the other components of the classical pathway (C1r, C1s, C4, C2, and C3 well as the phagocytic receptor CR3) are induced resulting in the elimination of weak or dysfunctional synapses (Hong et al., 2016). The anaphylactic receptors, C5aR1 and C3aR, are also upregulated in response to injury (Hernandez et al., 2017a, 2017b; Carvalho et al., 2022) and thus are poised to respond to challenges when the rest of the pathway is induced and activated.

While the critical enhancer elements at the DNA level remain to be determined, synthesis of complement proteins are produced in diverse CNS cells and in many cases separate induction factors. For example, C1q, which in one mouse model of AD was shown to be dependent on the expression of the common variant for TREM2 (triggering receptor expressed on myeloid cells 2; Rueda-Carrasco et al., 2023), is predominantly expressed in microglia (Fonseca et al., 2017; Scott-Hewitt et al., 2024), while C3 is dramatically upregulated in astrocytes (Nitkiewicz et al., 2017; Wu et al., 2019a, 2019b) and C4 is independently induced in astrocytes and oligodendrocytes (Zhou et al., 2020; Panitch et al., 2021) with aging and in NDD. Data on the temporal regulation of complement synthesis in mouse brain disease models are not extensive, but lifespan (Stephan et al., 2013; Shi et al., 2015) and disease induced synthesis is consistent with stepwise controlled induction of these components (Benoit et al., 2013; Shi et al., 2017; Wu et al., 2019a, 2019b; Schartz et al., 2024). Neurons produce a plethora of complement regulators, some being specific to certain brain regions and developmental stages. These include inhibitors of CP activation (Fig. 2) SRPX2 (Cong et al., 2020), SUSD4 (Zhu et al., 2020), the family of CSMD proteins (Gialeli et al., 2018, 2021; Ruiz-Martinez et al., 2017; Athanasiu et al., 2017; Baum et al., 2024, Byrne et al., 2025), neuropentraxin 1 and 2 (Kovács et al., 2021; Zhou et al., 2023a, 2023b) that regulate synaptic pruning. Clusterin (Gregory et al., 2020) and the membrane associated CD55 and CD59 (Morgan et al., 2005; Van et al., 2005; Cole et al., 2006) are also important to protect against MAC-induced lysis and "microlysis" (Morgan et al., 2005, 2016; Carpanini et al., 2022), protection essential for post-mitotic cells. While there is clear functional evidence of the presence of C1r, C1s, C2 (required for cleavage of C3 for synaptic pruning), transcript levels for these and the terminal complement pathway proteins in brain are quite low, though reported in MS and AD patient samples (Absinta et al., 2021; Brase et al., 2023). C5 transcripts have been detected again at low levels in neurons and astrocytes in mouse models (Schartz et al., 2024; (Ximerakis et al., 2019; Absinta et al., 2021; Holden et al., 2021). Local control of C5 production is quite important, as complement activation could generate the C5 convertases that in presence of C5 would produce the proinflammatory C5a fragment as well as C5b, the initiator of the MAC. Thus, normal homeostatic pruning and/or attempts to clear aggregates or cell debris could be converted into a neurotoxic process (Gomez-Arboledas et al., 2024) by the inflammatory action of C5a via C5aR1, the generation of the C5b-9/MAC at the synapse (Carpanini et al., 2022) and/or neuronal surface or both (Fig. 3). As single cell and single nuclei RNA-sequencing and spatial transcriptomics technologies enable increased sensitivity and sequencing depth, induction of complement components will be temporally and regionally verified, including in human brain samples. The cellular site of synthesis could be advantageous when therapeutically targeting specific complement components or their regulators to help modulate neuroinflammation and neuroprotection (Wang et al., 2024).

C3aR and C5aR1, in addition to being expressed on microglia (and in some contexts, astrocytes and neurons (Pavlovski et al., 2012)) early in response to challenge, are also upregulated in brain vascular endothelial cells (Jacob and Alexander, 2014; Propson et al., 2021). Global deletion of C3aR in the PS19 tauopathy mouse model suppressed an inflammatory endothelial phenotype and tau pathology (Litvinchuk et al., 2018). Increased C5aR1 expression on brain endothelial cells has been observed in various neurological disorders, including multiple sclerosis (MS), AD, and stroke (Schartz and Tenner, 2020). This upregulation may contribute to disease progression by promoting inflammation and BBB disruption in brain aging and disease.

It is important to note that cell-associated immunohistochemical detection of complement proteins does not always equate with the cell source of that component. For example, it was shown that C1q detected within neurons in mouse brain was ablated with microglial specific deletion of C1qa. The authors demonstrated that C1q, synthesized by microglia, was secreted and then ingested by neurons (Scott-Hewitt et al., 2024). C1qa is the gene for one of the 3 separate chains that encode the protein C1q which is a hexamer of trimers (A,B,C chains) held together by disulfide bonds (460,000 Da). The genes for all 3 C1q chains are co-ordinately expressed at the transcriptional level, but the absence of any one of the chains – i.e. the A chain product coded for by C1qa, results in the complete absence of the protein even though some transcripts of C1qb and C1qc are seen in the absence of C1qa mRNA (Fonseca et al., 2017).

4. The roles of the complement system in homeostasis and neurodevelopment.

As noted above, the complement system is an ancient system. It is known to be critical for defense against extracellular pathogens and also for safe removal of immune complexes (Ricklin et al., 2010). However, complement also participates in the rapid clearance of cell debris, directs and modulates the adaptive immune system (Reis et al., 2019; Lo and Woodruff, 2020) and responds to tissue damage (Huber-Lang et al., 2018). Continuing investigations have uncovered multiple additional functions in homeostasis, apoptotic cell removal, tumor biology and metastasis, intracellular metabolism, neurodevelopment and synaptic pruning (Stevens et al., 2007; Gorelik et al., 2017; Reis et al., 2018, Reis et al., 2019; Tenner et al., 2018; West et al., 2020; West and Kemper, 2023; King and Blom, 2024). Absence of these activities mediated by specific complement components or activation-generated products result in pathology and dysfunction.

C1q is one of the first genes to be induced in response to tissue injury, including in the CNS as mentioned above. While at times unclearly written, it is important to realize that C1q alone cannot be "activated" as it is not an enzyme, and that C1q alone cannot activate the CP. C1q must

be in complex with C1r and C1s which are the proenzymes, that become activated and then cleave the next components of the cascade. As noted above, C1q, C1r and C1s are not necessarily co-ordinately expressed (Bensa et al., 1983), and this is also true in brain (Benoit et al., 2013; Nguyen et al., 2025). Importantly, while C1 binding to apoptotic cells can lead to CP activation and C3b/iC3b opsonization, C1q binds to apoptotic cells even in the absence of the C1r and C1s through newly eternalized cellular constituents such as phosphatidyl serine (Paidassi et al., 2008; Martin et al., 2012), and induces ingestion by phagocytes thereby avoiding the leakage of intracellular constituents (such as for example HMGB1) that induce or enhance inflammation at the site (Mevorach, 2000; Fraser et al., 2009; Son et al., 2016). Similar effects were seen with ingestion of apoptotic neurons and neuronal cell blebs by microglia (Fraser et al., 2010) and astrocytes (Chung et al., 2016; Iram et al., 2016). In addition, C1q bound to the ingested apoptotic bodies modulates the response of the ingesting cells inhibiting inflammasome activation and suppressing proinflammatory cytokine production (Fraser et al., 2009; Benoit et al., 2012; Stephan et al., 2013; Spivia et al., 2014; Ho et al., 2016) which can result in suppression of T cell activation (Clarke et al., 2015). *In vitro*, C1q has a direct protective effect on neurons exposed to Aß or under nutrient stress (Benoit and Tenner, 2011; Benoit et al., 2013). Both *in vitro* and in vivo studies demonstrate a role for C1q in the initial stages of myelination (Yu et al., 2023a, 2023b) and in neurite outgrowth and spinal cord axon regeneration (Peterson et al., 2015). Finally, while hereditary C1q deficiency is rare, those that survive childhood infections present with systemic lupus erythematosus, type 1 interferon-pathway activation and CNS inflammation (Triaille et al., 2024). Thus, C1q is crucial for maintaining tissue health and preventing inflammation, activities that would be best not to suppress.

Complement also plays a role in the developing brain, guiding the migration of neurons, refining neural circuits and improving cognitive function (Gorelik et al., 2017; Coulthard et al., 2018). Furthermore, C3 cleavage is essential for appropriate synapse pruning in postnatal critical periods (Stevens et al., 2007), as well as adult plasticity (Wang et al., 2020; Parker et al., 2022) and neurogenesis (Rahpeymai et al., 2006; Shinjyo et al., 2009). Some complement components are involved in tissue repair and regeneration processes. Use of a C5aR1 antagonist was beneficial in the acute phase after spinal cord injury, but continued use in the chronic phase led to poorer functional outcomes (Brennan et al., 2015), suggesting other roles for C5aR1. In brain, Pekna and colleagues have shown that C3a activity can be beneficial in stimulating neural plasticity in an experimental stroke model (Stokowska et al., 2017) and inhibits neurodegeneration in a neonatal model of hypoxic ischemia (Pozo-Rodrigálvarez et al., 2021a, 2021b). Furthermore, constitutive global C3aR ablation led to hyperactivity and altered regional brain morphology (Pozo-Rodrigálvarez et al., 2021a, 2021b), again suggesting that spatial and temporal context are critical in determining the outcome of C3aR signaling, and that there may be differing roles for specific complement components or activation fragments at different stages of disease (Orsini et al., 2014), all of which must be considered when selecting a therapeutic target. As will be discussed below, when dysregulated or over activated, the system can lead to detrimental neuroinflammation, excessive cell damage and cell death. Identification of the specific detrimental events to suppress is critical for successful therapeutic outcome. However, the beneficial activities noted here also make conditional ablation of complement genes in mouse models the method of choice when assessing complex neurological outcomes in NDD, such that early life beneficial activities of complement are maintained.

5. The roles of complement in neurodegeneration and the therapeutic potential of anti-complement drugs.

Complement-mediated brain pathology can be driven by several mechanisms including synapse loss and dysfunction, microgliosis and astrocytosis (Fig.3), overactivation of complement by binding to neuroaggregates (e.g. Aβ, tau, αSyn), and neuroinflammation driven by C3a/C3aR and C5a/C5aR1 pathways (Fig. 2, Fig.3) discussed in detail below.

5.1. Complement mediated synapse loss and dysfunction.

Synapse loss is a hallmark of neurodegeneration and a key factor driving cognitive decline, particularly in AD. The role of complement in synapse elimination was first shown in 2007 (Stevens et al., 2007), with C1q tagging synapses for microglial removal during development. As noted above, C1q is key part of the C1 complex (with C1r and C1s) which initiates activation of the CP, leading to the deposition of C3 activation fragments, C3b and iC3b, on the targeted synapse, facilitating synaptic engulfment by microglia expressing complement receptors (CR3 and CR4) (Fig. 3A) and by astrocytes expressing Mertk and Megf10, a binding partner for C1q (Chung et al., 2013). Studies using mouse models lacking C1q, C3, C4, or CR3 highlighted significant impairments in developmental synaptic pruning (Chu et al., 2010; Schafer et al., 2012; Sekar et al., 2016). In AD, C1q also binds synapses, both prior to and after Aβ plaque deposition, and in the presence of the other early pathway components activates the CP tagging synapses for elimination (Hong et al., 2016; Shi et al., 2017; Gomez-Arboledas et al., 2024). This process is enhanced by downstream consequences of complement activation; C5a-C5aR1 signaling and MAC both contributing to synaptic loss and cognitive decline (Gomez-Arboledas et al., 2024; Zelek et al., 2024). MAC components colocalize with neuronal and synaptic markers in human AD brains, and inhibiting MAC formation through gene deletion or pharmacological blockade of complement component C7, essential for MAC formation, inhibits disease. For example, administration of a brain penetrant C7-blocking mAb in AD mouse model ($App^{NL\text{-}G\text{-}F}$) prevented synapse loss and improved cognition (Zelek et al., 2025a, 2025b), implicating MAC in neurodegeneration (Carpanini et al., 2022; Zelek et al., 2024). In PD, C1q and C3 are upregulated in the substantia nigra, where they mediate the loss of dopaminergic synapses, exacerbating motor deficits (Depboylu et al., 2011; Chi et al., 2025). However, the study by Chi et al. employed SB290157 as a C3aR antagonist, which exhibits agonist activity in some contexts (as elaborated below). While the overall findings remain of interest and contribute to the growing body of evidence implicating C3aR in PD pathology, this pharmacological limitation should be considered when interpreting this data, and future studies would benefit from the use of more selective and well-characterised C3aR inhibitors. A recent study demonstrated that aggregated αSyn activated the CP leading to complement-dependent cytotoxicity (Gregersen et al., 2021). This was shown in SH-SY5Y cells expressing αSyn, where the slight but statistically significant cellular toxicity in the presence of normal human serum (NHS) was mitigated by complement inhibitors RaCI (targeting C5) and Cp20 (targeting C3). Elevated C1q levels in the putamen of multiple system atrophy (MSA) subjects is consistent with a role of complement dysregulation in regions of significant neuronal and synaptic loss (Gregersen et al., 2021). Synapse loss is also prominent in neuropsychological diseases such as autism spectrum disorder (ASD) and Sz (Brown, 2012; Nimmo et al., 2024) and in cranial radiation induced cognitive decline (Markarian et al., 2021; Krattli et al., 2024; Hinkle et al., 2024). The key complement components implicated in neurodegenerative synapse loss, dendritic retraction and atrophy are C1, C3, C5a-C5aR1 and MAC, therefore complement inhibitors provide opportunistic therapeutic strategy to mitigate synaptic loss and slow or prevent the disease progression. A broad inhibition of C1q may pose risks due to its protective roles in tissue homeostasis and clearance, as discussed above, making more selective targeting of downstream effectors such as C1s, C5aR1, or MAC (Gomez-Arboledas et al., 2024; Kapps et al., 2024; Zelek et al., 2025a, 2025b) a preferable approach as elaborated above.

5.2. Complement involvement in glial activation, signalling and systemic inflammation.

Emerging evidence highlights potential pathways through which complement activation may drive neurodegeneration. Studies suggest that C1q, together with tumor necrosis factor (TNF) and interleukin-1α (IL-1α), secreted by activated microglia, promotes the transformation of astrocytes into a reactive phenotype (A1 astrocytes (Liddelow et al., 2017; Fig. 3B). This reactive state has been implicated in neurodegeneration, synaptic loss, and disruption of normal synaptic health (Ding et al., 2021). A1 astrocytes, characterised by elevated expression of complement component C3, have been identified in several neurodegenerative conditions, including AD (Clarke et al., 2018; Edison, 2024). C3, produced by reactive astrocytes, was shown to be an astroglia-derived driver of nuclear factor-κB (NFκB) signalling in neurons via C3aR, a G-protein-coupled receptor widely expressed in various cell types (Pekna and Pekny, 2021). In PD, complement-mediated astrocytosis significantly contributes to synaptic dysfunction and the loss of dopaminergic neurons in the substantia nigra. Elevated levels of complement component C3 and associated complement-driven neuroinflammation observed in PD models underscore the broader involvement of complement-mediated glial activation across neurodegenerative diseases (Loeffler et al., 2006; Wang et al., 2021a, 2021b; Zhou et al., 2023a, 2023b; Chen et al., 2024a, 2024b; Nimmo et al., 2024; Yao et al., 2024). Recent studies have further emphasized the impact of astrocyte-mediated inflammatory signalling in neuronal degeneration in PD (Zhao et al., 2024). For example, inhibition of interleukin-6 (IL-6) signalling has been shown to effectively reduce astrocyte-driven neuroinflammation and prevent subsequent neuronal loss in PD models (Tremblay et al., 2019; Miyazaki and Asanuma, 2020; Pons-Espinal et al., 2024). C3a/C3aR signalling plays important role in regulating BBB integrity during ageing (Wu et al., 2016; Bhatia et al., 2021; Zhang et al., 2024). Propson et al. demonstrated that activation of the C3a/C3aR pathway in brain endothelial cells led to changes in vascular structure, increased BBB permeability, and heightened microglial activation in aged wild-type (WT) mice (Propson et al., 2021). Importantly, these detrimental effects were mitigated by germline deletion of C3aR (Pekna et al., 2021). As highlighted above, some studies testing the link between C3aR and disease mechanisms, have used of a promiscuous C3a 'antagonist', SB290157, that has both C3aR antagonist and agonist actions (Woodruff and Tenner, 2015; Li et al., 2021b) and is a partial C5aR2 agonist (Li et al., 2020), limiting any conclusions made from those particular studies.

A recent report describing a role for C3/C3aR signalling in mediating *Helicobacter pylori*-induced brain injury suggested to contribute to AD pathology (Xie et al., 2023) highlights the broader impact of C3a/C3aR signalling in mediating vascular and neuroinflammatory responses, and its potential significance as a therapeutic target (Xie et al., 2023). In PD, evidence suggests that systemic inflammation driven by C3a/C3aR pathway activation and originating from the gut can heighten microglial reactivity and exacerbate neurodegeneration in dopaminergic pathways (Loeffler et al., 2006; Subramaniam and Federoff, 2017; Klann et al., 2022). While direct links between gut dysfunction and C3a/C3aR pathway activation in PD remain limited, findings from other diseases support the hypothesis that gut-brain interactions involving complement activation may contribute to disease progression (Kustrimovic et al., 2024).

Deficiency of C3aR in an AD mouse model reduced Aβ pathology and enhanced cognitive performance; transcriptomics identified metabolic alterations linked to the C3a/C3aR pathway, suggesting that targeting C3aR could serve as a potential therapeutic strategy for AD (Gedam et al., 2023). However, it must be noted that developmental deficiencies have been reported to result in behavioral alterations in adult C3aR knockout mice (Pozo-Rodrigálvarez et al., 2021a, 2021b), and thus experimental designs with either inducible adult ablation of C3aR (Quell et al., 2017) or better pharmaceutical probes would provide more compelling evidence to determine the contribution of C3aR to these disorders.

Microglia express both CR4 and CR3 which are implicated in microglia-mediated Aβ clearance. Microglial CR3 has been suggested to regulate Aβ homeostasis via proteolytic mechanisms that function independently of phagocytosis (Czirr et al., 2017). These findings highlight the dual roles of complement in mediating both detrimental and protective processes during AD progression (Wyss-Coray et al., 2002; Maier et al., 2008; Choucair-Jaafar et al., 2011;Chiee Sasaguri et al., 2017; Fu et al., 2012). In PD, CR3-mediated synapse elimination driven by αSyn aggregates suggests a similar dual role for microglia in both protecting and exacerbating disease pathology (Ferreira and Romero-Ramos, 2018).

Systemic infections, specifically viral infections, have also been implicated in exacerbating complement-mediated neuroinflammation in NDDs. For example, systemic hyperactivation of the complement system observed in SARS-CoV-2 infection has been linked to short- and long-term cognitive deficits and future risk of developing NDDs (Vlaicu et al., 2023). These findings highlight the broader impact of systemic inflammation on complement activation and neurodegeneration (Baillie et al., 2024). The role of viruses in neurodegeneration has been reviewed elsewhere (Farrer et al., 2024; Luo et al., 2024); one notable finding was that the recombinant shingles vaccine 'Shingrix' is protective against AD, reducing risk by ~20%, presumably by its capacity to "clear" herpesvirus from the brain (Taquet et al., 2024). The relationship between systemic viral infections and neuroinflammation predisposing to NDDs is now well-established; for instance, enterovirus and human herpesvirus infections have been associated with ALS (Xue et al., 2018), while Japanese encephalitis virus and influenza virus have been identified in patients with PD (Jang et al., 2009; Bantle et al., 2019). The contribution of complement to these other virus-associated neuroinflammatory events remains a topic of research (Tran et al., 2022).

As noted above, microglia are the predominant source of C1q in the brain; in mice challenged with peripheral injections of lipopolysaccharide (LPS), C1q levels in brain correlated with microglial phagocytosis, synapse loss and memory deficits (Xin et al., 2019), supporting the concept that peripheral inflammation can influence complement-mediated synapse loss and impairs learning in mice. In ALS, systemic inflammation and microglial activation through complement signalling contribute to the loss of motor neurons and disease progression (Liu and Wang, 2017).

In MS, complement contributes to demyelination and axonal death through complement dysregulation causing excessive opsonisation, microglia recruitment and direct MAC effects (Ziabska et al., 2021). In some neurodevelopmental diseases, including Sz and ASD, aberrant complement signalling has been implicated in excessive synaptic pruning during critical periods of brain development, contributing to altered connectivity (Fan et al., 2023). Multi studies have shown that traumatic brain injury (TBI) is associated with complement dysregulation adjacent to the lesion, leading to secondary neuroinflammation, neuronal damage and microgliosis (reviewed in Gomez-Arboledas et al., 2021). These reports emphasize the significant role of complement activation in promoting neuroinflammation and neurodegeneration in various neurological and psychiatric disorders, indicating its potential as a therapeutic target.

5.3. Complement activation by neuroaggregates.

Pathological aggregates of proteins (Aβ, p-tau, TDP-43, and αSyn), the hallmarks of many NDDs, including AD, FTD, progressive supranuclear palsy (PSP), Lewy body dementia (LBD), PD, and ALS, can activate the complement system contributing to neuroinflammation, synaptic dysfunction, and neuronal loss (Kwon and Koh, 2020; Bohlson and Tenner, 2023; Gao et al., 2023; Zhang et al., 2023). In AD, C1q binding to the beta sheet conformation of Aβ (as in fibrillar Aβ plaques) initiates CP activation (Velazquez et al., 1997) and deposition of C3

fragments on plaques for their recognition and uptake by microglia (Fonseca et al., 2011; Fig. 3C). The beneficial clearing of the pathological plaques may turn into a harmful process when too much complement activation accelerates microglia activation and phagocytosis, not only targeting the aggregates but also engulfing nearby healthy neurons, and synapses, exacerbating neuroinflammation (Zhou et al., 2008; Butler et al., 2021; Bohlson and Tenner, 2023; Heneka et al., 2024). Hyperphosphorylated tau aggregates into neurofibrillary tangles (NFTs) in AD, disrupting microtubule stability, axonal transport, and neuronal integrity (Iqbal et al., 2005; Grundke-Iqbal et al., 1986). Complement proteins and activation products (C1q, C3, C4, C3b, TCC) colocalise with both Aβ plaques and NFTs in AD (Fonseca et al., 2004; Lian et al., 2016; Dejanovic et al., 2018; Fig. 3B). Similar processes occur in PD and ALS, where αSyn and TDP-43 aggregates trigger inflammatory responses via C1q and C3b deposition (Klegeris and McGeer, 2007; Zhang et al., 2020)). Notably, complement activation is also observed in Down syndrome (DS), which features early-onset AD pathology, with C1q and C3 deposition around amyloid plaques and evidence of increased neuroinflammation (Stoltzner et al., 2000; Head et al., 2001; Wilcock and Griffin, 2013; Veteleanu et al., 2023a, 2023b). TCC/MAC formation disrupts cellular membranes and ionic balance in plaque-adjacent cells, leading to NLRP3 inflammasome activation (Triantafilou et al., 2013; Morgan, 2015), well known for amplifying inflammatory responses by releasing of IL-1β and IL-18 leading to neuronal dysfunction, as has been extensively reviewed elsewhere (Anderson et al., 2023).

5.4. Neuroinflammation mediated by C3a/C3aR and C5a-C5aR1 signalling.

The C3a/C3aR and C5a/C5aR1 axes represent key pathways of complement-mediated neurotoxicity in AD, connecting Aβ/tau pathology to neuroinflammation, synaptic loss, and cognitive decline. C3a and C5a fragments, two potent pro-inflammatory molecules signal via their respective receptors, C3aR and C5aR1, on microglia and astrocytes (Tenner, 2020; Batista et al., 2024), leading to the release of pro-inflammatory cytokines, TNF, IL-1β, and IL-6, which exacerbates synaptic dysfunction and neuronal loss (Carvalho et al., 2022; Gomez-Arboledas et al., 2024). In AD brain, elevated C5aR1 expression on microglia near amyloid plaques correlates with regions of synaptic and neuronal loss (Hernandez et al., 2017a, 2017b; Gomez-Arboledas et al., 2024). Pharmacological inhibition or deletion of C5aR1 altered microglial activation and mitigated synaptic loss in mouse models of amyloidosis (Carvalho et al., 2022; Gomez-Arboledas et al., 2024; Schartz et al., 2024). C5aR1 ablation reduces the expression of disease-associated microglia (DAM) genes such as triggering receptor expressed on myeloid cells 2 (TREM2) and CD33, as well as reactive astrocyte markers including S100A6 and glial fibrillary acidic protein (GFAP), suggesting that C5a/C5aR1 signalling amplifies the inflammatory responses of both microglia and astrocytes (Hernandez et al., 2017a, 2017b; *Fig. 3D*). C5a directly or via microglial induced mediators result in astrocyte reactivity that has been implicated in neuronal toxicity, with increased expression of Lcn2 and related markers contributing to synaptic loss (Bi et al., 2013; Carvalho et al., 2022). Importantly, while in some models C5aR1 inhibition decreases Aβ plaque accumulation, in the aggressive Arctic model plaque load is not decreased, but synaptic integrity and cognitive function are still rescued (Landlinger et al., 2015; Carvalho et al., 2022; Schartz et al., 2024; Gomez-Arboledas et al., 2024). Single cell and single nuclei RNA-Seq revealed specific microglial and astrocyte clusters expressing disease-enhancing genes induced in AD models, which are suppressed when C5aR1 is pharmacologically inhibited even after deposition of amyloid has started (Gomez-Arboledas et al., 2022; Schartz et al., 2024). Importantly, clusters of microglia induced in these amyloidosis models that express genes supporting reparative pathways are not suppressed, indicating that beneficial responses to injury are maintained while detrimental inflammatory/neurotoxic responses are inhibited.

The C3a/C3aR and C5a/C5aR1 signalling axes are increasingly recognised as key contributors to other NDDs; in PD, complement activation has been implicated in dopaminergic neuronal loss in the substantia nigra, a hallmark of the disease (Loeffler et al., 2006; Stennett et al., 2023). Altered levels of CSF C5a were reported in PD and ALS (Niimi et al., 2021). Upregulation of C5aR1 was observed in postmortem AD brains, particularly in regions associated with Aβ plaque deposition pathology (Carvalho et al., 2022). Numerous studies have shown that C5a activates microglial NLRP3 inflammasomes via C5aR1, contributing to neurodegeneration in AD and PD, and that inhibition of this pathway can attenuate these detrimental effects (Gordon et al., 2016; Negro-Demontel et al., 2024; Schartz et al., 2024). Increased expression of C3aR and C5aR1 on reactive astrocytes and microglia in ALS spinal cord is associated with enhanced neuroinflammatory responses and motor neuron degeneration (Pekna and Pekny, 2021). Inhibition of C5aR1, either by genetic deletion or pharmacologically e.g. utilizing the C5aR1 antagonist PMX205 in hSOD1ˆG93A mice delayed disease progression, reduced neuroinflammation, and extend survival (Lee et al., 2017). Dysregulation of C3aR and C5aR1 have also been implicated in susceptibility to psychiatric disorders (Westacott et al., 2022). For example, Chen et al. reported that C5aR1-deficient mice exhibited attenuated behavioral changes following stressor, suggesting roles in emotional regulation (Chen et al., 2024a, 2024b), although this may reflect alterations during development. Collectively, the C3a/C3aR and C5a/C5aR1 pathways mediate neuroinflammation across NDDs, linking complement activation to neuronal loss and cognitive or motor dysfunction.

6. Overview of current complement therapeutics and their application in CNS.

Complement-targeted therapies are being developed and tested across a broad range of diseases, with several agents currently in clinical trials or approved for use in systemic conditions (reviewed in Zelek et al., 2019a, 2019b; Mastellos et al., 2024; West et al., 2024; Table 1). These systemic advances have laid the groundwork for CNS-targeted strategies, which are beginning to emerge and are discussed in detail below.

6.1. Complement therapeutics in development for CNS application.

Numerous complement inhibitors have been evaluated in preclinical models (see Section 2), demonstrating promising potential for CNS-targeting. The C5aR1 antagonists, PMX53 and PMX205 (Li et al., 2021a, 2021b) have shown efficacy in reducing neuroinflammation and synaptic loss in several NDD models (Kumar et al., 2020; Serradas et al., 2024; Schartz et al., 2024). In the Tg2576 AD model, administration of PMX205 led to a significant reduction in fibrillar Aβ deposits and activated glial cells and improved behavioral performance in these mice (Fonseca et al., 2009; Gomez-Arboledas et al., 2022). In the same study, 3xTg-AD mouse model treated with PMX205 resulted in decreased levels of hyperphosphorylated tau and reduced neuroinflammatory markers, mitigating AD pathology (Fonseca et al., 2009). Similarly, in the ALS (hSOD1ˆG93A) mouse model, PMX205 treatment extended survival, reduced microglial activation, and preserved motor neurons (Lee et al., 2017), and in a HD rat model (3-nitropropionic acid-induced), C5aR1 inhibition attenuated neuroinflammation and neurodegeneration (Woodruff et al., 2006). Treatment with a brain penetrant blocking anti-C7 mAb (73D1) to inhibit the TP reduced MAC formation, synapse loss and cognitive decline in the $App^{NL\text{-}G\text{-}F}$ AD mouse (Carpanini et al., 2022; Zelek et al., 2024; Zelek et al., 2025a, 2025b). Another MAC-blocking mAb (anti-C6; CP010, Complement Pharma) demonstrated efficacy in a mouse MS model (experimental autoimmune encephalomyelitis; EAE), where inflammation disrupts the BBB allowing systemic mAb to reach the CNS (Gytz Olesen et al., 2023).

In human trials, riliprubart, a second generation C1s inhibitor that inhibits only the activated form of C1s and has increased half-life

Table 1
Current complement therapeutics; FDA-approved, in clinical trials, and in preclinical studies in NDDs.
This summary provides a comprehensive overview of all approved and in development complement therapeutics, to provide broader context and highlight opportunities for adaptation in NDDs, including details on drug mechanism of action, class, development stage, and company affiliation. *Abbreviations:* aHUS: atypical haemolytic uremic syndrome; ALS: amyotrophic lateral sclerosis; AMD: age macular degeneration; AP: alternative pathway; ARDS: acute respiratory distress syndrome; ARREST-BP: adult patients with bullous pemphigoid receiving adjunct oral corticosteroid therapy; CIDP: chronic inflammatory demyelinating polyneuropathy; CP: classical pathway; CHAPLE: CD55-deficiency-related haemolytic anaemia with PLE; EAE: experimental autoimmune encephalomyelitis (preclinical MS model); C3G: complement 3 glomerulopathy; GA: geographic atrophy (age-related macular degeneration); IgAN: immunoglobulin A nephropathy; IC-MPGN: immune-complex membranoproliferative glomerulonephritis; ICGN: idiopathic immune complex-mediated glomerulonephritis; HD: Huntington disease; HS: hidradenitis suppurativa; HSCT-TMA: hematopoietic stem cell transplant-associated thrombotic microangiopathy;
LN: Lupus Nephritis; LP: lectin pathway; MAC: membrane attack complex; MG: myasthenia gravis; mAb: monoclonal antibody NDDs: neurodegenerative diseases; NMOSD: neuromyelitis optica spectrum disorder; PNH: paroxysmal nocturnal haemoglobinuria; RNAi: RNA interference therapy.

Agent	Mechanism of Action	Drug class	Stage	Company
FDA-approved complement inhibitors				
Sutimlimab (TNT009)	C1s inhibitor (blocks CP activation)	mAb	FDA-approved for CAD; not tested in NDDs	Sanofi
Pegcetacoplan	C3-cleavage inhibitor (blocks AP activation)	Linear peptide	FDA-approved for GA. C3G, IC-MPGN: phase III completed (NCT05067127) HSCT-TMA: phase II ongoing. (NCT04784455) AIHA: phase II completed (NCT03538041) Discontinued in ALS Phase II trials due to lack of efficacy	Apellis Pharmaceuticals
Eculizumab	C5-cleavage inhibitor (prevents C5a and MAC generation)	mAb	FDA-approved for NMOSD, MG, PNH; not tested in NDDs	Alexion Pharmaceuticals
Ravulizumab	C5 inhibitor (extended half-life version of eculizumab)	mAb	FDA-approved for NMOSD, PNH, aHUS; not tested in NDDs	Alexion Pharmaceuticals
Zilucoplan	C5-cleavage inhibitor (prevents C5a and MAC generation)	Cycling peptide	Approved for gMG and GA; phase II in ALS (NCT04436497); not tested in NDDs	UCB Biopharma
Crovalimab	C5-cleavage inhibitor (prevents C5a and MAC generation)	mAb	FDA-approved for PNH; not tested in NDDs	La Roche Ltd.
Pozelimab	C5-cleavage inhibitor (prevents C5a and MAC generation)	mAb	FDA-approved for CHAPLE; PNH, phase II/III (NCT04162470), MG; phase II (NCT05070858) not tested in NDDs	Regeneron Pharmaceuticals
Avacincaptad pegol	C5-cleavage inhibitor (blocks AP activation)	Linear peptide	FDA-approved for GA; not tested in NDDs	Iveric Bio/ Astellas
Avacopan	C5a receptor antagonist (blocks C5aR1 signaling)	Small molecule	FDA-approved for ANCA-AAV; HS, phase II (NCT03852472) C3G: phase II (NCT03301467) not tested in NDDs	ChemoCentryx/Amgen
Danicopan	FD inhibitor (blocks AP activation by preventing C3bBb formation)	Small molecule	FDA-approved for PNH; not tested in NDDs	Alexion AstraZeneca
Iptacopan	FB inhibitor (blocks AP activation by preventing C3bBb formation)	Small molecule	FDA-approved for PNH and IgAN; C3G, phase III (NCT04817618), aHUS, LN phase II (NCT04889430, NCT05097912) not tested in NDDs	Novartis
Berinert, Cinryze, Ruconest (C1 esterase inhibitors)	C1inhibitor replacement	Recombinant proteins	FDA-approved for HAE; not tested in NDDs	CLS Behring/ Takeda Pharmaceuticals/ Pharming Group NV
Complement inhibitors in clinical trials				
ANX-005	C1q inhibitor (blocks CP activation)	mAb (IgG4)	Phase IIb in HD (NCT04514367) and phase IIa in ALS (NCT04569435)	Annexon Biosciences
Riliprubart	Complement C1s Inhibitor (blocks CP activation)	mAb (IgG1)	CIDP, phase: phase II (NCT06290128) completed; phase III recruiting (NCT06290141); CAG (NCT04269551	Sanofi
Narsoplimab	MASP-2 inhibitor (blocks LP activation)	mAb	TA-TMA, phase III (NCT02222545); COVID-19 and ARDS IgAN,LN, MN, & C3G including DDD, phase II (NCT02682407). not tested in NDDs	Omeros Corporation
Zaltenibart	MASP-3 inhibitor (blocks LP/ AP activation)	mAb	C3G and ICGN: phase II (NCT06209736) PNH: phase II: (NCT05972967) not tested in NDDs	Omeros Corporation
OMS1029	long-acting MASP-2 inhibitor (blocks LP activation)	mAb	N/A, phase I (healthy volunteers) not tested in NDDs	Omeros Corporation
APL-9	C3 inhibitor	cyclic peptide	ARDS: COVID-19, phase II (NCT04402060)	Apellis Pharmaceuticals
AMY-101	C3 inhibitor	cyclic peptide	Periodontal Inflammation (Gingivitis), phase II (NCT03694444) COVID-19-Associated ARDS, phase II (NCT04395456)	Amyndas Pharmaceuticals

(*continued on next page*)

Table 1 (*continued*)

Agent	Mechanism of Action	Drug class	Stage	Company
			PNH, phase II (NCT03316521)	
IONIS-FB-L	FB inhibitor (reduce production of factor B)	Ligand Conjugated Antisense (LICA)	IgAN: phase II (NCT04014335) and GA due to AMD: phase II (NCT03815825)	La Roche Ltd.
Vemircopan	Factor D inhibitor (AP inhibition)	Small molecule	PNH and GA in AMD; phase II/III (NCT05047549, NCT05025925)	Alexion AstraZeneca
ALXN1720	C5-cleavage inhibitor (prevents C5a and MAC generation)	mAb (bi-specific VHH targeting C5 and human serum albumin (HSA)	PNH and gMG, phase II (NCT04438059, NCT04597488)	Alexion Pharmaceuticals
Cemdisiran	C5-gene; RNA interference (RNAi) therapeutic to generate C5 in liver	mAb	PNH and IgAN, phase II (NCT02352493, NCT03841448)	Alexion Pharmaceuticals / Alnylam Pharmaceuticals
			Pozelimab and Cemdisiran combination therapy: PNH, Phase II (NCT03841448); MG, Phase II, (NCT05070858)	
Nomacopan	C5-cleavage inhibitor; dual inhibitor of both C5 and leukotriene B4 (LTB4)	mAb (bi-specific recombinant tick-derived protein)	ARREST-BP: phase III (NCT05061771)	Akari Therapeutics
ALS-205	C5aR1	Cyclic peptide	Motor neuron disease Phase I (ACTRN12622000927729)	Alsonex
Preclinical complement inhibitors for NDDs				
PMX53; PMX205	C5a receptor antagonist (blocks C5a induced signaling through C5aR1)	Cyclic peptide	AD; APP/PS1) mouse ALS; SOD1) mouse HD; 3-nitropropionic acid (3-NP) rat	n/a
EP67	Weak C5a receptor 1 agonist; C3aR agonist	Linear peptide	AD; 5XFAD mouse AD; Tg19959 mouse	n/a
CP010	C6 inhibitor (prevents MAC formation)	mAb	Induced EAE and EAMG (myelin oligodendrocyte glycoprotein (MOG immunisation in rat)	Complement Pharma/ Alexion
73D1	C7 inhibitor (prevents MAC formation)	mAb (brain penetrant)	AD; $App^{NL\text{-}G\text{-}F}$ mouse	n/a

relative to the earlier sutimlimab (TNT009), is in phase II/III trials for chronic inflammatory demyelinating polyneuropathy (CIDP) (NCT06290128; NCT06290141). C1q has also emerged as a key therapeutic target. ANX-005 (Annexon Biosciences) is a C1q blocking mAb in phase II trials for HD and ALS (NCT04569435, NCT04514367), and phase III for Guillain-Barré syndrome (GBS; NCT04701164). In the HD trial ANX-005 showed target engagement in CSF and serum, and a subset of these "early manifest" HD patients with higher evidence of CP activation (C4a/C4 ratio) in CSF showed slower decline on the drug than those with lower suggestion of CP activation (Kumar et al., 2023). A key limitation of large therapeutics like mAb in NDDs is their restricted BBB penetration (~0.1% passive diffusion into the brain). A recent preclinical study in an AD mouse model explored modifying ANX-005 with triozan biopolymers in combination with kinin B1 and B2 receptor (B1R/B2R) peptide agonists to facilitate targeted brain uptake (Gagnon et al., 2023). This study showed the potential of improving brain penetrance for more effective complement-based therapies in NDDs.

7. Challenges and opportunities in developing anti-complement drugs for NDDs

7.1. Overcoming drug delivery barriers: the BBB and the "sink effect"

A key factor for drug delivery to the brain is the BBB which significantly restricts access. In neuromyelitis optica spectrum disorder (NMOSD) and MS the BBB is impaired or disrupted, enabling access of systemically administered drugs as noted above for the C5-blocking mAbs (Table 1). In other NDDs, e.g. AD, where BBB integrity is largely intact in early stages, systemic drugs have limited CNS access. Since early intervention is crucial to prevent synaptic and neuronal damage, the development of brain penetrant complement inhibitors is essential for effective therapeutic intervention in these NDDs. The BBB is a highly selective diffusion barrier composed of brain microvascular endothelial cell tight junctions, pericytes, astrocytes, and associated basement membranes (Galea, 2021). This protective shield prevents the entry of pathogens, toxins, blood proteins, and immune cells, but also restricts access of systemically administered drugs. Ions and salts traverse between cells in the BBB by paracellular routes, whereas small lipophilic molecules penetrate directly through cells via transcellular transport. Larger molecules e.g. mAb ((~150 kDa) depend on active transport mechanisms in endothelial cells, such as receptor-mediated transcytosis (RMT) to shuttle the cargo from the blood-facing (luminal) side to the brain-facing (abluminal) surface (Abbott et al., 2010). This delivery strategy is known as the Trojan horse in which therapeutics are linked to ligands or mAbs that hijack endogenous BBB transport systems to enter the CNS. The transferrin receptor (TfR) is the most studied strategy for drug delivery to the CNS. It facilitates iron transport and can be used by ligands or antibody-drug conjugates to deliver large molecules across the BBB. Several brain shuttle systems use TfR-binding domains to transport large molecules efficiently (Niewoehner et al., 2013; Thomsen et al., 2022; Wouters et al., 2022; Zelek et al., 2025a, 2025b). Optimised constructs developed by Pizzo et al. (https://www.alzforum.org/papers/engineering-anti-amyloid-antibodies-transferrin-receptor-targeting-improves-safety-and-brain; Arguello et al., 2022) have demonstrated promising CNS uptake and are undergoing further preclinical and clinical validation. These platforms often incorporate bivalent or monovalent TfR-binding arms for efficient trafficking. Other RMT systems under investigation for CNS drug delivery include the insulin receptor (IR), low-density lipoprotein receptor-related protein 1 (LRP1), CD98hc, diphtheria toxin receptor (HB-EGF), folate receptor (FR), and nicotinic acetylcholine receptor (nAChR), as reviewed elsewhere (Baghirov, 2025; Haqqani et al., 2024). Among recent advances, Roche's Brain-Shuttle platform (https://www.roche.com/stories/brain-shuttle-in-research-technologies); a bispecific mAb that binds both TfR and the therapeutic target Aβ has shown enhanced brain uptake.

Current complement therapeutics are not designed to cross the BBB or the blood-spinal cord barrier (BSCB). Most current small molecule anti-complement drugs also lack CNS penetration with the exception of the C5aR1 antagonist, PMX205, demonstrated in rodent brain (Kumar et al., 2020). Addressing these issues requires either designing BBB penetrant small molecule drugs or employing innovative delivery strategies for existing drug; e.g. RMT or IgG Fc engineering to increase receptor binding or reduce peripheral clearance (Kariolis et al., 2020), nanoparticle (NP) formulations, prodrug approaches and/or intrathecal

delivery, as reviewed elsewhere (Zeiadeh et al., 2018; Zelek and Morgan, 2022; Zhao et al., 2022; Narsinh et al., 2024). NPs are increasingly used for CNS-targeted drug delivery due to their versatility and capacity for BBB penetration. However, their lipid composition and surface properties may activate complement, leading to rapid immune clearance and reduced half-life (Moghimi and Simberg, 2017; Wang and Brenner, 2021). Furthermore, the physicochemical properties of NPs, including charge, hydrophobicity, and size, impact their degradation rates and biodistribution, affecting not only delivery efficiency but also safety and toxicity profiles (Wang and Brenner, 2021).

Other emerging approaches include the use of patient-derived extracellular vesicles (EVs) as biocompatible, BBB-permeable carriers for delivery of drugs or siRNA to the CNS (Ha et al., 2016). Cell-derived EVs, engineered to deliver neuroprotective cargo such as miR-124-3p, can exert therapeutic effects in AD models by modulating neuron–glia interactions (Évora et al., 2025). However, challenges related to scalable production, consistent cargo loading, and standardization remain.

In addition to molecular and carrier-based strategies, non-invasive approaches such as focused ultrasound (FUS) with microbubbles are being tested to transiently open the BBB, enhancing drug delivery to the brain parenchyma. Early-phase clinical trials have demonstrated the safety and feasibility of FUS in AD (e.g., with aducanumab) and glioblastoma, showing increased drug penetration and regional amyloid clearance (Rezai et al., 2022; Park et al., 2021; Lipsman et al., 2018).

Beyond enhancing CNS penetration, addressing the 'sink effect' where high systemic concentrations of complement proteins saturate the drug before entering the brain. A two-step dosing regimen targeting C7, first saturating systemic C7 with non-brain-penetrant mAb, then administering the BBB-permeable anti-C7 mAb, has shown promising results in a preclinical AD model (Zelek et al., 2025a, 2025b). Adeno-associated viruses (AAVs) are a promising strategy for sustained complement modulation in the CNS, bypassing peripheral complement and targeting disease sites. AAV delivery has shown effectiveness in overcoming the blood-retina barrier (BRB), reducing retinal vascular leakage by 60% and ganglion cell apoptosis by 200% (Adhi et al., 2013). Phase II clinical trials are ongoing to evaluate safety and efficacy of HMR59 (AAVCAGsCD59) in AMD (Janssen; JNJ-81201887). AAV2-CFI, a subretinal delivery of AAV2 encoding complement factor I, showed sustained intraocular CFI increase in dry AMD over two years, despite not meeting GA efficacy endpoints (Novartis, GT005). These studies show effective delivery of complement therapeutics to challenging targets like eye, but long-term complement inhibition requires rigorous safety evaluations (Bors and Erdő, 2019).

7.2. Balancing efficacy and safety in complement-targeted NDDs therapies

Selecting the right complement drug target is crucial to effective local inhibition without impacting the entire complement cascade and interfering with protective functions of the complement system. In the TP, C5 blockade has a well-characterised safety profile, with the associated *Neisseria* infection risk mitigated by vaccination and antibiotic prophylaxis (Winthrop et al., 2018). AP inhibitors, are associated with a higher infectious risk due to their interference with opsonisation and microbial clearance (Hillmen et al., 2024). Selective inhibitors, such as sutimlimab (anti-C1s) and ANX-005 (anti-C1q) targeting the CP while preserving AP/LP functions, have shown promising clinical outcomes. But, targeting C1q requires caution; over 90% of individuals with complete C1q deficiency develop severe lupus-like symptoms (Macedo and Isaac, 2016). In addition, the relative contribution of neuroprotective functions of C1q as discussed above in countering NDD remain to determined, and thus targeting C1q may be less effective particularly in early stages of disease. Combining complement inhibitors with other disease-modifying therapies for example, anti-amyloid or anti-tau agents, may offer a viable strategy to address the multifactorial nature of NDDs. A major challenge with the current FDA-approved amyloid clearing mAbs is amyloid-related imaging abnormality (ARIA), characterised by brain edema (ARIA-E) and microhemorrhages (ARIA-H), occurring in 20–40% of treated patients and carrying a risk of severe or even fatal complications (Adhikari et al., 2023; Hampel et al., 2023). Complement dysregulation in the brain vasculature emerges as a key driver of ARIA pathogenesis, likely through excessive inflammation and compromised vascular integrity (https://www.alzforum.org/news/conference-coverage/aria-inflammatory-reaction-vascular-amyloid#:~:text=ARIA%20may%20be%20iatrogenic%20CAA). In this context, selective inhibition downstream of CP may be a promising approach. For example, targeting MAC in combination with anti-Aβ therapy, which is directly implicated in vascular damage, may mitigate ARIA without disrupting upstream complement functions necessary for immune defence and waste disposal. In addition, since C5a would also be generated, C5aR1 inhibition could suppress increased inflammation and increased vascular permeability (Batista et al., 2024).

7.3. Stratifying to identify the right patients for complement therapeutics

Not all patients with NDDs show complement dysregulation, and the heterogeneity in disease progression demonstrates the need for a personalised treatment approach. For example, in MS, distinct lesion patterns have been identified, with some showing robust complement activation and others demonstrating no complement involvement at all (Lucchinetti et al., 2000). As discussed above, the C1q inhibitor ANX005 in HD patients showed clinical improvement in a subgroup with higher baseline CSF C4a/C4 ratios, suggesting that greater initial complement activation may predict better treatment response (NCT04514367 (https://www.neurologylive.com/view/anx005-demonstrates-safety-huntington-disease-improvements-found-in-subgroups-of-patients). Similarly, in AD, variability in the levels of several complement proteins including C3, C4, Clu, and FH in CSF and plasma has been observed Krance et al., 2021). It remains to be seen if this inconsistency is due to technical issues or if it is indeed patient-specific biomarker signatures. Importantly, disease stage may significantly influence complement protein levels, as immune activation may vary across early, progressive, and late phases. This should be carefully considered when interpreting their diagnostic or predictive value as biomarkers. While plasma complement markers; C3, C4, and TCC are more accessible and scalable than CSF-based readouts, they may be more susceptible to peripheral confounders, and their clinical utility likely depends on integration with CSF, neuroimaging, or genetic data to enhance specificity. Identifying individuals with complement overactivation based on genetic risk factors (e.g., *CR1, CLU, FH, C4A, CSMD1*) (Steen et al., 2013; Torvell et al., 2021; Hatzimanolis et al., 2022; Veteleanu et al., 2023a, 2023b), or fluid biomarkers of complement activation and integrating these with CSF biomarkers or neuroimaging has the potential to enhance treatment efficacy and optimize clinical trials. Alterations in complement proteins within blood and CSF offer potential biomarkers for diagnosis, monitoring disease progression, and tailoring therapeutic interventions. A meta analysis (Krance et al., 2021) showed elevated clusterin and C3 in the CSF in AD subjects. Other studies also reported elevated levels of C1q, C4b, and TCC in CSF and plasma in AD patients relative to age controls (Negro-Demontel et al., 2024; Daskoulidou et al., 2025), that correlated with disease severity and cognitive decline, suggesting their utility in patient stratification and therapeutic monitoring. In MS the activation products TCC and Ba are increased during acute phases (Kodosaki et al., 2024), differentiating between relapsing and remitting phases, and potentially useful for informing treatment decisions. In other NDDs e.g. ALS, and PD complement dysregulation has been observed, but specific fluid biomarkers are less well-defined (Negro-Demontel et al., 2024). The importance of appropriate patient selection and biomarker monitoring is evident by lessons learned from past clinical trials, where the absence of robust stratification methods may have limited success rate. Trials in ALS with C3 inhibitor (pegcetacoplan) and C5 inhibitor (e.g., zilucoplan), were discontinued due to lack of efficacy (NCT04436497,

NCT04579666; Nimmo et al., 2024; Paganoni et al., 2025;(https://www.biopharmadive.com/news/apellis-als-pegcetacoplan-study-failure/651257/; https://www.massgeneral.org/news/press-release/healey-als-platform-trial-update-ilucoplan-arm-stopped-early-for-futility). This is raising important questions about whether the disappointing outcomes were because of the lack of efficacy of the drug or the need for better-defined patient subgroups who would benefit most from the treatment. In AD, although no complement inhibitors have advanced to clinical trials, preclinical studies suggest that targeting components may mitigate neurodegeneration and improve cognitive function (Fonseca et al., 2009; Mastellos et al., 2013; Morgan and Harris, 2015; Ricklin et al., 2019, Zelek et al., 2019a, 2019b; Schartz et al., 2024; Zelek et al., 2024). To maximise the success of future clinical trials, it is essential to integrate fluid (plasma/CSF) biomarker-guided selection criteria. Utilising complement activation markers (e.g., C3/C4 fragments, C5a, Ba, TCC) alongside genetic risk factors (e.g., CR1, CLU, C4A, CSMD1, ApoE4) may help stratify patients typified by complement dysregulation and identify those most likely to benefit from treatment. Notably, ApoE4 carriers in AD show increased inflammation, complement activation, and microglial reactivity, which may impact treatment response (Raulin et al., 2022).

Despite encouraging preclinical data, complement therapeutics have struggled to translate into clinical success; raising critical questions about whether the issue is the target validity, insufficient CNS penetration and thus poor target engagement, or the lack of informative biomarkers for disease state and participant stratification. In many cases, inclusion criteria were not aligned with biological markers of complement dysregulation, making it difficult to interpret negative outcomes. In AD, the lack of progress into late phase trials highlights persistent challenges, particularly around demonstrating CNS target engagement. Improved access to clinical samples from existing studies could support retrospective stratification and mechanistic insight. Going forward, integrating biomarker-informed inclusion criteria based on appropriate CSF or/and plasma biomarkers, genetic risk, and disease stage will be critical to de-risk trial design and improve the likelihood of clinical impact.

8. Conclusion and future directions.

The complement system has emerged as a compelling therapeutic target in NDDs with central roles in synaptic pruning, neuroinflammation, and neuronal injury (Schartz and Tenner, 2020; Nimmo et al., 2024), strongly supported by preclinical studies in AD, ALS, and HD models (Ricklin et al., 2019; Bohlson and Tenner, 2023; Batista et al., 2024), yet translating complement drugs into clinical success in NDDs remains challenging. The most significant barrier is a lack of brain penetrant complement drugs. Brain delivery systems (e.g. RMT, NP-based carriers) and direct intrathecal delivery show promise but require further optimisation to enhance targeted delivery to sites of injury (Song et al., 2021; Hersh et al., 2022; Zelek and Morgan, 2022; Khoury et al., 2025; Zuchero et al., 2016). MS and NMOSD may be exceptions to the BBB penetration challenge because BBB leakage occurs early in the disease (Winkler et al., 2021; Steinruecke et al., 2023), but for other NDDs the challenge remains. Measurement of markers of BBB integrity, for example, leakage of albumin or immunoglobulins into the brain or specific brain cell components into plasma, may inform on BBB status and identify treatment windows (Lindblad et al., 2020; Abdelhak et al., 2022; French et al., 2025; Hong et al., 2025). Avoiding the "sink effect" might be achieved by designing inhibitors that selectively target pathogenic assembly-stage complexes rather than native proteins that are highly abundant in plasma; for example, targeting MAC complexes rather than intact C5 could offer selective inhibition of TP, significantly reducing the required drug dose, or inhibiting activated C1s rather than the proenzyme C1s (Xu et al., 2024). Such selective approaches may improve therapeutic specificity and reduce systemic side effects by sparing homeostatic functions. Timing of therapy in terms of both disease stage and duration of treatment, target selection and degree of blockade can all be optimised to retain homeostasis while inhibiting pathology.

The development of a single agent and protocol for complement therapeutic approaches to NDDs is challenging because of the different complement activation profiles within and across the diverse NDDs (Nimmo et al., 2024; Daskoulidou et al., 2025; Tenner and Petrisko, 2025). Genetics and biomarkers are needed to select the right tool for the specific job. Future trials must adopt precision medicine inclusion strategies, selecting patients with relevant complement risk genetics and elevated complement activation markers (C3/C4 fragments, Ba, TCC) in plasma and/or CSF, thus enhancing the likelihood of a positive outcome. However, implementing such precision medicine strategies depends on the availability of reliable, standardised assays for complement biomarkers. While progress is being made (Kirschfink et al., 2024; Prohászka and Frazer-Abel, 2021, Frazer-Abel et al., 2021) many assays currently lack clinical validation. Pre-analytical variability, assay sensitivity, and differences in sample handling remain key limitations that must be addressed before biomarker-guided complement therapies can be routinely adopted.

In neurologically complex diseases such as AD and ALS, complement inhibitors may be most effective when used in synergistic therapeutic approaches alongside agents targeting parallel pathological pathways, such as anti-amyloid or anti-tau agents, neuroprotective drugs, or immunomodulators. Future clinical trials should explore such rational combinations to enhance efficacy and ultimately deliver more meaningful clinical outcomes for patients.

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Data availability

Data will be made available on request.

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