Received: 20 April 2022 | Revised: 17 July 2022 | Accepted: 19 July 2022

DOI: 10.1002/psp4.12852

WHITE PAPER

Hallmarks of neurodegenerative disease: A systems pharmacology perspective

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Abstract

Age-related central neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, are a rising public health concern and have been plagued by repeated drug development failures. The complex nature and poor mechanistic understanding of the etiology of neurodegenerative diseases has hindered the discovery and development of effective disease-modifying therapeutics. Quantitative systems pharmacology models of neurodegeneration diseases may be useful tools to enhance the understanding of pharmacological intervention strategies and to reduce drug attrition rates. Due to the similarities in pathophysiological mechanisms across neurodegenerative diseases, especially at the cellular and molecular

levels, we envision the possibility of structural components that are conserved across models of neurodegenerative diseases. Conserved structural submodels can be viewed as building blocks that are pieced together alongside unique disease components to construct quantitative systems pharmacology (QSP) models of neurodegenerative diseases. Model parameterization would likely be different between the different types of neurodegenerative diseases as well as individual patients. Formulating our mechanistic understanding of neurodegenerative pathophysiology as a mathematical model could aid in the identification and prioritization of drug targets and combinatorial treatment strategies, evaluate the role of patient characteristics on disease progression and therapeutic response, and serve as a central repository of knowledge. Here, we provide a background on neurodegenerative diseases, highlight hallmarks of neurodegeneration, and summarize previous QSP models of neurodegenerative diseases.

Significance

A quantitative mechanistic understanding for the pathophysiological mechanisms involved in neurodegenerative diseases could facilitate the discovery and development of novel therapeutics. We hope that this review provides a valuable resource for learning about the current state of and serving as a basic blueprint for the development of systems pharmacology models of neurodegenerative diseases.

INTRODUCTION

With an aging global population and the lack of effective disease modifying therapies, age-related neurodegenerative diseases are an increasing public health concern. A holistic systems-level understanding of the pathophysiological mechanisms involved in the etiology and progression of neurodegenerative diseases could lead to improved preventative measures and pharmacological treatment strategies. Neurodegenerative diseases result in mental and physical impairments, depending upon the types of degenerating neurons and their spatial organization within the brain. For example, the loss of pyramidal neurons in the cerebral cortex is responsible for the cognitive impairments observed in Alzheimer's disease (AD), whereas the loss of dopaminergic neurons in the substantia nigra results in the motor alterations associated with Parkinson's disease (PD). Despite the phenotypic differences across neurodegenerative diseases, there are striking similarities at the cellular and molecular level. We believe that these similar features can be grouped into four main hallmarks: disrupted proteostasis, oxidative and endoplasmic reticulum stress, metabolic dysfunction, and neuroimmune system alterations (Figure 1). In each of the neurodegenerative diseases, proteostasis becomes disrupted due to the aggregation of certain proteins. For example, β-amyloid and tau in AD, α-synuclein in PD, huntingtin in Huntington's disease (HD), and TDP-43 in amyotrophic lateral sclerosis (ALS). Physiological processes responsible for the clearance of pathological proteins decline as a function of age, increasing susceptibility for the accumulation of neurotoxic protein aggregates in the aged brain.[1] The accumulation of neurotoxic protein aggregates has been hypothesized to induce neuroinflammation and oxidative stress, leading to the development and progression of neurodegenerative diseases.[2] Oxidative and endoplasmic reticulum stress is a well-established feature of neurodegenerative diseases.[3,4] Metabolic alterations, especially in peripheral immune and neuroimmune cells, have emerged as an important feature associated with neurodegenerative diseases and cellular phenotypes. Neuroinflammation, the morphological change in glial cells and alteration of neuroimmune microenvironment, is present in and attributed to be a primary driver of neurodegenerative diseases.[5]

At the turn of the 21st century, there has been a paradigm shift from understanding biological systems via a reductionist approach that study components in isolation toward a holistic approach at the systems level.[6] Quantitatively understanding the holistic effects of pharmacological perturbations on the modulation of biological systems is an underlying aim of quantitative systems pharmacology (QSP). The QSP models have been gaining popularity as a tool in drug discovery/development

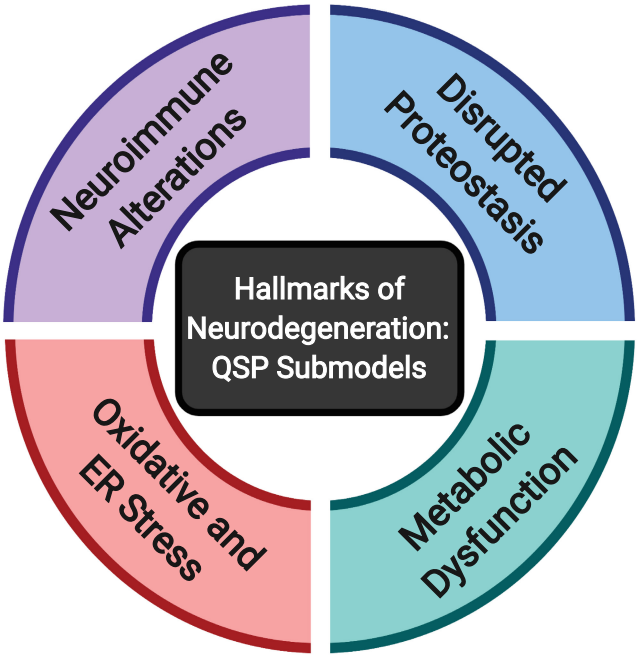

FIGURE 1 Hallmarks of neurodegeneration. Neuroimmune alterations, disrupted proteostasis, oxidative and endoplasmic reticulum stress, and metabolic dysfunction are key components that could be primary submodels in a platform quantitative systems pharmacology (QSP) model of neurodegenerative diseases.

to generate hypotheses, guide experimental design, and support internal/regulatory decisions. QSP models act as a central repository of knowledge through the integration of multiple datasets and data types, which can be used to recapitulate existing knowledge and provide predictions about unknown scenarios. As data are generated and fed into a continual cycle of model development and validation, knowledge about the system of interest increases and predictive uncertainty should decrease. In a recent cross-industry survey to assess the landscape for the use of QSP within pharmaceutical industries, neuroscience was reported to have the greatest potential for future growth.[7] Due to the complex and multifactorial nature of neurodegenerative diseases, a systems-level approach is warranted to enhance our understanding of these diseases and to identify novel therapeutic strategies. Because there are many commonalities in the pathophysiological mechanisms of neurodegenerative diseases at the cellular and molecular levels, QSP models could potentially contain structural submodels that are conserved across models of neurodegenerative diseases. The parameterization of the model would be disease/patient-specific. There could be several submodels within each of the outlined key hallmarks. For example, the disrupted proteostasis hallmark contains protein aggregation (Aβ, tau, and α-synuclein), autophagy, and proteasomal degradation submodels. Challenges remain on how to integrate mathematical models that span multiple levels of neurobiological organization and disparate timescales. However, technological advancements enabling the generation of novel data types and methodological improvements in mechanistic and machine learning modeling could help to overcome these knowledge gaps.[8]

We have outlined biological maps for the key hallmarks of neurodegenerative diseases that could serve as an initial blueprint for submodels within QSP models of neurodegenerative diseases. We have reviewed previously developed QSP models of neurodegenerative diseases and highlight some of the challenges and future opportunities.

NEURODEGENERATIVE DISEASES

Alzheimer's disease

The pathogenesis of AD is a complex multifactorial process that remains unclear. AD research has focused on the aggregation of beta-amyloid (Aβ) to form senile plaques and aggregation of tau to form neurofibrillary tangles (NFTs). The hypothesis that amyloid pathology is the primary driver of AD includes a sequence of pathological events starting with the accumulation and oligomerization of Aβ, deposition of Aβ as plaques, glial activation and inflammatory responses, altered ionic homeostasis and oxidative injury, and altered phosphorylation activity, which leads to neuronal dysfunction and loss.[9] Aβ is generated by the proteolytic cleavage of the Aβ precursor protein (APP). Mutations in APP presenilin-1 (*PSEN1*) and presenilin-2 (*PSEN2*) are associated with increased risk of developing AD and have been shown to alter the dynamics of Aβ.[10] Aβ pathology is thought to precede and facilitate the development of tau pathology, although pure tauopathies where Aβ is absent suggest that tau could be a greater driver of neuronal dysfunction. An alternative dual-cascade hypothesis posits that AD-associated molecular pathways can drive tau pathology independent of Aβ.[11] Tau pathology appears to originate in the transentorhinal region (stages 1–2), spreads to the limbic system (stages 3–4), and then spreads to the isocortical region (stages 5–6), according to the Braak stages of AD pathology.[12]

As there are no fully approved disease-modifying therapies, AD is managed with symptomatic treatments consist of acetylcholinesterase inhibitors (donepezil, rivastigmine, and galantamine) and/or NMDA receptor antagonists (memantine). The drug development landscape for AD includes ~100 disease-modifying drug candidates.[13] Despite the large body of evidence supporting the amyloid hypothesis, clinical investigations using amyloid-targeting therapies have repeatedly failed to show benefit on primary efficacy end points. Inhibitors of beta-secretase 1

(BACE1), an enzyme that converts APP to Aβ, decreased Aβ burden in the brain, but had no effect on clinical end points and, in certain cases, unexpectedly worsened cognition.[14] Antibody therapeutics targeting Aβ did not improve cognitive outcomes, despite lowering amyloid levels and even reducing tau burden.[15] Although a topic of debate, aducanumab, an anti-Aβ antibody, was granted accelerated approval by the US Food and Drug Administration (FDA) in July 2021 as the first disease-modifying therapy for AD. Tau-targeting strategies have been gaining momentum for the treatment of AD and other tauopathies.[16] However, there has been conflicting clinical results in the use of anti-tau antibodies for AD. In phase II of clinical development, gosuranemab failed to slow cognitive decline and was discontinued, however, semorinemab significantly reduced the rate of cognitive decline for on one of two co-primary end points. Clinical drug development is not limited to targeting Aβ/tau, other mechanisms and pathways of interest are neurotransmission (cannabinoids, NMDA receptor antagonists, orexin antagonists, melatonin receptor agonists, serotonin receptor agonists, and selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor), metabolism (SGLT2 inhibitors and insulin), neuroimmune system (CD33, TREM2, RIPK1 inhibitors, phosphodiesterase inhibitors, leukotriene inhibitors, and inflammasome inhibitors), neuroprotection (neurotrophins and HDAC inhibitors), and a variety of nutraceuticals (thiamine, polyphenolics, resveratrol).[13] The microbiome has emerged as a potential target for AD and in 2019 the first drug candidate, oligomannate, thought to act primarily through modification of the microbiome, received conditional marketing approval in China for the treatment of AD.[17,18]

Parkinson's disease

PD is characterized by the presence of intra-neuronal inclusion bodies, Lewy bodies (LBs) and Lewy neurites (LNs), in postmortem histopathological analyses on the brains of patients with PD.[19] Braak and coworkers proposed a staging system based on postmortem examinations of LB/LN and suggested that PD progresses through six stages, initiating in a peripheral location and progressing to the central nervous system (CNS) via olfactory and/or vagal nerves in presymptomatic stages 1/2. The underlying pathology of PD is believed to develop over a decade or longer before clinical motor symptoms manifest.[20] Nonmotor symptoms, such as constipation, gastric dysmotility, sleep disturbances, and depression, may precede motor symptoms and appear in prodromal stages. In stages 3/4, the substantia nigra, thalamus, and amygdala are all affected and the classical motor symptoms are clinically evident. In stages 5/6, pathology spreads to sensory and motor areas of the neocortex and the disease manifests maximally. In advanced stages of PD, patients may exhibit more severe motor symptoms, including loss of stability, increased risk of falls, dysphagia, and non-motor symptoms, including dementia and psychosis.[21]

The etiology of PD is thought to be multifactorial and complex, with genetics, age, and environmental factors playing a role in the manifestation and progression of disease. Aggregates of α-synuclein (Asyn) are a primary component of LB/LN. Multiple feedback interactions among misfolded Asyn, oxidative stress, and protein degradation machinery as well as dysregulation of mineral homeostasis and neuroinflammation have been implicated in PD pathogenesis and progression.[22] A large proportion of PD cases are sporadic, with the familial cases accounting for ~10% of cases. *SCNA* mutations were the first to be linked with PD and over 20 different genetic associations have now been identified.[23] Many of these genes are involved in mitochondrial oxidative stress and autophagy pathways. Exposure to environmental toxins has been associated with PD.[24]

Currently, there are no disease-modifying therapies for PD and symptomatic treatments aimed at reducing motor symptoms by restoring dopamine are the standard of care. This is achieved by either supplementing with a dopamine precursor (levodopa), dopamine agonists (ropinirole and rotigotine), or by blocking enzymes responsible for dopamine clearance, such as monoamine oxidase B and catechol-O-methyltransferase. Deep brain stimulation (DBS) is also able to achieve symptomatic relief from motor symptoms of PD. Emerging therapies against PD are exploring alternative targets, such as Asyn, glucocerebrosidase, and leucine-rich-repeat kinase 2, which are in various stages of clinical development.[25]

Amyotrophic lateral sclerosis

ALS, traditionally considered a neuromuscular disease, is characterized by the progressive loss of motor neurons in the CNS with a heterogenous clinical presentation of muscle weakness and motor deficits with either a limb/spinal-onset (arms and legs) or bulbar-onset (speaking and swallowing).[26] About 10% of ALS cases exhibit familial inheritance.[27] Familial ALS in persons of European descent is primarily driven by mutations in *C9ORF72* (33.7%), *SOD1* (14.8%), *TARDBP* (TDP-43; 4.2%), and *FUS* (2.8%), whereas the remaining genetic drivers are unknown (44.5%).[28] The genetics of familial ALS in persons of Asian descent is less understood and *SOD1* mutations are the largest known contributor (30%).[28] Sporadic ALS cases have exhibited mutations in some of the identified

familial ALS genes, however, the majority of cases have no known genetic association (~95%).[28] The proteostasis of TDP-43 is disrupted in ALS, characterized by ubiquitinated TDP-43 inclusions in motor neurons. SOD1 is an enzyme that functions as an antioxidant, which is impaired through mutations in patients with ALS. There is a growing body of evidence for metabolic reprogramming and dysfunction in patients with ALS, especially CNS glucose metabolism.[29]

There is no curative treatment for ALS. Two FDA drugs approved for ALS are modest disease-modifying therapies. Riluzole, which the FDA approved in 1995, is an anti-glutamatergic drug that showed to improve median survival time of patients with ALS by a few months.[30] Edaravone is thought to work primarily as an antioxidant and demonstrated efficacy on the ALS functional rating scale (ALSFRS-R). Treatment with edaravone for 6 months resulted in approximately a 33% reduction in the rate of decline on the ALSFRS-R scale.[21] However, the efficacy of edaravone on prolonging the survival of patients with ALS remains unknown. There are many emerging therapies under clinical investigation for the treatment of ALS and neuroinflammation appears to be the primary area of focus.[31]

Huntington's disease

HD is a neurodegenerative disorder characterized by motor, cognitive, and behavioral symptoms and commonly occurs in the prime of adult life.[32] The disease exhibits autosomal dominant inheritance of the variable CAG trinucleotide repeat expansion in the *HTT* gene on chromosome four that encodes the mutant form of the multifunctional protein huntingtin. Mutant huntingtin has an abnormally long polyglutamine (polyQ) domain in the N-terminus leading to the expansion of the CAG repeats. An expansion of ~40 CAG repeats in comparison to ~6–35 CAG repeats in normal *HTT* gene results in highly penetrant mutation characteristic of disease manifestation, whereas 36–39 CAG repeats have low penetrant mutation. These variable repeats lead to variable manifestation of HD with some patients having a clinical diagnosis and others leading a normal life without clinical manifestation of HD. Although largely unknown, the normal huntingtin protein plays a critical role in the development of the nervous system and the protein is expressed ubiquitously throughout the body. The mutant form of the protein is unable to perform normal functions and the polyQ repeats result in a toxic gain-of-function expansion primarily leading to alterations in the conformational structure of the protein. The highly aggregation prone mutant protein causes neuronal dysfunction and death through mechanisms related to direct toxicity and dysregulation of transcription-related proteins, mitochondrial function, and proteostasis by sequestration of proteins in cytoplasmic aggregates and nuclear inclusions.[32,33]

The clinical treatment of HD is still largely symptomatic. Tetrabenazine and deutetrabenazine were approved by the FDA for the treatment of chorea. Treatment of psychiatric symptoms is managed with atypical antipsychotics and antidepressants.[34] Silencing the mutant protein through the development of RNA interference (RNAi) and antisense oligonucleotides (ASO) are therapeutic approaches under development in recent years. The antisense oligonucleotide IONIS-HTTRx has been shown to reduce the concentrations for the mutant protein huntingtin by inhibiting the messenger RNA for *HTT*. A recent phase I/IIa trial investigating intrathecal administration of IONIS-HTTRx in adults with early HD showed a dose-dependent decrease in mutant huntingtin in cerebrospinal fluid (CSF). The follow-up GENERATION HD phase III trial was halted recently due to concerns about risk/benefit. Two other ASO based therapies (WVE-120101 and WVE-120102) targeting gene silencing of the mutant *HTT* are currently in phase I/II clinical trials have also been suspended due to lack of efficacy. Several neuroprotective and anti-inflammatory therapies are also under clinical investigation. VX15/2503 is an antibody targeting the protein semaphorin 4D (SEMA4D) that causes severe neuroinflammation and neurodegeneration via activation of microglia and astrocytes. Early results have shown that the antibody prevents the decrease in brain volume (magnetic resonance imaging [MRI]) and metabolic activity in cortical regions in comparison to the placebo group.

Deep brain simulation, which involves surgical intervention and implantation of an electrode in the globus pallidus region of the brain, stimulates the brain via controlled electronic pulses, is currently being evaluated in patients with clinically symptomatic and genetically confirmed HD.

Tauopathies

Tauopathies comprises a group of ~20–30 neurodegenerative diseases and are pathologically defined by the presence of aggregated tau species in the brain.[35] The most common are AD, fronto-temporal dementia, progressive supranuclear palsy (PSP), Pick's disease, chronic traumatic encephalopathy (CTE), cortico-basal degeneration (CBD), and primary age-related tauopathy (PART). Post-translational modifications of tau, such as hyperphosphorylation, acetylation, methylation, glycosylation, glycation, nitration, polyamination, truncation, and

ubiquitination, have been shown to occur early in neurofibrillary pathology and neurodegeneration.[36]

Alternative splicing of exons in the primary tau transcript results in six isoforms of tau in the human brain, characterized by zero (0N), one (1N), or two (2N) inserts in the amino-terminus domain and three (R3) or four (R4) repeats in the Microtubule Binding Repeat.[37] The presence of specific isoforms in tau aggregates can differ across neurodegenerative diseases. For example, 3R and 4R isoforms are present in tau aggregates in AD, PART, and CTE, whereas tau aggregates in PSP and CBD only contain 4R isoforms, and Pick's disease only contains 3R isoforms. Intracellular tau exists in multiple forms, monomeric, oligomeric, filamentous, and NFTs.[38] Extracellular tau exists in free form, exosomes, ectosomes, and nanotubes. Pathological tau species are hypothesized to spread along neuronal projections via prion-like neuron-to-neuron transmission at the neuronal synapse. Normal tau proteins can be converted to pathological tau through interactions with pathological tau species. Exosomes containing tau with seeding activity have been isolated from the brains of tau transgenic mice.[39] In addition, seed-competent tau species, in both free and vesicular forms, have been detected in CSF and interstitial fluid (ISF) from experimental models and CSF from patients with AD.[40,41] Tau fibrilization is thought to start as a loss of microtubule binding function followed by accumulation and self-association, likely regulated by post-translational modifications. Pathological tau consists of oligomeric, filamentous, and NFTs.[38,42] Tau pathology exhibits an initial spatial localization and spreading pattern that is specific for the type of neurodegenerative disease. The diversity in the clinical presentation of tauopathies results most likely from the spatial localization of tau burden and neural circuitry, which damages different types of neuronal populations and governs the pathological spread.[43]

Based on the hypothesis that disease trajectory will be modified by reducing the extracellular transmission of tau, several passive immunotherapy strategies targeting tau are under clinical development.[43] These therapeutics bind extracellular tau and reduce tau seeding in preclinical experimental models. However, the following considerations are important when evaluating the potential of tau immunotherapy strategies. First, there is a significant amount of heterogeneity, within and between neurodegenerative diseases, regarding the regional localization, spreading trajectory, types of tau isoforms, post-translational modifications, and the structure of NFTs. Second, there are multiple routes of extracellular transmission, such as nanotubes and vesicles, of pathological tau species, which could shield tau from interacting with an antibody.[43] These underlying mechanistic processes may govern the potential degree of disease modification.

HALLMARKS OF NEURODEGENERATIVE DISEASE

This section addresses the commonalities among pathological mechanisms across different neurodegenerative diseases that provides a starting point for the construction of a biological map of neurodegeneration, which could be used to inform the development of QSP models.

Disrupted proteostasis

Protein degradation systems play an important role in the clearance of toxic protein aggregates. The autophagy-lysosomal pathway (ALP) and ubiquitin-proteosome system (UPS) are the two major protein degradation mechanisms in cells (Figure 2). The activity of these pathways has been shown to decline with age, which contributes to the accumulation of pathological proteins.[44,45] ALP consists of three forms: macroautophagy, microautophagy, and chaperon-mediated autophagy (CMA).[46] Proteins enter lysosomes via membrane invagination during microautophagy and through a transmembrane protein translocation complex during CMA. Tau and alpha-synuclein are substrates for CMA and post-translational modified and aggregated forms have been shown to inhibit CMA.[47,48] Macroautophagy, the major form of ALP, eliminates damaged organelles and toxic protein aggregates through the formation of autophagosomes and subsequent fusing with lysosomes to form autolysosomes.[49]

The ALP is disrupted across neurodegenerative diseases. In AD, there is an accumulation of autophagosomes in neurons.[50] There are a few potential mechanisms for this increase, such as deficient microtubule transport, impaired autophagosome-lysosome fusion, and reduced vesicle clearance, rather than autophagy induction.[50,51] Increases in autophagosomes does not necessarily translate to increased clearance of protein aggregates, as there could be decreased amounts of pathological protein inside the vesicles or impaired degradation ability. For example, defects in the ability of autophagosomes to recognize and sequester cargo has been observed in preclinical models of HD, which results in decreased huntingtin protein clearance despite the increased abundance of autophagosomes.[52] Impaired acidification and proteolytic activity of lysosomes due to mutations in presenilins have been linked to the development of familial AD.[53] Although the mechanisms have not been fully elucidated, alterations in endo-lysosomal compartment conditions, such as pH, could facilitate the formation of toxic oligomeric Aβ species.[54] Release of Aβ oligomers into the extracellular environment via exocytosis could facilitate the progression of

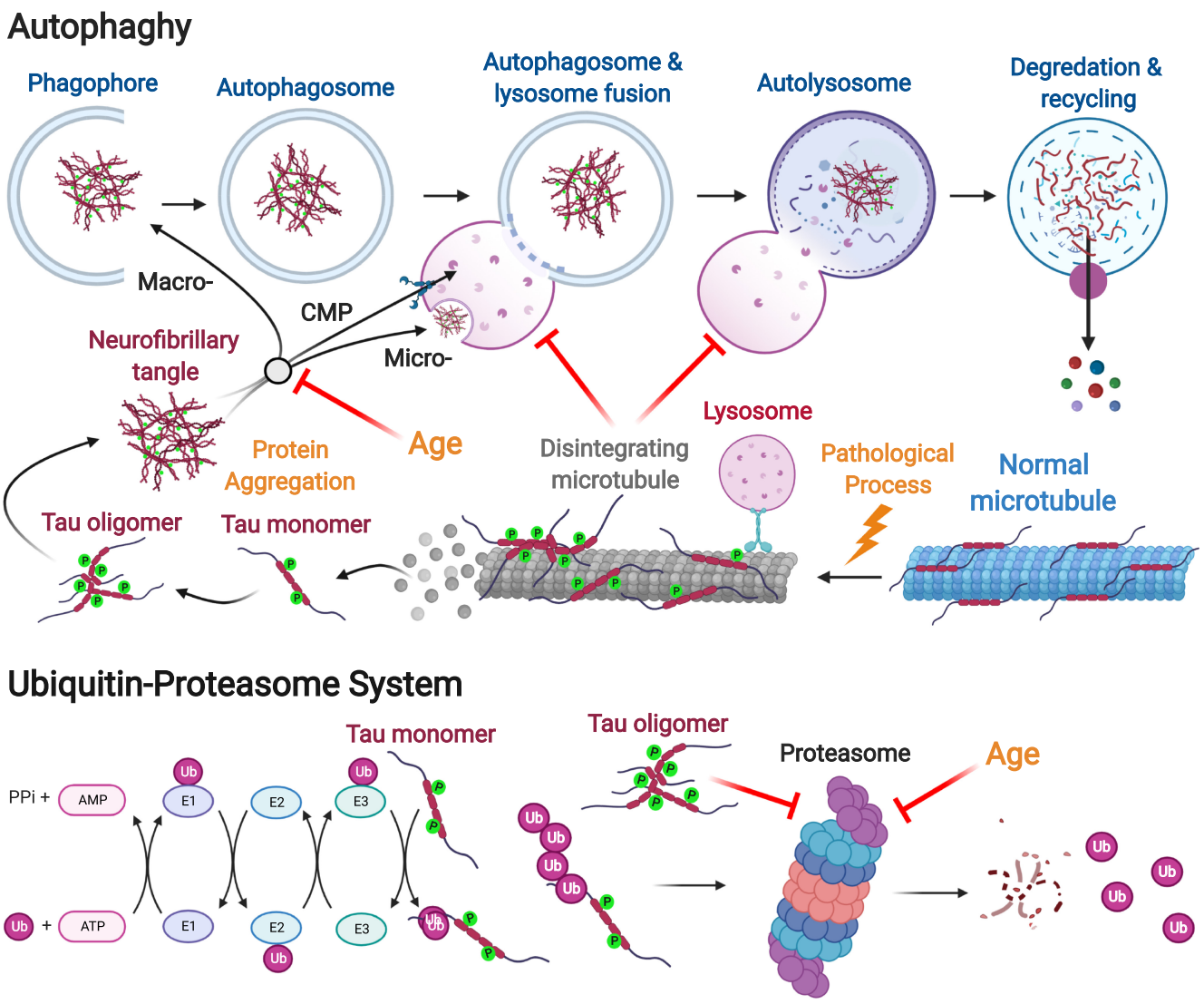

FIGURE 2 Disrupted proteostasis in neurodegenerative disease. Cellular and molecular processes involved in disrupted proteostasis of pathological proteins in neurodegenerative diseases, focusing on tau protein in this example. Pathological processes cause the aberrant hyperphosphorylation of tau compromising its ability to maintain a healthy normal microtubule function, which results in the disintegration of microtubules and their ability to transport important cargo and organelles. Tau is subsequently released from microtubules, where monomers begin to aggregate into oligomers and form neurofibrillary tangles (NFTs). Intracellular proteins are cleared through autophagy proteasomal degradation. Proteins directly enter lysosomes via microautophagy and chaperone-mediated autophagy (CMP). Macroautophagy initiates through the formation of a phagophore, which forms vesicle (autophagosome) around tau proteins of all forms to be cleared. Autophagosomes fuse with lysosomes to form autolysosomes, which breaks down proteins through acidification. The ubiquitin-proteasome system is limited to the clearance monomeric tau and is inhibited by tau oligomers. Tau is ubiquitinated and fed through the proteasome for proteolytic cleavage. Both of these clearance processes experience functional decline with age, which contributes to an increase in pathological protein burden.

tau pathology and subsequent neurodegeneration. The production, intracellular disposition, and elimination of autophagosomes/autophagolysosomes are processes dependent upon microtubule transport, which becomes disrupted by pathological hyperphosphorylated tau.

Metabolic homeostasis is achieved by cells ability to sense and respond to nutrient availability. Autophagy is intricately connected to cellular metabolism through nutrient signaling pathways, where periods of low nutrients stimulate autophagy to meet energetic demands. Autophagy is primarily regulated by the mTOR pathway, where the activation of mTORC1 by nutrient surplus and growth factors result in the inhibition of autophagy.[55] The inhibition of mTOR by rapamycin stimulates autophagy and attenuates amyloid/tau pathology in mice.[56,57] AMPK is a kinase that is activated in response to energy-depletion, which activates autophagy. AMPK and mTOR both regulate autophagy through

the phosphorylation of ULK1.[58] Beclin 1, another protein involved in autophagy regulation, is decreased in AD brain tissue and its heterozygous deletion in APP-transgenic mice results in an increase in Aβ plaque formation.[59]

UPS is responsible for the majority of cellular proteolysis, ~80–90%.[60] Ubiquitin-mediated proteolysis is an energy-dependent process, which consists of enzymes, chaperons, and shuttles that tag specific substrates with ubiquitin, unfold proteins, and direct ubiquitin conjugated proteins to the proteasome for degradation. There is cross-talk between UPS and ALP, and these pathways act in a compensatory manner. The UPS preferentially degrades monomeric and misfolded proteins, whereas ALP degrades protein aggregates and organelles. Aggregated forms of Aβ/tau have been shown to inhibit proteasome function, which facilitates the accumulation of Aβ/tau and induces neuronal degeneration and death.[61,62]

Post-translational modifications (PTMs) of proteins regulate their structure and function. PTMs of proteins involved in neurodegenerative diseases has been reviewed in detail.[63] In neurodegenerative disease, aberrant PTM could impact aggregation/seeding propensity and serve as potential biomarkers of disease. For example, specific phosphorylated sites on tau positively correlate with seeding capacity and plasma concentrations of phosphorylated threonine 181/217 on tau is associated with AD brain pathology.[64,65] Calpain-mediated tau cleavage is increased in AD and tau N-terminal fragments are prevalent in AD CSF.[66]

Increasing evidence suggests a spatio-temporal progression of misfolded proteins along well-defined connected neuronal projections in a number of neurodegenerative diseases. Large cross-sectional studies of AD/PD brain tissue indeed suggest a well-defined trajectory of pathological changes.[67] This hypothesis has been largely confirmed in patients with AD using tau positron emission tomography (PET) imaging and in preclinical animal models of PD investigating the inter-neuronal spread of Asyn.[68,69] Intracerebral injection of tau protein from AD brain extract in mice leads to a very specific tau pathology progression along interconnected anatomic pathways.[70] In general, this process consist of the following steps: (1) activity-dependent secretion of misfolded proteins from a presynaptic nerve ending, (2) diffusion to the post-synaptic membrane and along axonal compartments, (3) binding to an acceptor protein, (4) internalization into the second neuron, (5) delivery to the intracellular compartment, (6) binding and templating of monomeric proteins leading to protein aggregates, (7) axonal transport of the misfolded oligomers over the neuronal projection, (8) degradation by UPS and ALP, and (9) secretion in the second synapse.

Oxidative and endoplasmic reticulum stress

Oxidative and endoplasmic reticulum (ER) stress pathways induce neuronal apoptosis through a complex cellular signaling network (Figure 3). Oxidative stress in neurodegenerative disease is a complex multifactorial process comprised of age-related changes, genetic mutations, lifestyle factors, and environmental exposures, which has been an active topic of research for several decades and extensively reviewed.[3,71,72] Oxidative stress is the imbalance between the production and removal of reactive oxygen (ROS) and reactive nitrogen species (RNS), which results in oxidative damage to biomolecules. ROS/RNS play an important physiological role in intracellular signaling to maintaining cellular homeostasis, but at high concentrations can induce pathological states leading to cell damage and death.[73] Neurons are particularly susceptible to oxidative stress due to high polyunsaturated fatty acid content in the membranes, high metabolic activity and oxygen consumption, and low antioxidant defenses.[74] Additionally, the brain is thought to be highly susceptible to oxidative stress due to its high oxygen consumption (~20% of total body oxygen use) relative to its size (~2% of total body mass).[75] Oxidative damage manifests as an increase in lipid peroxidation, oxidative modification to proteins, and nucleic acid oxidation. Lipid peroxidation can disrupt biological membranes, alter cellular signaling, and cause DNA damage and cytotoxicity. Many studies have reported increased lipid peroxidation in the brains of patients with AD relative to age-matched controls.[76] Post-translational modifications to proteins by oxidative stress can disrupt protein structure, which could alter its biological function, aggregation propensity, and turnover rate. Oxidative damage to DNA and RNA can result in alterations to gene transcription, protein translation, and epigenetics, in addition to its mutagenic effects. ROS-induced DNA damage can accelerate aging, induce inflammation (TNFα and IL-1β), and increase susceptibility to neurodegenerative disease.[77] Damaged DNA also increases PARP1, which depletes NAD+ and sirtuins, facilitating neurodegeneration.[77]

ROSs often have a negative connotation as they have been implicated in a variety of neurodegenerative diseases, but they are important second messengers for intracellular signaling pathways and play a vital role in the determination of cellular fates and phenotypes, such as synaptic plasticity, autophagy, apoptosis, necrosis, and pyroptosis.[78] ROSs are produced in the mitochondria, endoplasmic reticulum, peroxisomes, cytosol, plasma membrane, and extracellular space.[79] Historically, the mitochondria was thought to be the primary source of ROS, but the relative contribution of ROS from each of these

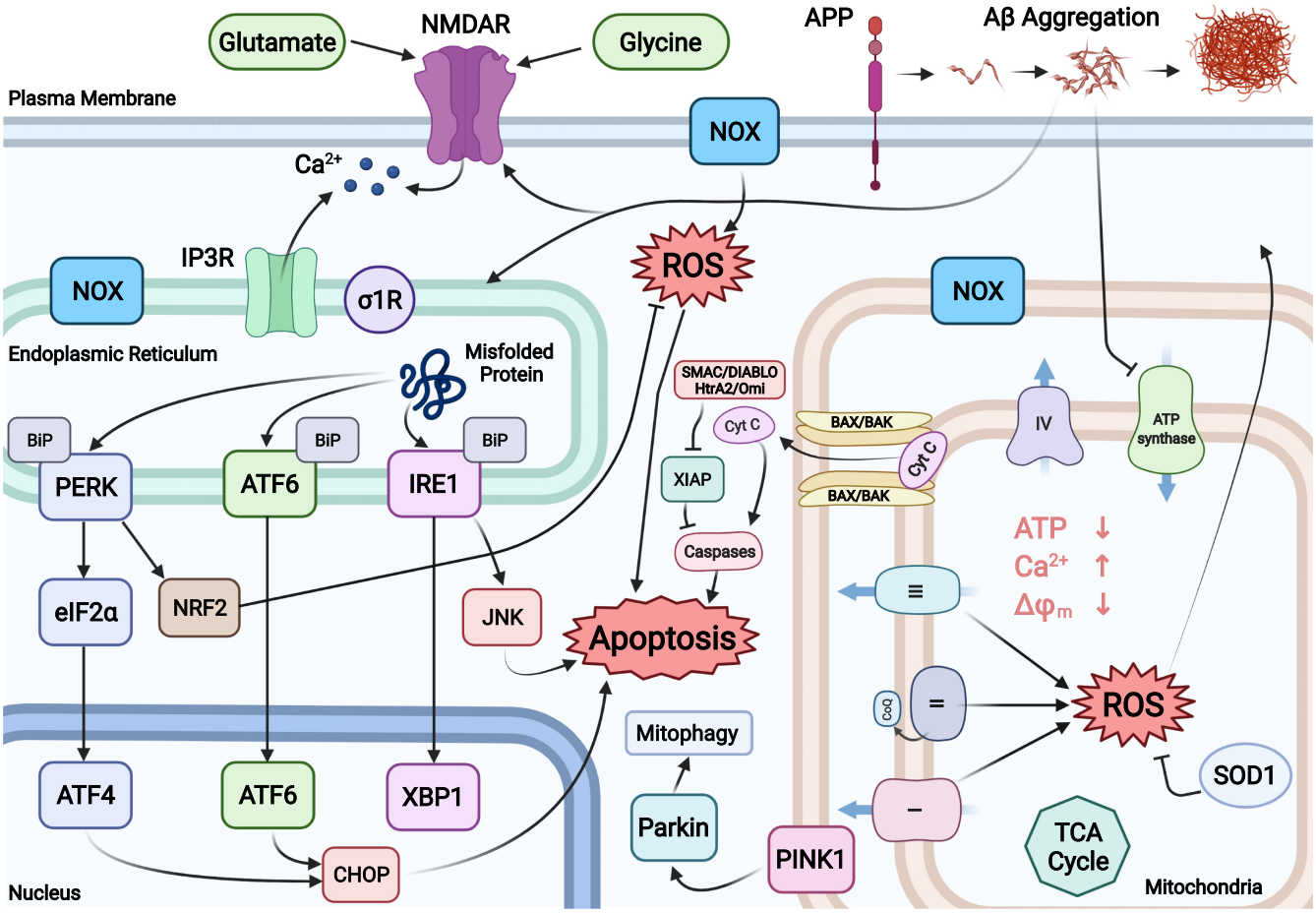

FIGURE 3 Oxidative and endoplasmic reticulum (ER) stress pathways in neurodegenerative disease. Oxidative and ER stress leads to neuronal apoptosis through a complex intracellular network. Pathological proteins, such as Aβ, disrupt cellular processes and organelles, such as the plasma membrane, ER, and mitochondria. APP is cleaved to Aβ, which aggregates to form oligomeric Aβ and amyloid plaques. Aβ oligomers activate NMDA receptors, induce the unfolded protein response (UPR), and inhibit components of the mitochondrial electron transport chain, which increases intracellular calcium, decreases ATP production, and increases reactive oxygen species (ROS). The ROS directly induces apoptosis. Mitochondrial dysfunction leads to the mitochondrial permeability transition (MPT) pore opening, releasing cytochrome C (Cyt C), and leading to the intrinsic apoptosis cascade. Misfolded proteins induce the UPR. The UPR has three main signaling pathways, PERK, ATF6, and IRE1, which upregulate genes during stressed conditions. The activation of NRF2 by PERK leads to a decrease in ROS. The upregulation of CHOP by ATF4/ATF6 and JNK by IRE1 leads to apoptosis through shifting the balance between pro- and anti-apoptotic proteins.

sources remain to be elucidated and are dependent on several factors, such as ROS/cell type, species, and disease state.[79] The antioxidant system, comprised of antioxidants and antioxidant enzymes, is responsible for inhibiting the oxidation of molecules by suppressing the amount oxidative radicals. The spatial localization of ROS production, ROS type (O_2^- vs. H_2O_2), concentration, and elimination rate are drivers of ROS-mediated cellular signaling dynamics that govern various cellular processes and fates.

The ER is a major site of protein synthesis and folding in eukaryotic cells. Although the ER is associated with several chaperones and folding enzymes to ensure correct protein folding, mistakes in protein synthesis and folding occur and are dealt with by the unfolded protein response (UPR). The UPR is a highly conserved signaling pathway, which is triggered in the presence of misfolded proteins and designed to maintain ER/protein homeostasis. In some cases, the UPR is insufficient to clear misfolded proteins resulting in several problems, including cellular signaling alterations, toxicity due to protein accumulation, and apoptosis, which contributes to the pathogenesis of several neurodegenerative diseases.[4] Protein aggregates in neurodegeneration have been shown to be heavily ubiquitinated indicating that they have been targeted by the proteasome degradation system, but the cell has not successfully cleared them.[4] The dynamics of the UPR are complex as acute versus chronic stress/activation results in differences in gene expression leading to acute versus adaptive responses, which can shift the balance between cell survival and death. In neurodegenerative diseases, the

UPR is thought to be chronically activated by a variety of stressors, such as genetics, aging, sleep deprivation, ROS, and nutritional deficiencies.

Several genetic mutations involved in the ROS/ER stress pathways have been associated with neurodegenerative diseases, particularly in the early onset or familial diseases.[80] Mutations could impact the function and/or abundance of proteins. For example, misfolded protein aggregates disrupt ER function by associating with ER chaperones or inhibiting traffic of proteins from the ER to the Golgi.[81–83] Mutant SOD1 aggregates and mutant huntingtin disrupt ER associated protein degradation by causing aberrant protein–protein interactions.[84,85] PTEN-induced putative kinase protein 1 (PINK1) accumulates on the outside of depolarized mitochondria recruiting E3 ubiquitin ligase parkin, which ubiquitinates mitochondrial proteins targeting them for degradation. Mutations in PINK1 are associated with hereditary early-onset PD.[86] Mutations in parkin cause ER stress, which is thought to contribute to PD.[87] A mutation in a protein associated with vesicle trafficking that reduces the UPR is thought to be associated with ALS.[88]

Each neurodegenerative disease has a misfolded protein problem that generates oxidative stress and activates the UPR, which in turn can modulate posttranslational modifications, such as the hyperphosphorylation of tau.[89] Therefore, there could potentially be a positive feedback loop, where tau increases ROS and ROS increases the posttranslational modification and aggregation of tau, further increasing ROS. The molecular mechanisms of UPR activation by misfolded proteins appear to be conserved between the different diseases. However, there may be quantitative differences in the extent that these pathways are activated. For example, XBP1 and ATF6 activation were activated in both ALS and AD, but genes involved in co-chaperone activity and ERAD were more prominent in ALS, whereas genes involved in protein folding were more prominent in AD.[90] We believe that this supports the concept of a structurally conserved QSP submodels with disease-specific parameterizations.

Different neuronal populations and circuits may be more or less sensitive to ROS and ER stress. In the stressor threshold model, subsets of neurons subjected to high levels of excitation and intracellular calcium are vulnerable to stressors.[91] For example, substantia nigra pars compacta neurons in PD are particularly vulnerable to mitochondrial dysfunction, whereas neurons in the hippocampus and entorhinal cortex in AD are vulnerable to energy deprivation, and cortical medium spiny neurons in HD are vulnerable to high calcium mediated excitability. Therefore, the combination of genetics, environmental exposures, and lifestyle factors could all contribute to stress thresholds of these different neuronal populations and govern the etiology and progression of different neurodegenerative diseases.

Metabolic dysfunction

Metabolic disturbances in the body's capacity to process macronutrients such as fat, protein, and carbohydrate contribute to the aging process and is found to be linked to neurodegenerative diseases.[92] Obesity, characterized by an excessive fat accumulation leading to body mass index (BMI) greater than 30 kg/m^2 is found to double the risk of AD compared to an individual with BMI in the normal range. Adult and pediatric obese populations display brain atrophy in the frontal lobe and thalamus, decreased volume of frontal, limbic gray matter, reductions in microstructural integrity, and hippocampal atrophy, compared to individuals with healthy BMI (18.5–25).[93–95] Postmortem evaluation of elderly obese patients displayed higher concentrations of Aβ, APP, and tau than non-obese individuals.[96] A recent study conducting a meta-analysis of 243 observational prospective studies and 153 randomized controlled trials identified high BMI and diabetes as a risk factor for AD.[97] Among other metabolic disorders, metabolic syndrome (MetS) is a set of common pathologies including dyslipidemia, hypertension, insulin resistance, and abdominal obesity.[98] Dysregulation in adipokines and leptin levels initiate the development of MetS causing changes to the hypothalamic appetite/satiety set point. Abnormalities in fatty acid metabolism cause the nutritional signaling in the brain to be altered. Dysregulation of the hypothalamic–pituitary–adrenal axis in MetS is associated with the downregulation of glucocorticoid receptors in the hippocampus.[98] Epidemiological studies have linked cognitive impairment,[99] vascular dementia,[100] and AD[101] to MetS. A prospective study with 165 participants (mean age 76.4 years) from 2005 to 2016 measured Aβ using PET neuroimaging. MetS is significantly associated with increased rates of Aβ accumulation in superior parietal and precuneus regions, however, MetS was not associated with amyloid positivity.[102] There is conflicting evidence evaluating MetS as a risk factor in AD. A recent study conducted on 350 middle-aged non-AD Hispanics suggests MetS as an arbitrary measure does not capture the risk of AD in late middle-aged men.[103] Further evaluation is needed to understand the link between MetS and the onset/progression of AD. Insulin resistance could be the bridge linking MetS and AD. Accumulating evidence suggests AD is closely related to the dysfunction in insulin signaling and glucose metabolism in the brain. Sites of neurodegeneration in AD, such as the hippocampus and temporal lobe, have the highest abundance of insulin receptors.[104] The transcription of anti-amyloidogenic

proteins, such as insulin-degrading enzyme and alpha-secretase, that eliminate Aβ is stimulated by insulin.[105] A decrease in the activity and expression of insulin receptors[106] and CSF insulin has been observed in patients with AD with worsening progression.[107] Aβ can compete with insulin for binding to the insulin receptor, which interrupts signaling and contributes to insulin resistance. Impaired insulin signaling impacts the PI3K/Akt pathway and increases Aβ and tau phosphorylation.[108] Willette et al. reported that high insulin resistance in 187 middle-aged adults was found to be highly correlated with increased Aβ deposition in the brain.[109] According to the Mayo Clinic Alzheimer Disease Patient Registry, 81% of cases with AD had either type 2 diabetes mellitus (T2DM) or impaired fasting glucose,[110] which clearly indicates overlapping pathology between AD and T2DM. Impairment in glucose and energy metabolism in both T2DM and AD has been evidenced in multiple PET and MRI studies.[111–113] Several large epidemiology studies across diverse ethnicities have shown patients with T2DM have an elevated risk of developing AD.[114–116] Altered glucose metabolism and insulin resistance has also been observed in PD, ALS, and HD.[29,117,118]

Metabolic reprogramming and aberrant inflammation of microglial cells has been observed in several neurodegenerative diseases. An unfavorable microenvironment created by circulating immune cells, glucocorticoids, pro-inflammatory cytokines, adipokines, and dyslipidemia disrupts microglial and induces a transition out of their homeostatic state.[119] Gliosis and aberrant morphology characterized by microglia dystrophy, fragmentation of microglial cytoplasm, enlarged cell bodies, and shortened processes are observed in obese subjects compared to individuals with normal BMI.[120] Impaired energy homeostasis is found to occur in chronically inflamed hypothalamus inducing neuronal apoptosis and reduction of synaptic inputs.[121,122] Hypothalamic inflammation has been shown to be highly correlated with worsening of cognitive performance in obese subjects.[123] Aβ has been shown to cause acute microglial inflammation, which promotes metabolic reprogramming from oxidative phosphorylation to aerobic glycolysis. Subsequently, Aβ initiates immune tolerance and defects in glucose metabolism in microglia.[124] Disrupted carbohydrate metabolism in astrocytes and microglia was shown to be one of the most important pathological features in AD based on a postmortem brain proteomics analysis.[125] Microglia expressing a TREM2 mutation associated with AD were found to have increased autophagy and reduced clustering around amyloid plaques, which was restored upon increasing ATP levels.[126]

Dysbiosis in gut microbial diversity and abundance has been found in neurodegenerative diseases (Figure 4).[127,128] The prominent genera identified was highly correlated to AD CSF biomarkers and the genera with least abundance were suggested to be protective against AD progression.[127] PET imaging results have identified a higher abundance of pro-inflammatory bacteria and decreased abundance of anti-inflammatory bacteria in cognitively impaired individuals with amyloidosis.[129] Using AD mouse models, Wang et al. discovered the alteration in gut microbiota leads to peripheral accumulation of phenylalanine and isoleucine, which promotes proliferation of pro-inflammatory T cells. The infiltration of T cells in the brain is associated with microglial activation and drives neuroinflammation.[130] In PD, pathological Asyn is thought to originate in the gut and propagate to the brainstem via the vagus nerve, leading to loss in dopaminergic neurons. Preclinical experiments in mice demonstrated that severing the vagus nerve prevents gut-to-brain spread of Asyn, supporting the hypothesis of a transneuronal propagation of pathological Asyn from the gut to the brain.[131] Emerging clinical evidence recognizes that metabolic disorders and altered gut microbiota are implicated in the etiology and progression of various neurodegenerative diseases. Until recently, metabolic disturbances were considered as risk factors for clinicians to identify vulnerable populations that may develop neurodegenerative diseases. Elucidation of mechanisms underlying the impact of metabolic dysfunction and gut dysbiosis holds promise in identifying targets and therapeutic interventions for neurological disorders. Clinical studies support dietary interventions, such as a Mediterranean diet[132] and low carbohydrate ketogenic diet,[133–135] as a prophylactic measure to reduce pathological biomarkers of AD and potentially delay the onset of neurodegenerative diseases.

Neuroimmune system

Historically, the brain has been thought to be completely devoid of immunological components. However, the concept that the brain is an immune privileged organ has been reconsidered and refined.[136] Brain microglia are resident macrophages, have a diverse set of functions, and play an important role in health and disease.[137] Astrocytes and oligodendrocytes crosstalk with microglia to coordinate various physiological functions and immunological responses. Macrophages and dendritic cells exist in the CNS, but are located in regions outside of brain tissue.[138] The number of glial cells in the human brain is ~70%–80% of the number of neurons with regional differences in the relative amount of glial cell types and a considerable amount of variability between studies.[139] Overall, oligodendrocytes are most abundant at 45%–75% of all glial cells, follow by astrocytes (20%–40%) and microglia (~10%).[139] Through

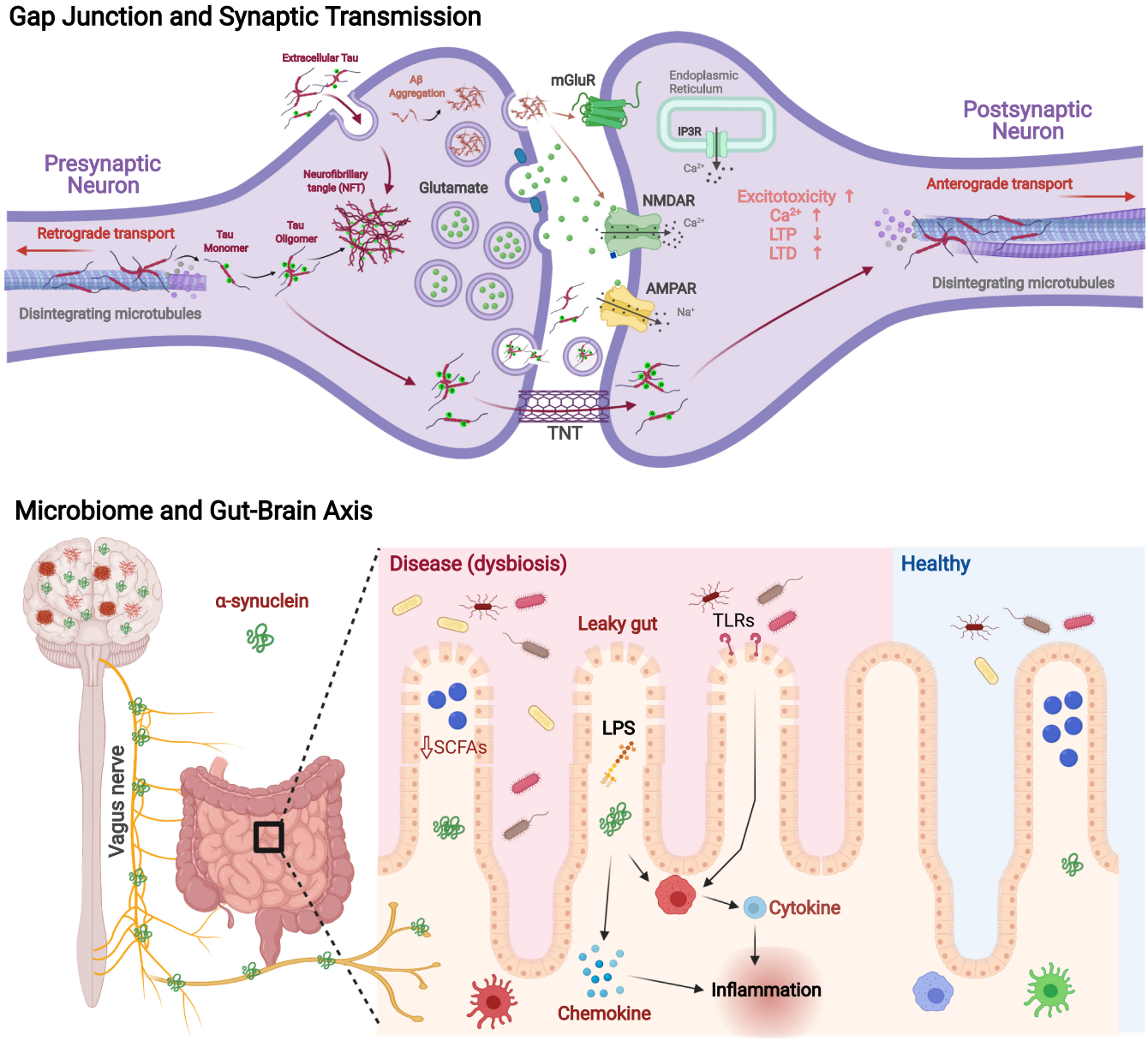

FIGURE 4 Transneuronal propagation and gut microbiome dysbiosis in neurodegenerative disease. Top: Transneuronal spread of tau protein occurs via the extracellular space, synaptic vesicles, and transneuronal nanotubes (TNTs). Tau dissociates from microtubules upon post-translational modifications and aggregates into tau oligomers and neurofibrillary tangles (NFTs). Aβ oligomers can impact synaptic transmission through presynaptic release of glutamate and direct modulation of postsynaptic NMDA receptors, which increases intracellular calcium in postsynaptic neurons and drives excitotoxicity. Bottom: The transition from a healthy gut to dysbiosis has been associated with neurodegenerative diseases. Bacterial components can permeate through the intestinal wall to activate resident intestinal immune cells, which generates chemokines and cytokines that induce inflammation. Based on preclinical evidence, it is hypothesized that the transneuronal migration of pathological proteins, such as alpha-synuclein, could occur from the gut to the brain via the vagus nerve.

complex interactions among neuroglia, neurons, and the brain microenvironment, the neuroimmune system is responsible for maintaining homeostasis and protecting the brain against pathological proteins, pathogens, and injury.

Oligodendrocytes are the myelinating cells of the CNS. The myelination of axons is a complex and regulated process involving the proliferation of oligodendrocyte precursor cells, migration to the appropriate site, differentiation into myelin-forming oligodendrocytes, and formation of a myelin sheath around axons.[140] Myelination of axons is determined through the communication between oligodendrocytes and neurons, which is dependent on a variety of chemical and electrical factors as well as the thickness of the axon (>0.2 μm).[141] There is a finite amount of time (~12–18 h) that the myelinating oligodendrocyte has to myelinate the axon before the cell has differentiated into a mature oligodendrocyte and its ability to myelinate is reduced.[140,142] The myelination process is

energetically demanding and consumes a large amount of oxygen and ATP, which leads to the formation of ROS. Oligodendrocytes also have the largest intracellular stores of iron in the brain because iron is required by several enzymes involved in myelination, which under pathological conditions could result in the formation of oxidative radicals. These two factors and the low concentration of anti-oxidative enzymes, such as glutathione, in oligodendrocytes makes these cells particularly susceptible to oxidative damage.[143]

There are two main astrocytes subtypes determined by their morphology and localization.[144] Protoplasmic astrocytes are more prevalent, mainly found in gray matter, have many synaptic connections, and exhibit a large cell soma and relatively short thick processes. Fibrous astrocytes are found in white matter, form connections with nodes of Ranvier, and exhibit longer thinner less branched processes. Astrocytes are responsible for regulating synaptic function, glutamate and energy metabolism, transportation of water, and support blood–brain-barrier function.[145] Importantly, they clear neurotransmitters from the synaptic cleft through various transporters, such as glutamate transporters GLT-1 (EAAT2) and GLAST (EAAT1).[144] Astrocyte projections are often coupled via gap junctions to form large intercellular networks allowing ions and neurotransmitters to dissipate through the astrocytic network.[144] Astrocytic end-feet processes are a component of the blood–brain-barrier that regulate the movement of solutes and aquaporin-mediated water transport into and out of the brain. CNS glymphatic system facilitates fluid exchange between the CSF and brain ISF, which removes metabolic waste out of the brain.

Microglia are the primary immune cells of the brain and constantly surveil their surroundings, provide housekeeping functions, and defense against infections pathogens and pathological insults, resulting in three different functional states.[146] In the sentinel state, a unique set of genes (sensome) is used to move around and project out long thin processes sampling the environment to pick up on any microenvironmental cues that would warrant a change in behavior. In the nurturer state, microglia remodel neuronal synapses, undergo chemotaxis toward pathological sites, phagocytose cells and cellular debris, secrete growth factors, and communicate with other glial cells. In the warrior state, a neuroimmune response can be mounted against invading pathogens or pathological protein aggregates, which includes the production of inflammatory cytokines (TNFα, IL-1β, and IL-6) and chemokines (CCL2).[146] Microglia are commonly classified as homeostatic versus disease-associated. Disease-associated microglia (DAM) were first identified using single-cell sorting on the brains of mice and humans with AD.[147] Further studies on the spatial and temporal heterogeneity of microglia have provided insights into unique microglia subpopulations and their transcriptional differences in health and disease.[148,149] Recently, Olah et al. identified nine unique clusters of microglia in the human brain.[150]

CNS-associated macrophages (CAMs) exist in regions outside of brain tissue, such as the perivascular space, meninges, and the choroid plexus, with choroid plexus macrophages the most heterogenous.[138] The physiological function of CAMs is less understood, but it is thought that CAMs are responsible for maintaining the integrity of CNS barriers, filtering the CSF, and phagocytosing biomolecules and potential pathogens.[138] Although their function has not been fully elucidated, it has been suggested that they may play a role in neuroinflammatory and neurodegenerative diseases.[151] Under pathological conditions, peripheral immune cells, such as monocytes, neutrophils, T cells, and B cells can infiltrate the CNS.[152] One possible function of CAMs could be regulating the entry of immune cells from the periphery into the brain.

Neuroimmune cells shift from a homeostatic to an acute or chronic activated state based upon various signals in the neuroimmune microenvironment (Figure 5). Microenvironmental cues induce morphological and transcriptional changes in microglia and astrocytes. Astrogliosis is a process where astrocytes become reactive in response to CNS damage and disease by secreting and responding to a variety of molecular factors, which determines their phenotypic fate on the astrogliosis gradient. Astrogliosis is a highly regulated event with changes ranging from cytoskeletal modifications to astrocyte proliferation and formation of astroglial scars.[153] Similarly, upon CNS challenges, homeostatic microglia transform into DAM with unique morphological changes, gene expression profiles, and diverse phenotypes, such as chemotaxis and barrier formation. Essentially astroglial scarring and microglia barrier formation, create a barrier or shield between pathological areas and vulnerable healthy brain tissue.[153,154] Although we have diagrammatically represented the neuroimmune cell transition simplistically in Figure 5, these cells should be viewed as a heterogenous population consisting of multiple subtypes. For example, reactive astrocytes have been commonly described as a binary division (neurotoxic vs. neuroprotective or A1 vs. A2). However, in 2021, a consensus statement was published to address the shortcomings of this simplification and advocated for further research to characterize astrocyte heterogeneity and understand the relative importance of various subtypes/signatures in CNS diseases.[155] There are age-related changes in white matter degeneration that correlates with cognitive decline, which highlights the potential importance of oligodendrocytes.[156] Additional research is needed to

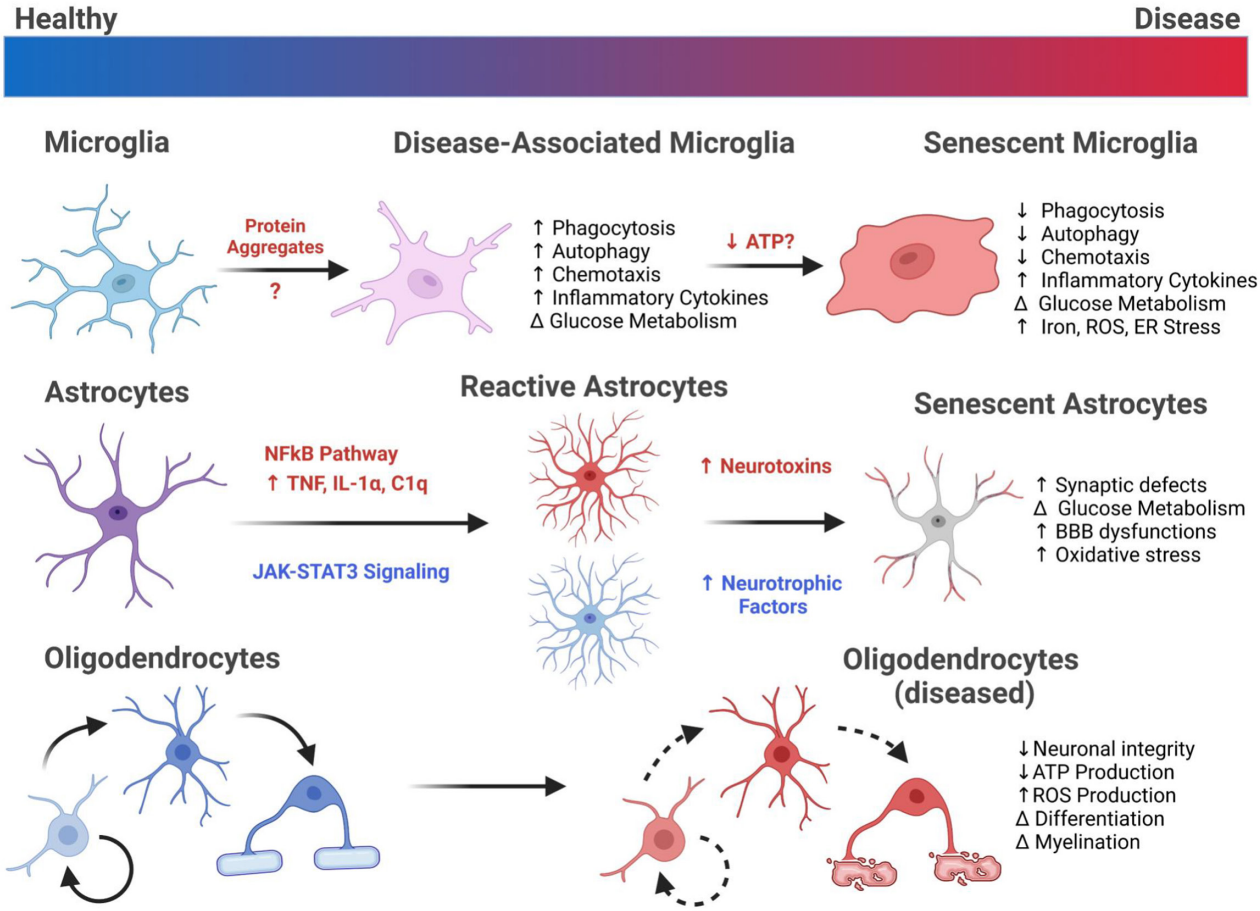

FIGURE 5 Neuroimmune system alterations in neurodegenerative disease. Glial cells (microglia, astrocytes, and oligodendrocytes) transition from homeostatic (healthy) toward disease-associated and senescent states throughout the course of disease progression. Disease induced alterations in the neuroimmune microenvironment modulates cellular signaling pathways, which triggers the transition of glial cells to altered states and results in phenotypic and functional differences. These include changes in phagocytosis, autophagy, chemotaxis, secretion of a variety of biomolecules, generation of oxidative stress, alterations in neuronal synapses and brain barrier function, energy metabolism, and myelination. Although it is represented simplistically, glial cells can assume many different states due to their high plasticity and the categorization of these cells into distinct subtypes is an ongoing area of research. Gene regulatory mechanisms that drive these transition states and the different glial cell subtypes are largely unknown and an active area of research. BBB, blood–brain barrier; ER, endoplasmic reticulum; ROS, reactive oxygen species.

understand changes in oligodendrocyte differentiation, myelination, general senescence mechanisms, intercellular interactions, and function in the aging brain and disease. Whereas normal activation of neuroimmune cells is an important beneficial physiological response, aberrant activation and dysfunction of neuroimmune components can lead to the manifestation and acceleration of neurological diseases.

Neuroimmune dysfunction can result from age-related changes, overwhelming disease pathology, genetic mutations, and environmental factors. For example, mice deficient in CCR2, a chemokine receptor on microglia cells, displayed decreased microglia accumulation and increased Aβ deposition in the brain.[157] Mutations in TREM2, a receptor on microglia required for the homeostatic to DAM transition, were found to be strong risk factors for AD, tau pathology, and cognitive decline.[158,159] Aβ pathology has been shown to accelerate tau pathology in transgenic mouse models with TREM2 deletions.[160,161] Aβ-induced activation of NLRP3 inflammasome in microglia has been shown to enhance the progression of AD pathology in mice.[162] Age-related changes in microglia function that may play a role in neurodegenerative diseases include increased MHC II expression, reduced anti-inflammatory response, and a greater and prolonged pro-inflammatory

response, leading to exaggerated neuroinflammation.[163] Environmental exposures, such as metals and air pollution, have also been considered as potential links to AD through disruption of the neuroimmune system.[164,165]

QSP MODELS OF NEURODEGENERATIVE DISEASE: MODELS AND APPLICATIONS

A review of the literature was conducted for mathematical models of neurodegenerative diseases. We noticed that there were many efforts to qualitatively describe interactions among system components, which were excluded from our review. We identified 33 QSP models of neurodegenerative diseases, 22 AD, 9 PD, 1 ALS, and 1 AD–PD (Table 1 and Figure 6). The majority of models have been developed for AD, and PD is second. Ninety-one percent of models contain biological components at the molecular level, whereas only 27% of models contain phenomena at the organism/patient level (cognition, behavior, and function). This percentage appears to decline with increasing levels of biological organization. Surprisingly, only a small fraction of QSP models of neurodegenerative disease have code that is publicly available (7 of 33; 21%). We have summarized the development and application of these previous modeling efforts in brief.

Alzheimer's disease

Many AD QSP models have been constructed to account for Aβ formation, accumulation, distribution, clearance, and impact at the cellular or synaptic level (Table 1). Most models fall into one subset of three categories, which we refer to as dynamical, electrophysiological, and network models. Dynamical models have characterized Aβ deposition and its dynamics intracellularly, in specific brain regions, and the whole brain using a series of ordinary differential equations. Electrophysiological models utilize conductance-based models of neurons to ascribe electrophysiological changes during neurodegeneration to cognition outcomes. Network models consider the three-dimensional connectivity of the brain with each node attributed to a voxel of the discretized brain in a particular state, which leverages the availability of clinical imaging data.

Dynamical models prioritize Aβ deposition's involvement on system dynamics at the cellular, interstitial, regional, or whole brain level. These models often make the assumption that Aβ is homogenously distributed throughout the brain, which is an oversimplification. Sensitivity analysis for a model of neuron-derived Aβ accumulation suggested that microglial activation is a key process in pathogenesis initiation. Fgaier et al. investigated cholinergic dysfunction in AD using a two-enzyme two-compartment model at the level of a pre- and post-synaptic neuron, with Aβ aggregates disrupting choline acetyltransferase (ChAT) activity.[166] A minimalist mathematical model was applied to understand the pharmacodynamics of bexarotene, a retinoid X receptor agonist, which displayed an age-dependent removal of Aβ in mice, where improved efficacy was observed in older mice.[167]

Results from a model of APP processing into Aβ in plasma and CSF indicated that BACE1 inhibition had a greater effect on Aβ40 than Aβ42 and suggested a potential compensatory mechanism for the dissociation of Aβ oligomers. This model was later extended to include the combination of gamma secretase with BACE1 inhibition.[168] Gamma secretase inhibition yielded lower Aβ40 formation compared to BACE1 inhibition, whereas both were predicted to lower oligomeric Aβ levels.

A QSP model of Aβ dynamics using compartmental representations for plasma, CSF, brain interstitial fluid, and other tissues, with a separation of Aβ40 and Aβ42, was developed using several datasets from preclinical animal experiments and applied to predict Aβ42 dynamics for various dosing regimens of avagacestat in mice, monkeys, and humans.[169] The human parametrization of this model was later expanded to incorporate pools of soluble Aβ species and insoluble aggregates formed through nucleation events.[170] The model was utilized to explore differences between healthy and AD subjects, mechanisms governing Aβ dynamics, and the effectiveness of various treatment strategies. Predictions were generated for ADAS-Cog change in patients with preclinical-mild AD who were administered therapies that either eliminate insoluble Aβ aggregates or inhibit Aβ production. Model predictions suggest that inadequate removal of insoluble Aβ is the main reason for Aβ accumulation and a longer treatment duration is required to attain clinical benefits in preclinical AD compared to mild AD. Subsequently, a probabilistic model for multisite phosphorylation of tau with specific kinases and sites was developed, and sensitivity analysis suggested that kinase inhibition plays a key role in preventing tau hyperphosphorylation.[171]

A QSP model was developed to better understand the causes of failure of amyloid-targeted therapies in AD clinical studies and provide guidance for future development.[172] The model characterized clinical pharmacokinetic (PK)-pharmacodynamic data for the exposure of four Aβ antibody therapeutics and three BACE inhibitors on Aβ dynamics in plasma, CSF, and the brain. The model was utilized to simulate various dosing regimens for

TABLE 1 Quantitative systems pharmacology models of neurodegenerative diseases

Disease	Model	M	N	C	B	O	Description
ALS	Cell–cell Communication Network Model	X	X				Characterization of immune cell and cytokine dynamics in ALS disease progression
AD	Aβ pathway with aducanumab	X			X		Aducanumab PKs on Aβ aggregation dynamics and ADCP to clear Aβ aggregates
AD	Model of Aβ therapeutics	X			X		Model for the effect of Aβ-antibodies and BACE inhibitors on Aβ dynamics
AD	Virtual patients, comedication, genotype, neuronal circuit, and an ADAS-Cog network		X	X	X		Incorporation of antidepressants, cholinergics, antipsychotics, benzodiazepines, and genotype variants (APOE, 5-HTTLPR rs 23,351 and COMTVal158Met)
AD	Aβ/tau/neuron homeostasis	X		X	X	X	Translational model of Aβ/tau pathology. Aβ/tau accumulation, failure of protein degradation, role of lipid/sphingolipid metabolism
AD	Brain Network Model of Tau Protein Spread	X	X	X	X		Describes propagation of misfolded tau protein in brain over 40 years using 3 kinetic models and potential treatments to delay progression
AD	Multiscale model of tractography data with Aβ pathology	X	X	X	X		Simulation of EEG readouts in a brain connectome network, informed by ADNI-3 data, implemented with the effect of Aβ load on inhibitory interneurons
AD	Tau dynamics	X		X	X	X	Tau turnover, phosphorylation, microtubule binding, propagation across brain regions, and brain atrophy
AD	Calcium Signaling	X					Effect of Aβ deposition on calcium dynamics in the cytosol, mitochondria, and endoplasmic reticulum
AD	AD neuronal cortical network	X	X	X		X	Neuronal network of 80 pyramidal cells and 40 interneurons, with multiple neurotransmitter dynamics coupled to ion channels
AD	Lipid dysregulation	X					Integration of APP processing, Aβ aggregation, cholesterol metabolism, and sphingolipid metabolism submodels
AD	Cholinergic modulation of pyramidal neuron	X	X				Comprises different subcellular models that participate in cholinergic modulation via M1 activation on pyramidal cell excitability and downstream intracellular Ca^{2+} dynamics
AD	Aβ/Longitudinal Aβ	X			X	X	Aβ turnover and distribution, mechanistic protein polymerization, empirical description of amyloid toxicity on ADAS-cog
AD	Multi-factorial causal model (MCM)	X			X	X	Multiscale model of Aβ burden, glucose metabolism, vascular flow, functional activity, structural properties, and cognitive integrity
AD	Bexarotene PK/pharmacodynamic	X	X				Bexarotene effect on Aβ pathway dynamics and neuronal viability
AD	Periarterial Drainage	X			X		2D simulations of diffusive and convective fluid/solute flow from the brain
AD	Large-scale Brain Network			X	X		Brain network of 74 regions for the interaction of neural subpopulations

Calibration/qualification	Application/prediction	Code public	Year	Reference (PMID/DOI)
Data from the literature in a mouse model of ALS	Optimize therapeutic strategies to improve survival and quality of life	No	2013	23287963
Clinical data of Aβ in brain (PET), CSF, and plasma	Predict aducanumab plaque reduction for longer treatment durations and dose titration	Yes	2022	35029320
Clinical data for 4 mAbs and 3 BACE inhibitors	Understand Aβ species change with treatments	No	2021	33938131
Drug pharmacology, target exposure, imaging, and genotype information	Virtual patient clinical trial simulation and reconstructing COVID-19 paused clinical trials	No	2020	33016912
Data for Aβ and tau targeting therapies from humans and AD mouse models	Prediction for the combinatorial effect of Aβ/tau targeting therapies	No	2019	29232559
Tractography from Human Connectome Project; Tau spatio-temporal dynamics	Predict tau propagation in the brain and treatment options that may delay progression	No	2019	31615329
Individual connectomes and Aβ deposition (AV-45 PET)	Reproduces observed slowing of the EEG spectrum	No	2019	31456676
Mouse (P301S), human, and in vitro data	Validation (hypothesis testing) on mouse immunotherapy data	No	2018	29408874
Captures reported qualitative behavior	Predicted molecular events leading to neuronal death	Yes	2018	29671396
Previously calibrated to 28 clinical treatment outcomes on ADAS-Cog	Understand the relationship between baseline Aβ and response to Aβ therapies	No	2018	29394903
APP/Aβ dynamics from BACEi in NHP and simvastatin clinical data	Predict the modulation of sphingolipids and Aβ by a S1PR5 receptor agonist	No	2018	30207429
Experiments on subcellular (kv7 & SK channels, ER Ca^{2+} buffering, CA1 cell spiking)	Cholinergic modulation via M1 activation on pyramidal cell excitability and intracellular Ca^{2+} PD	No	2018	30440653
Mouse (Tg2576), human, and NHP data	Retrospective validation of phase II avagacestat and bapineuzumab hypotheses	No	2017	28571112 28913897
Clinical study with 561 patients and six different neuroimaging modalities	Predicted brain alterations, identified pathological events, and therapeutic strategies	No	2017	28257929
Aβ dynamics in APP/PS1 mice	Bexarotene effects on neuronal viability and Aβ dynamics	No	2016	27073866
Fluorescent dextran spread in vivo mouse brain	Evaluate the role of diffusion on perivascular solute transfer	No	2016	26903861
Temporal dynamics of 74 cortical areas using an isolated Jansen-Rit model	Synchronization is key for changes in spatio-temporal pattern formation by tDCS	No	2016	26883068

TABLE 1 (Continued)

Disease	Model	M	N	C	B	O	Description
AD	APP/Aβ Dynamics	X					APP cleavage to sAPP/Aβ in brain and disposition to CSF
AD	Mathematical model on AD	X	X				Model contains Aβ and tau dynamics, formation of protein aggregates, neurons, astrocytes, and several investigational treatments for AD
AD	Two-Enzyme Two-Compartment (2E2C)	X					2E2C model of the neuronal junction for the interplay of acetylcholine (ACh) and Aβ
AD	Serotonergic synaptic cleft and cognition	X	X	X		X	Consists of 12 membrane CNS targets and neuronal network firing activity of 80 pyramidal cells and 40 interneurons
AD	Cell–cell interaction in AD progression	X	X				Effect of cell–cell interaction on AD progression and neuron death including microglia, astrocyte and generic neurons
AD	Neuroinflammation and AD pathology	X	X				2D & 3D diffusion of Aβ and cytokines, microglia chemotaxis, Aβ fiber growth and nucleation, and cytokine receptor binding kinetics
AD PD	Aβ aggregation and reactive microglia	X					Effect of Aβ aggregation on the number of reactive microglia during dementia
PD	Population-level neuronal model of thalamocortical basal ganglia network			X			Neuronal population model to study DBS and the emergence of oscillations, using Wilson-Cowan approach
PD	Basal ganglia loop with receptor competition	X	X	X		X	Firing activity of basal ganglia circuit to calculate local field potential power in STN for kinetic symptoms with different treatment
PD	Insulin resistance and intracellular biochemical pathways	X	X				Biochemical systems model of insulin signaling, inflammation, dopamine, ROS/RNS production, protein aggregation, cell death, and drug effects
PD	QSP PD Platform	X	X	X		X	QSP platform to test possible use of repurposed drugs to reduce tremor. Contains receptor competition and a cortico-striatal-thalamic loop.
PD	Dopaminergic neurons and energy consumption	X	X				Pacemaking dopaminergic neurons, membrane voltage, ion channels and concentrations, calcium buffers, and energy expenditure
PD	Dopamine metabolism with biological pathways and enzymes	X					Sensitivity of dopamine levels to changes in various pathway components such as DAT, VMAT2, and MAO
PD	Metabolic model of α-synuclein aggregation	X	X				Metabolic model of α-synuclein aggregation, dopamine metabolism, ubiquitin-proteasome system, and lysosomal degradation
PD	Probabilistic model of presynaptic dopamine release and reuptake	X					Parameter dependence of various clinical motor fluctuations in response to L-dopa in a probabilistic model of vesicular dopamine
PD	Levodopa, dopamine, and basal ganglia neurotransmission	X	X	X		X	Basal ganglia neurocomputational model with dopamine dynamics to study the progression of levodopa effect with denervation

Abbreviations: Aβ, beta-amyloid; AD, Alzheimer's disease; ADAS-Cog, Alzheimer's disease assessment scale–cognitive (ADAS-Cog) subscale; ADCP, antibody-dependent cellular phagocytosis; ADNI, Alzheimer's Disease Neuroimaging Initiative; ALS, amyotrophic lateral sclerosis; B, brain; BACE, beta-secretase; C, circuitry; CSF, cerebrospinal fluid; COVID-19, coronavirus disease 2019; DBS, deep brain stimulation; EEG, electroencephalography; EMG, electromyography; ER, endoplasmic reticulum; M, molecular; mAbs, molecular antibodies; N, neuronal; NHP, non-human primate; O, organism; PD, Parkinson's disease; PET, positron emission tomography; PK, pharmacokinetic; QSP, quantitative systems pharmacology; ROS/RNS, reactive oxygen and reactive nitrogen species; STN, subthalamic nucleus; tDCS, transcranial direct current stimulation.

Calibration/qualification	Application/prediction	Code public	Year	Reference (PMID/DOI)
Model fit to sAPP/Aβ CSF dynamics in NHP	Anticipate human Aβ response to BACE inhibition	No	2016	26826190
Qualitatively describes trends from clinical data	Predict single and combination treatment effects on Aβ and neuronal death	No	2016	27863488
Inhibition of ACh transferase by Aβ in vitro	Understand mechanisms of Aβ for inhibiting ACh activity	No	2015	26413144
In vivo preclinical and human data for 5-HT levels and imaging	Predict a phase I scopolamine trial with 5-HT4 partial agonist	No	2013	10.4236/aad.2013.23012
None	Understand the relationship between glial cells, neuronal death and Aβ in AD	No	2010	21179474
Cell arrangement and plaque size distribution from human AD brain	Spatial and temporal changes in plaque formation and death of neurons	No	2002	12183120
Microglia cluster in Parkinsonian dementia patients	Understand the relationship between reactive microglia and Aβ in PD	No	2017	10.30707/SPORA3.1Kinney
Clinical EMG data from electrodes implanted in the motor thalamus	Generation and propagation of pathological oscillations and DBS effects	Yes	2020	32210779
Calibration with 34 drug-dose combinations from historical clinical trials	Predictions of beta/gamma ratio in STN with various medications	No	2016	26869923
In vitro experiments and qualitative validation using clinical trends	Identification of potential drug targets and comparing dosing regimens	Yes	2015	25897824
Retrospective qualitative calibration from historical clinical trials	Identification of 5 serotonergic compounds to test in preclinical PD models	No	2013	24192755
In vitro pacemaking dopaminergic neurons and ion channel blocker	Identification of L-type calcium channel blockers as potential therapeutic intervention	Yes	2013	23686304
Qualitative comparison with preclinical data	Identified determinants of dopamine imbalance and therapeutic strategies	Yes	2009	18568086, 19670315
In vitro experiments and qualitative validation using clinical trends	Predict components of disease progression and evaluate different treatment strategies	Yes	2009	19136028
Qualitative comparison with clinical data	Identification of presynaptic mechanisms governing the duration of drug response	No	2004	14960500
Parameters from literature, qualitative comparison with clinical trends	Identified mechanisms leading to loss of levodopa duration effect with denervation	No	2020	33084988

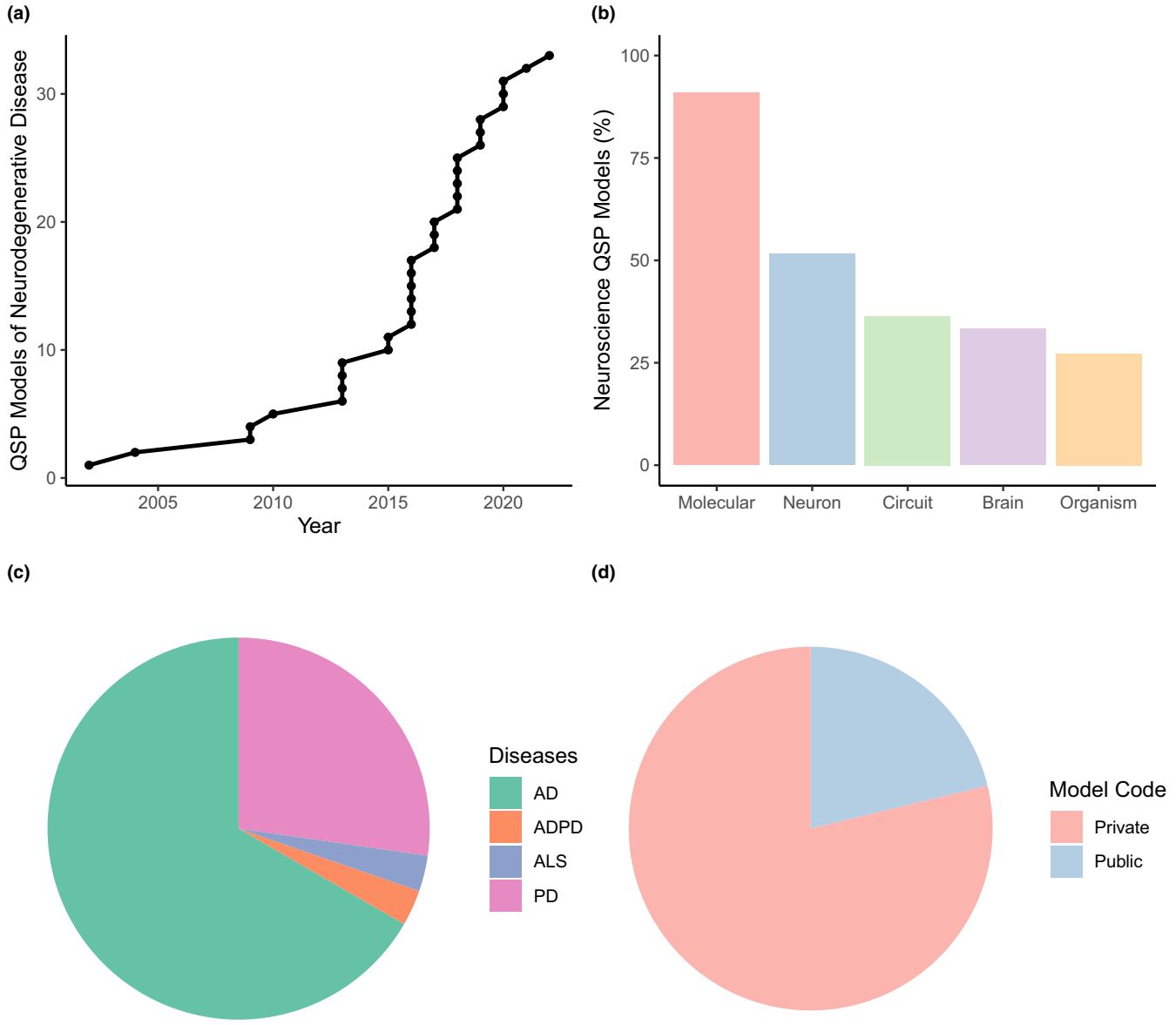

FIGURE 6 Quantitative systems pharmacology (QSP) models of neurodegenerative diseases. (a) Cumulative number of published models over time, (b) level of biological detail modeled, (c) types of neurodegenerative diseases modeled, and (d) proportion of code in the private versus public domain for published QSP models of neurodegenerative diseases. AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; PD, Parkinson's disease.

each of the Aβ antibodies to understand inter-antibody differences in dose-exposure-response relationships. Specifically, Aβ engagement in plasma and CSF as well as the change in Aβ plaques in the brain. The impact of antibody affinity and the endogenous plaque turnover rate on Aβ dynamics were explored. Modeling results suggest that antibody binding to plaques and the induction of plaque clearance, possibly through antibody-dependent cellular phagocytosis, could be the most effective approach to reduce amyloid plaques. A subsequent analysis using this model was performed to understand the relationship between aducanumab exposure on Aβ plaque dynamics in the human brain.[173] Alternative dosing regimens were explored, which helped to inform the design of future clinical studies.

A QSP model linking Aβ dynamics to metabolic dysregulation was constructed by combining pre-existing models of sphingolipid metabolism, Aβ pathway, and cholesterol metabolism.[174] Healthy and AD parameterizations of the model were calibrated using private and published biomarker data and validated for a variety of pharmacological interventions. The model improved confidence in the strategy of targeting S1PR5 receptors for the treatment of AD.

A model of calcium increase due to Aβ deposition was developed by combing various submodels of mitochondrial

calcium regulation and metabolism, the pore dynamics of mitochondrial permeabilization, and the interaction of Aβ and intracellular calcium.[175] This work suggested that calcium increases beyond basal concentrations in AD, leading to dysregulation of ER calcium channel receptors and tracks with progression from increased amyloid to the induction of cell death.

The second set of models incorporate conductance-based neuronal circuit models to facilitate simulation of cognitive outcomes. A QSP model for activation of the serotonin 5-HT4 receptor within a cortical circuit simulates a scopolamine challenge study of an experimental 5-HT4 partial agonist on cognitive outcome. The model used the stability of a memory trace during a working memory task and correctly predicted that the investigational drug would worsen cognitive outcome. A later version implemented the differential effects of various Aβ forms on glutamatergic neurotransmission with low levels of Aβ40, providing a stimulatory effect on synaptic transmissions, whereas Aβ42 and high levels of Aβ40 providing an inhibitory effect.[176] The neuroprotectivity of low Aβ40 levels was necessary to achieve compatibility with three different clinical datasets. The model predicts the transient cognitive worsening associated with BACE-inhibitors and quantitatively predicted the effects of solanezumab on ADAS-Cog. This cortical model was later extended to study pharmacodynamic interactions of comedications and genotypes on dose–response of Aβ antibodies.[177] The model was applied for aducanumab clinical trial design by generating virtual patients with different genotypes, medications, and Aβ loads to test hypotheses on responder genotypes.

The last set of models consider the brain from a macroscopic sense. Some models implement partial differential equations to study spatiotemporal spreading of protein aggregates. A model of periarterial drainage in the brain for Aβ elimination through diffusion and bulk flow was developed and validated, suggesting reduced bulk flow along basement membranes as a key pathological process and important for passive immunotherapy treatment strategies.[178] A network diffusion model created using MRI data from 418 healthy subjects in the Human Connectome Project explains kinetic growth, fragmentation, and prion-like spreading of tau, which can be used for in silico therapeutic strategies to predict longitudinal spatial disease progression.[179]

AD has also been modeled specifically using a connectivity matrix for the brain, where nodes represent neurological activity in particular brain regions. A cerebral model of transcranial direct current stimulation (tDCS) combines a pre-existing neural mass model representing 74 cerebral areas whose connection strengths were determined by the human connectome.[180] Results from bifurcation analysis and network dynamics indicated that synchronization played a major role in emergent functional connectivity in cerebral areas and spatiotemporal pattern changes after tDCS. Using Alzheimer's Disease Neuroimaging Initiative (ADNI) connectivity imaging data, a state-space model of brain alteration and disequilibrium levels was developed that considered the influence of vascular flow, Aβ deposition, glucose metabolism, functional activity at rest, and gray matter density in different brain regions.[181] The model suggested that vascular dysregulation was the most likely initial event leading to pathology and that combinatorial treatment strategies have clear advantage over single-treatment counterparts.

Parkinson's disease

Published mechanism-based models of PD have explored various pathobiological mechanisms, including Asyn aggregation, Asyn feedbacks with protein degradation systems, and bioenergetics of dopaminergic neurons.[182] Predominantly, these models can be divided into two main categories, dopamine metabolism and electrophysiological properties of neuronal networks. A few of these models have used the terminology of biochemical systems theory (BST) models, originally introduced by Savageau in 1969.[183]

Dopamine metabolism models were developed to identify important mechanisms and investigate pharmacodynamics. A probabilistic model including vesicular and terminal concentrations of dopamine to study motor fluctuations captured clinical observations of motor fluctuations as well as duration of response to levodopa therapy.[184] Notably, the vesicular release rate was identified as a key parameter for the modification of motor response.

A BST model of the nigrostriatal pathway in PD identified significant parameters involved in the disruption of dopamine homeostasis and metabolism, such as the synthesis rate of tyrosine.[185] Model predictions suggest a beneficial effect for the combination of an MAO inhibitor with either the activation of VMAT2 or inactivation of DAT. In a subsequent analysis, simulations identified MAO, VMAT2, and DAT as favorable single targets and the combination of VMAT2 activation and MAO inhibition appeared to be the most efficacious.[186]

A BST model of PD included Asyn aggregation, lysosomal degradation, ubiquitin–proteasome system, and dopamine metabolism.[187] Disease state was emulated by modulating Asyn expression, Asyn aggregation, vesicle packaging, and neurotoxins, which provided semiquantitative insights into the pharmacodynamic effects of various treatment strategies on dopamine levels, ROS, degradation processes, and various forms of Asyn. Further work expanded the model to include insulin signaling, inflammation, dopamine dynamics, ROS/RNS dynamics,

tau aggregation and phosphorylation, p38 phosphorylation, and cell death.[188] This model reproduced three states: healthy, disease, and treatment. Model predictions suggest a decrease in insulin signaling and vesicular dopamine as well as an increase in inflammation, cytosolic dopamine, ROS, tau, and cell death occur in the diseased state. The benefits of treatment at the onset of PD were highlighted.

Some QSP models of PD have used a biophysical neuronal network-based approach. Previously developed receptor competition and pyramidal neuron models were combined and applied to the Prestwick library to identify non-dopaminergic drugs for treating of tremors.[189–191] Another model, based on connectomics, of a closed cortico-striatal-thalamic-cortical basal ganglia loop used the ratio of beta and gamma frequencies in the subthalamic nucleus (STN) as an in silico biomarker, which was calibrated with data from 24 different drugs on the clinical Unified Parkinson Disease Rating Scale (UPDRS).[192]

A population-level neuronal model combining thalamocortical and basal ganglia networks using a Wilson-Cowan approach was used to study DBS and the emergence of oscillations.[193] The thalamocortical basal ganglia network, STN, external part of the globus pallidus (GPE), and cortex were first developed to study essential tremor and oscillations through bifurcation analysis.[194,195] Changes in the thalamocortical and the STN-GPE connections were identified as significant pathological drivers. DBS eliminated low-frequency high-amplitude pathological oscillations and replaced them with high-frequency low-amplitude activity. A neurocomputational model of the basal ganglia was combined with a PK model of levodopa to study finger tapping frequencies, an item in Movement Disorder Society-UPDRS.[196] The higher sensitivity of D2 receptors over D1 receptors to reduce disease symptoms was highlighted.

The potential effects of L-type calcium blockers were investigated using a model of transmembrane potential through the study of pacemaking activity in the substantia nigra.[197] L-type calcium channel blockers abolished stable limit cycle oscillations or reduced them.

Motor neuron diseases

A QSP model of ALS characterized interactions between the immune system and motor neurons.[198] The model assumes that a population of normal motor neurons convert into mSOD1-producing motor neurons at the onset of disease.

Huntington's disease

The complexity in the molecular pathogenesis of HD that ultimately leads to the progression of the disease makes it an ideal candidate for investigation using QSP approaches. A model to identify mechanisms of disease and neuronal protection from toxicity due to mutant huntingtin was developed from an experimental striatal neuronal cell model of HD treated with small molecule probes and their combinations that exert protective effects.[199] A computational systems level analysis of the perturbed pathways predicted optimal pathways and networks based on phenotypic assays of neuroprotection.[200,201] The identified pathways were then re-assessed via experiments using pharmacological or genetic probes. The computational systems level analysis identified pathways that converge in the activation of protein kinase A as a major neuroprotective mechanism. The QSP-based methodology adopted by the authors provided an unbiased evaluation of HD biology at a systems-level enabling an efficient approach toward therapeutic design.

NEURODEGENERATIVE DISEASE QSP MODELING CONSIDERATIONS

When developing QSP models of neurodegenerative diseases, it is important to initially define the scope and level of granularity required to answer the desirable questions of interest as model complexity can become overwhelming. Incorporating processes across multiple scales of neurobiological organization can be highly complex, resulting in multiple feedback loops, model instability, and parameter uncertainty. For example, synaptic transmission and neuronal plasticity impact the intracellular signaling through calcium regulation, which occurs on a timescale of seconds to minutes, whereas autophagy operates in hours, and disease progression and cognitive/functional decline occurs over years. The wide temporal scale could cause model stiffness and instability. Understanding the minimal amount of mechanistic detail required to accomplish a specific goal is key for obtaining a balance between model complexity and applicability.

QSP models of neurodegenerative disease often use a simplifying assumption of a homogenous population of neurons, which do not consider the spatial localization and connectomics of neuronal populations as well as their functional differences. A homogenous distribution assumption is also commonly used for biomarkers of disease. The need for a spatio-temporal QSP model is underscored by the stage-specific interaction between tau pathology and other pathological processes, such as Aβ dynamics and neuroinflammation. Because specific brain regions are involved in different behavioral processes, the clinical effect of interventions can be dependent upon the stage and spatial localization of the pathology.

Modeling-disrupted proteostasis requires detail for the various mechanisms of pathological protein production, aggregation, accumulation, and elimination. There are several different protein subtypes, post-translational modifications, aggregation propensity, spatial localization, regulation, and functions. Depending on the type of protein these processes could occur intracellularly and/or extracellularly. Incorporating oxidative stress components into a QSP model can be challenging due to the many sources of ROS generation, the different types of ROS and RNS, and differences in their respective functions. Detailed calcium dynamics increase model complexity due to its regulation by intracellular components and very short timeframes. Simplifying assumptions could be considered to describe calcium dynamics via a smooth rise to a new steady state, rather than detailed oscillatory behavior. There is crosstalk among multiple brain cell types, neurons, and glial cells, which govern the microenvironment to determine glial cell phenotypes and transition into different states. Mathematically describing microglial transition from homeostatic to various disease-associated states depending upon their microenvironment and spatial localization in the brain is challenging. A major challenge is that the molecular mechanisms governing the transition of glial cells from homeostatic to disease-associated phenotypes largely remains unknown. A recent review has started to shed light on the molecular processes governing these transition states.[202]

As described throughout this review, neurodegenerative diseases have many commonalities. Thus, there could exist conserved structural components among QSP models that could serve as building blocks for further model development. In disrupted proteostasis, protein aggregation, spreading, and clearance are important processes. The α-synuclein is involved in the pathophysiology of both PD and AD.[203] Disrupted proteostasis processes for α-synuclein could be structurally similar between QSP models of PD and AD, however, the underlying reaction rates for these processes, spatial localization for where the pathology is occurring in the brain/body, and the types of neurons and neural circuits affected will be different. In other words, α-synuclein equations or an "α-synuclein building block" could be reused across QSP models of neurodegenerative diseases, but the parameterization would be disease/patient-specific. This concept of submodels or building blocks extends to all of the proposed hallmarks of neurodegenerative diseases. Examples of potential submodels are autophagy, proteasomal degradation, carbohydrate and lipid metabolism pathways, ROS generation and antioxidant defense systems, unfolded protein response, apoptosis, select intracellular signaling pathways, calcium signaling, and neuroimmune cell transitions. Although metabolic pathways are well-studied, detailed biochemical information relating to the reaction rates of enzymatic processes can sometimes be challenging to find. Databases for enzymatic reaction kinetics, such as SABIO-RK, could serve as a great resource.[204] Submodels for the transition of glia from homeostatic to disease-associated could be envisioned once more information exists on the regulatory processes governing these transition states and the fraction of these cell populations across various stages of disease.

Often, it is challenging to integrate data from various preclinical cellular and animal experiments to predict observations in humans. For example, almost all preclinical in vivo models use injection of brain extract in specific regions of the brain and monitor the appearance of insoluble aggregates at distant projections over time. Scaling and translating between mice and humans can be problematic. Tau PET imaging captures longitudinal trajectories of NFT deposition. Although one can extrapolate the axonal projections to the corresponding length in the human brain, questions remain whether the temporal scales of the molecular processes, such as seed-competent tau uptake, oligomerization, degradation, and slow axonal transport, are comparable between mice and humans. Other approaches use a top-down analysis of brain connectomics using a model of misfolded protein generation, transport, and clearance along well-defined neuronal projections.[205]

ADDRESSING THE TRANSLATIONAL GAP

The objective of neuroscience clinical trials is to generate evidence for improved functional, behavioral, and cognitive outcomes in patients to support approval of the therapeutic intervention. Clinical end points include structured questionnaires, such as ADAS-Cog or CDR-SB for cognition and Neuropsychiatric Inventory (NPI) for behavioral symptoms in AD. Clinical end points related to motor function, such as UPDRS, have been utilized for PD/HD. QSP models are often pathway-focused and characterize the dynamics of molecular biomarkers representative of disease pathology and target engagement. However, predicting clinical outcomes based on a change in a molecular biomarker is notoriously challenging as there are a multitude of complex processes involved between these scales of neurobiological organization. Functional performance of a patient is most likely driven by neuronal activity in specific neuronal circuits. For instance, in motor disorders, there is a strong causal relationship between changes in power spectra of local field potentials in the STN of the motor circuit and clinical outcomes of rigidity and bradykinesia.[206,207] Working memory performance, which underlies many cognitive processes, is related to the capacity to hold

a memory trace active after stimulation has finished.[208,209] Therefore, incorporating pathological effects on neuronal firing driven by changes in voltage and ligand gated ion channels is an essential step in modeling brain function.

For instance, Aβ oligomers can interfere with normal synaptic transmission resulting in a loss of synapses that is correlated with the decline in cognitive function (Figure 4). The pathological effects of Aβ oligomers are hypothesized to take place both at the presynaptic terminal, resulting in an increase in glutamate release, and postsynaptic site through its binding to NMDA receptors, leading to excitotoxicity, desensitization of glutamate receptors, inhibition of long-term potentiation (LTP), and increase in long-term depression (LTD). Aβ mediated NMDA-receptor channel opening results in glutamate-independent calcium inward currents leading to dysregulations in the postsynaptic calcium dynamics and an imbalance in expression of LTP/LTD. The prolonged calcium influx into the neurons can lead to mitochondrial calcium overload, mitochondrial membrane depolarization, and generation of ROS. A QSP model has been developed to address the relative importance of these processes.[210]

BOLD functional MRI (fMRI) imaging is a biomarker associated with brain region specific changes in neuronal activity. There is extensive literature documenting the biophysics of the voxel-based BOLD signal associated with neuronal activity, which could be implemented in QSP approaches.[211] A recent QSP model illustrates the relationship between BOLD fMRI signal and cognitive performance associated with patient genotype and after ketamine treatment in healthy volunteers.[212] This approach is based on the open-source platform NEURON, a tool commonly used in computational neurosciences to model individual and networks of neurons.[213] Incorporating the effect of pathology and therapeutic interventions on the electrophysiological properties of neurons, can substantially expand the utility of neuroscience QSP platform models and allow for multiple levels of validation beyond traditional preclinical studies.

An obvious next step is to link the voxel-based imaging readout (for instance, BOLD fMRI or molecular PET imaging) to a network connectomics approach covering the whole brain. In this case, detailed modeling of individual neuron activity is often substituted by mean-field approaches to mitigate the tremendous computational burden. In principle, this allows to personalize the modeling based on the baseline connectivity, which might be useful when simulating spatio-temporal progression of misfolded proteins, such as tau and α-synuclein.

FUTURE DIRECTIONS

The expression, "success has many fathers, but failure is an orphan," captures the prevailing path of drug development. The saying "learn from your mistakes" is popular but rarely supported by actionable strategies that could systematically advance human understanding and knowledge in the field of neuroscience drug discovery and development. The combined knowledge from clinical trials into a mechanistic QSP model of neurodegenerative disease pathophysiology is uniquely positioned to provide a systematic framework for understanding reasons of drug failure and to generate hypotheses about novel treatment strategies.

The complicated multifactorial nature of neurodegenerative diseases makes trial-and-error approaches prohibitively expensive and impractical. The failure rate in the development of therapeutics for AD is over 99%.[214] The complexity of neurodegenerative disease makes it difficult for humans to understand, represent, quantify, and visualize multiple inter-relationships and nonlinear interactions. We believe that QSP models can act as a central repository of knowledge that could be used to systematically integrate clinical data over time into actionable insights. A precompetitive academic, regulatory, and industry-wide consortium ("collaborate on the tools, compete on the compounds") to integrate data consistently and systematically from neuroscience clinical trials into QSP platforms offers a unique solution to leverage data from failed clinical trials to enhance our overall understanding for the pathophysiology of neurodegenerative diseases.

There are several examples where consortia and open-source resources are used by regulators, academia, and industry as a precompetitive option to collect and share preclinical and clinical data: Neurodata Without Borders, OpenNeuro, Alzheimer DataLENS, SYNAPSE, Critical Path Institute, ADNI, Parkinson's Progression Marker Initiative (PPMI), and Answer ALS. Centralizing and standardizing data would significantly help and enable the development of QSP models. There are also open-source repositories for sharing mathematical models of biological and physiological systems, such as BioModels. Sharing data and code is paramount for improving transparency and advancing the field of systems pharmacology. An open-source cloud research platform for The Virtual Brain, EBRAINS, has recently been launched by members of the Human Brain Project.[215] This project could provide valuable resources. Another challenge is that the QSP models reviewed are in many different coding languages and software, such as MATLAB, SimBiology, Kronecker, and Heta, which can be burdensome to learn a diverse set of languages and tools. Pushing the field toward using open-source programming languages with a lot of community support (R, Python, and Julia), making models available as a Systems Biology Markup Language (SBML) file, and the use of version control systems (Git)

could help improve model transparency, usability, and credibility. In 2020, the Committee on Credible Practice of Modeling and Simulation in Healthcare has developed 10 rules for the credible practice of modeling, which could be adopted by the QSP modeling community.[216] There are many ongoing efforts to develop QSP models of neurodegenerative diseases that are currently being done in isolation. Nonprofit and precompetitive public-private partnerships could help overcome time and resource loss from duplication of efforts on data architecture and model development.

CONCLUSION

A quantitative mechanistic understanding of processes involved in the pathophysiology of neurodegenerative diseases could help to facilitate the discovery and development of novel therapeutic interventions for these unmet medical needs. As technology continues to advance, the spatiotemporal granularity of mathematical models will begin to improve. As illustrated in this paper, multiscale models that span multiple scales of neurobiological organization will soon be able to bridge cellular/molecular changes to emergent behavior at the patient/population level, such as cognition, behavior, and function. Data on individual patient's neuronal connectomics and regional longitudinal disease progression, will be key to bridge these vastly different spatial scales. The integration of novel technologies, such as digital devices, that measure longitudinal changes in clinical end points with multiscale quantitative modeling approaches could improve our understanding for relationships between molecular mechanisms of disease and clinical outcomes. Additional personalized information related to genetics, environment, lifestyle, education, socioeconomic status, and other factors could potentially improve upon the understanding of individual rates of disease progression and response to therapeutic interventions.

Developing a QSP model that is able to describe the complexity of neurodegenerative disease is challenging. Our findings reinforce the need for improving data and model sharing efforts in the field of QSP modeling in neuroscience. Nonprofit and precompetitive public-private partnerships will likely play an important future role in data and model sharing endeavors. A mathematical representation for our current understanding of neurodegenerative disease would provide a tool for the identification of novel drug targets, predicting combinatorial treatment strategies, understanding interindividual differences in disease progression and therapeutic response, and many other applications, which ultimately translates to an enhanced understanding for the pharmacological modification of neurodegenerative diseases and the improvement of human health.

FUNDING INFORMATION

No funding was received for this work.

CONFLICT OF INTEREST

The authors declared no competing interests for this work.

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REFERENCES

1. Kaushik S, Cuervo AM. Proteostasis and aging. *Nat Med*. 2015;21:1406-1415.
2. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. *Science*. 2002;297:353-356.
3. Barnham KJ, Masters CL, Bush AI. Neurodegenerative diseases and oxidative stress. *Nat Rev Drug Discov*. 2004;3:205-214.
4. Hetz C, Saxena S. ER stress and the unfolded protein response in neurodegeneration. *Nat Rev Neurol*. 2017;13:477-491.
5. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. *Science*. 2016;353:777-783.
6. Kitano H. Systems biology: a brief overview. *Science*. 2002;295:1662-1664.
7. Nijsen M, Wu F, Bansal L, et al. Preclinical QSP modeling in the pharmaceutical industry: an IQ consortium survey examining the current landscape. *CPT Pharmacometrics Syst Pharmacol*. 2018;7:135-146.
8. Bloomingdale P, Karelina T, Cirit M, et al. Quantitative systems pharmacology in neuroscience: novel methodologies and technologies. *CPT Pharmacometrics Syst Pharmacol*. 2021;10:412-419.
9. Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO mol Med*. 2016;8:595-608.
10. Tcw J, Goate AM. Genetics of beta-amyloid precursor protein in Alzheimer's disease. *Cold Spring Harb Perspect Med*. 2017;7(3):135-146.
11. van der Kant R, Goldstein LSB, Ossenkoppele R. Amyloid-beta-independent regulators of tau pathology in Alzheimer disease. *Nat Rev Neurosci*. 2020;21:21-35.
12. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathol*. 1991;82:239-259.
13. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2019. *Alzheimers Dement (NY)*. 2019;5:272-293.
14. Egan MF, Kost J, Tariot PN, et al. Randomized trial of verubecestat for mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2018;378:1691-1703.
15. Panza F, Lozupone M, Logroscino G, Imbimbo BP. A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease. *Nat Rev Neurol*. 2019;15:73-88.

16. Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer disease. *Nat Rev Neurol*. 2018;14:399-415.
17. Syed YY. Sodium oligomannate: first approval. *Drugs*. 2020;80:441-444.
18. Seo DO, Boros BD, Holtzman DM. The microbiome: a target for Alzheimer disease? *Cell Res*. 2019;29:779-780.
19. Lotharius J, Brundin P. Pathogenesis of Parkinson's disease: dopamine, vesicles and alpha-synuclein. *Nat Rev Neurosci*. 2002;3:932-942.
20. Kalia LV, Lang AE. Parkinson's disease. *Lancet*. 2015;386:896-912.
21. Jaiswal MK. Riluzole and edaravone: a tale of two amyotrophic lateral sclerosis drugs. *Med Res Rev*. 2019;39:733-748.
22. Lotharius J, Brundin P. Pathogenesis of Parkinson's disease: dopamine, vesicles and α-synuclein. *Nat Rev Neurosci*. 2002;3:932-942.
23. Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. *Lancet Neurol*. 2020;19:170-178.
24. Ball N, Teo WP, Chandra S, Chapman J. Parkinson's disease and the environment. *Front Neurol*. 2019;10:218.
25. Lang AE, Espay AJ. Disease modification in Parkinson's disease: current approaches, challenges, and future considerations. *Mov Disord*. 2018;33:660-677.
26. van Es MA, Hardiman O, Chio A, et al. Amyotrophic lateral sclerosis. *Lancet*. 2017;390:2084-2098.
27. Chen S, Sayana P, Zhang X, Le W. Genetics of amyotrophic lateral sclerosis: an update. *Mol Neurodegener*. 2013;8:28.
28. Mejzini R, Flynn LL, Pitout IL, Fletcher S, Wilton SD, Akkari PA. ALS genetics, mechanisms, and therapeutics: where are we now? *Front Neurosci*. 2019;13:1310.
29. Tefera TW, Steyn FJ, Ngo ST, Borges K. CNS glucose metabolism in amyotrophic lateral sclerosis: a therapeutic target? *Cell Biosci*. 2021;11:1-17.
30. Bensimon G, Lacomblez L, Meininger V. A controlled trial of riluzole in amyotrophic lateral sclerosis. ALS/Riluzole study group. *N Engl J Med*. 1994;330:585-591.
31. Barp A, Gerardi F, Lizio A, Sansone VA, Lunetta C. Emerging drugs for the treatment of amyotrophic lateral sclerosis: a focus on recent phase 2 trials. *Expert Opin Emerg Drugs*. 2020;25(2):1-20.
32. Bates GP, Dorsey R, Gusella JF, et al. Huntington disease. *Nat Rev Dis Primers*. 2015;1:15005.
33. Jimenez-Sanchez M, Licitra F, Underwood BR, Rubinsztein DC. Huntington's disease: mechanisms of pathogenesis and therapeutic strategies. *Cold Spring Harb Perspect Med*. 2017;7:a024240.
34. Roos RA. Huntington's disease: a clinical review. *Orphanet J Rare Dis*. 2010;5:40.
35. Spillantini MG, Goedert M. Tau pathology and neurodegeneration. *Lancet Neurol*. 2013;12:609-622.
36. Gong CX, Liu F, Grundke-Iqbal I, Iqbal K. Post-translational modifications of tau protein in Alzheimer's disease. *J Neural Transm (Vienna)*. 2005;112:813-838.
37. Buee L, Bussiere T, Buee-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. *Brain Res Brain Res Rev*. 2000;33:95-130.
38. Cowan CM, Mudher A. Are tau aggregates toxic or protective in tauopathies? *Front Neurol*. 2013;4:114.
39. Baker S, Polanco JC, Götz J. Extracellular vesicles containing P301L mutant tau accelerate pathological tau phosphorylation and oligomer formation but do not seed mature neurofibrillary tangles in ALZ17 mice. *J Alzheimers Dis*. 2016;54:1207-1217.
40. Guix FX, Corbett G, Cha D, et al. Detection of aggregation-competent tau in neuron-derived extracellular vesicles. *Int J Mol Sci*. 2018;19:663.
41. Takeda S, Commins C, DeVos SL, et al. Seed-competent high-molecular-weight tau species accumulates in the cerebrospinal fluid of Alzheimer's disease mouse model and human patients. *Ann Neurol*. 2016;80:355-367.
42. Serrano-Pozo A, Frosch MP, Masliah E, Hyman BT. Neuropathological alterations in Alzheimer disease. *Cold Spring Harb Perspect Med*. 2011;1:a006189.
43. Colin M, Dujardin S, Schraen-Maschke S, et al. From the prion-like propagation hypothesis to therapeutic strategies of anti-tau immunotherapy. *Acta Neuropathol*. 2020;139:3-25.
44. Keller J, Fa H, Markesbery W. Decreased levels of proteasome activity and proteasome expression in aging spinal cord. *Neuroscience*. 2000;98:149-156.
45. Rubinsztein DC, Marino G, Kroemer G. Autophagy and aging. *Cell*. 2011;146:682-695.
46. Yim WW, Mizushima N. Lysosome biology in autophagy. *Cell Discov*. 2020;6:6.
47. Martinez-Vicente M, Talloczy Z, Kaushik S, et al. Dopamine-modified alpha-synuclein blocks chaperone-mediated autophagy. *J Clin Invest*. 2008;118:777-788.
48. Caballero B, Bourdenx M, Luengo E, et al. Acetylated tau inhibits chaperone-mediated autophagy and promotes tau pathology propagation in mice. *Nat Commun*. 2021;12:2238.
49. Yim WW-Y, Mizushima N. Lysosome biology in autophagy. *Cell Discovery*. 2020;6:1-12.
50. Nixon RA, Wegiel J, Kumar A, et al. Extensive involvement of autophagy in Alzheimer disease: an immuno-electron microscopy study. *J Neuropathol Exp Neurol*. 2005;64:113-122.
51. Boland B, Kumar A, Lee S, et al. Autophagy induction and autophagosome clearance in neurons: relationship to autophagic pathology in Alzheimer's disease. *J Neurosci*. 2008;28:6926-6937.
52. Martinez-Vicente M, Talloczy Z, Wong E, et al. Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. *Nat Neurosci*. 2010;13:567-576.
53. Lee JH, Yu WH, Kumar A, et al. Lysosomal proteolysis and autophagy require presenilin 1 and are disrupted by Alzheimer-related PS1 mutations. *Cell*. 2010;141:1146-1158.
54. Schutzmann MP, Hasecke F, Bachmann S, et al. Endo-lysosomal Abeta concentration and pH trigger formation of Abeta oligomers that potently induce tau missorting. *Nat Commun*. 2021;12:4634.
55. Kim YC, Guan KL. mTOR: a pharmacologic target for autophagy regulation. *J Clin Invest*. 2015;125:25-32.
56. Spilman P, Podlutskaya N, Hart MJ, et al. Inhibition of mTOR by rapamycin abolishes cognitive deficits and reduces amyloid-beta levels in a mouse model of Alzheimer's disease. *PLoS One*. 2010;5:e9979.
57. Ozcelik S, Fraser G, Castets P, et al. Rapamycin attenuates the progression of tau pathology in P301S tau transgenic mice. *PloS One*. 2013;8:e62459.
58. Kim J, Kundu M, Viollet B, Guan K-L. AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat Cell Biol*. 2011;13:132-141.
59. Jaeger PA, Wyss-Coray T. Beclin 1 complex in autophagy and Alzheimer disease. *Arch Neurol*. 2010;67:1181-1184.

60. Rock KL, Gramm C, Rothstein L, et al. Inhibitors of the proteasome block the degradation of most cell proteins and the generation of peptides presented on MHC class I molecules. *Cell*. 1994;78:761-771.
61. Keck S, Nitsch R, Grune T, Ullrich O. Proteasome inhibition by paired helical filament-tau in brains of patients with Alzheimer's disease. *J Neurochem*. 2003;85:115-122.
62. Tseng BP, Green KN, Chan JL, Blurton-Jones M, LaFerla FM. Abeta inhibits the proteasome and enhances amyloid and tau accumulation. *Neurobiol Aging*. 2008;29:1607-1618.
63. Schaffert L-N, Carter WG. Do post-translational modifications influence protein aggregation in neurodegenerative diseases: a systematic review. *Brain Sci*. 2020;10:232.
64. Thijssen EH, la Joie R, Strom A, et al. Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study. *Lancet Neurol*. 2021;20:739-752.
65. Dujardin S, Commins C, Lathuiliere A, et al. Tau molecular diversity contributes to clinical heterogeneity in Alzheimer's disease. *Nat Med*. 2020;26:1256-1263.
66. Chen HH, Liu P, Auger P, et al. Calpain-mediated tau fragmentation is altered in Alzheimer's disease progression. *Sci Rep*. 2018;8:16725.
67. Braak H, Del Tredici K. Potential pathways of abnormal tau and alpha-synuclein dissemination in sporadic Alzheimer's and Parkinson's diseases. *Cold Spring Harb Perspect Biol*. 2016;8:a023630.
68. Lowe VJ, Wiste HJ, Senjem ML, et al. Widespread brain tau and its association with ageing, braak stage and Alzheimer's dementia. *Brain*. 2018;141:271-287.
69. Dehay B, Vila M, Bezard E, Brundin P, Kordower JH. Alpha-synuclein propagation: new insights from animal models. *Mov Disord*. 2016;31:161-168.
70. Goedert M, Spillantini MG. Propagation of tau aggregates. *Mol Brain*. 2017;10:18.
71. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nat Rev Neurosci*. 2019;20:148-160.
72. Halliwell B, Gutteridge JM. *Free Radicals in Biology and Medicine*. Oxford University Press; 2015.
73. Sies H, Jones DP. Reactive oxygen species (ROS) as pleiotropic physiological signalling agents. *Nat Rev Mol Cell Biol*. 2020;21:363-383.
74. Halliwell B. Reactive oxygen species and the central nervous system. *J Neurochem*. 1992;59:1609-1623.
75. Rolfe DF, Brown GC. Cellular energy utilization and molecular origin of standard metabolic rate in mammals. *Physiol Rev*. 1997;77:731-758.
76. Sultana R, Perluigi M, Butterfield DA. Protein oxidation and lipid peroxidation in brain of subjects with Alzheimer's disease: insights into mechanism of neurodegeneration from redox proteomics. *Antioxid Redox Signal*. 2006;8:2021-2037.
77. Hou Y, Dan X, Babbar M, et al. Ageing as a risk factor for neurodegenerative disease. *Nat Rev Neurol*. 2019;15:565-581.
78. Zhao RZ, Jiang S, Zhang L, Yu ZB. Mitochondrial electron transport chain, ROS generation and uncoupling (review). *Int J Mol Med*. 2019;44:3-15.
79. Brown GC, Borutaite V. There is no evidence that mitochondria are the main source of reactive oxygen species in mammalian cells. *Mitochondrion*. 2012;12:1-4.
80. Cabral-Miranda F, Hetz C. ER stress and neurodegenerative disease: a cause or effect relationship? *Curr Top Microbiol Immunol*. 2018;414:131-157.
81. Kikuchi H, Almer G, Yamashita S, et al. Spinal cord endoplasmic reticulum stress associated with a microsomal accumulation of mutant superoxide dismutase-1 in an ALS model. *Proc Natl Acad Sci USA*. 2006;103:6025-6030.
82. Cooper AA, Gitler AD, Cashikar A, et al. Alpha-synuclein blocks ER-Golgi traffic and Rab1 rescues neuron loss in Parkinson's models. *Science*. 2006;313:324-328.
83. Bellucci A, Navarria L, Zaltieri M, et al. Induction of the unfolded protein response by alpha-synuclein in experimental models of Parkinson's disease. *J Neurochem*. 2011;116:588-605.
84. Nishitoh H, Kadowaki H, Nagai A, et al. ALS-linked mutant SOD1 induces ER stress- and ASK1-dependent motor neuron death by targeting Derlin-1. *Genes Dev*. 2008;22:1451-1464.
85. Yang H, Liu C, Zhong Y, Luo S, Monteiro MJ, Fang S. Huntingtin interacts with the cue domain of gp78 and inhibits gp78 binding to ubiquitin and p97/VCP. *PLoS One*. 2010;5:e8905.
86. Valente EM, Abou-Sleiman PM, Caputo V, et al. Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science*. 2004;304:1158-1160.
87. Takahashi R, Imai Y, Hattori N, Mizuno Y. Parkin and endoplasmic reticulum stress. *Ann NY Acad Sci*. 2003;991:101-106.
88. Nishimura AL, Mitne-Neto M, Silva HCA, et al. A mutation in the vesicle-trafficking protein VAPB causes late-onset spinal muscular atrophy and amyotrophic lateral sclerosis. *Am J Hum Genet*. 2004;75:822-831.
89. Melov S, Adlard PA, Morten K, et al. Mitochondrial oxidative stress causes hyperphosphorylation of tau. *PLoS One*. 2007;2:e536.
90. Montibeller L, de Belleroche J. Amyotrophic lateral sclerosis (ALS) and Alzheimer's disease (AD) are characterised by differential activation of ER stress pathways: focus on UPR target genes. *Cell Stress Chaperones*. 2018;23:897-912.
91. Saxena S, Caroni P. Selective neuronal vulnerability in neurodegenerative diseases: from stressor thresholds to degeneration. *Neuron*. 2011;71:35-48.
92. Duarte JMN, Schuck PF, Wenk GL, Ferreira GC. Metabolic disturbances in diseases with neurological involvement. *Aging Dis*. 2013;5:238-255.
93. Maayan L, Hoogendoorn C, Sweat V, Convit A. Disinhibited eating in obese adolescents is associated with orbitofrontal volume reductions and executive dysfunction. *Obesity (Silver Spring)*. 2011;19:1382-1387.
94. Yau PL, Castro MG, Tagani A, Tsui WH, Convit A. Obesity and metabolic syndrome and functional and structural brain impairments in adolescence. *Pediatrics*. 2012;130:e856-e864.
95. Verstynen TD, Weinstein AM, Schneider WW, Jakicic JM, Rofey DL, Erickson KI. Increased body mass index is associated with a global and distributed decrease in white matter microstructural integrity. *Psychosom Med*. 2012;74:682-690.
96. Mrak RE. Alzheimer-type neuropathological changes in morbidly obese elderly individuals. *Clin Neuropathol*. 2009;28:40-45.
97. Yu J-T, Xu W, Tan CC, et al. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. *J Neurol Neurosurg Psychiatry*. 2020;91:1201-1209.

98. Farooqui AA, Farooqui T, Panza F, Frisardi V. Metabolic syndrome as a risk factor for neurological disorders. *Cell Mol Life Sci*. 2012;69:741-762.
99. Exalto LG, van der Flier WM, van Boheemen CJM, et al. The metabolic syndrome in a memory clinic population: relation with clinical profile and prognosis. *J Neurol Sci*. 2015;351:18-23.
100. Raffaitin C, Gin H, Empana JP, et al. Metabolic syndrome and risk for incident Alzheimer's disease or vascular dementia: the three-city study. *Diabetes Care*. 2009;32:169-174.
101. Vanhanen M, Koivisto K, Moilanen L, et al. Association of metabolic syndrome with Alzheimer disease: a population-based study. *Neurology*. 2006;67:843-847.
102. Gomez G, Beason-Held LL, Bilgel M, et al. Metabolic syndrome and amyloid accumulation in the aging brain. *J Alzheimers Dis*. 2018;65:629-639.
103. Palta P, Rippon B, Tahmi M, et al. Metabolic syndrome and its components in relation to in vivo brain amyloid and neurodegeneration in late middle age. *Neurobiol Aging*. 2021;97:89-96.
104. Sara VR, Hall K, von Holtz H, Humbel R, Sjögren B, Wetterberg L. Evidence for the presence of specific receptors for insulin-like growth factors 1 (IGE-1) and 2 (IGF-2) and insulin throughout the adult human brain. *Neurosci Lett*. 1982;34:39-44.
105. Pandini G, Pace V, Copani A, Squatrito S, Milardi D, Vigneri R. Insulin has multiple antiamyloidogenic effects on human neuronal cells. *Endocrinology*. 2013;154:375-387.
106. Steen E, Terry BM, Rivera EJ, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease—is this type 3 diabetes? *J Alzheimers Dis*. 2005;7:63-80.
107. Hokama M, Oka S, Leon J, et al. Altered expression of diabetes-related genes in Alzheimer's disease brains: the Hisayama study. *Cereb Cortex*. 2014;24:2476-2488.
108. Townsend M, Mehta T, Selkoe DJ. Soluble Abeta inhibits specific signal transduction cascades common to the insulin receptor pathway. *J Biol Chem*. 2007;282:33305-33312.
109. Willette AA, Johnson SC, Birdsill AC, et al. Insulin resistance predicts brain amyloid deposition in late middle-aged adults. *Alzheimers Dement*. 2015;11:504-510.e501.
110. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes*. 2004;53:474-481.
111. Roberts RO, Knopman DS, Przybelski SA, et al. Association of type 2 diabetes with brain atrophy and cognitive impairment. *Neurology*. 2014;82:1132-1141.
112. Wennberg AMV, Spira AP, Pettigrew C, et al. Blood glucose levels and cortical thinning in cognitively normal, middle-aged adults. *J Neurol Sci*. 2016;365:89-95.
113. Beckett LA, Donohue MC, Wang C, et al. The Alzheimer's disease neuroimaging initiative phase 2: increasing the length, breadth, and depth of our understanding. *Alzheimers Dement*. 2015;11:823-831.
114. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the Rotterdam study. *Neurology*. 1999;53:1937-1942.
115. Arvanitakis Z, Wilson RS, Bienias JL, Evans DA, Bennett DA. Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function. *Arch Neurol*. 2004;61:661-666.
116. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: the Honolulu-Asia aging study. *Diabetes*. 2002;51:1256-1262.
117. Bosco D, Plastino M, Cristiano D, et al. Dementia is associated with insulin resistance in patients with Parkinson's disease. *J Neurol Sci*. 2012;315:39-43.
118. Lalić NM, Marić J, Svetel M, et al. Glucose homeostasis in Huntington disease: abnormalities in insulin sensitivity and early-phase insulin secretion. *Arch Neurol*. 2008;65:476-480.
119. Alexaki VI. The impact of obesity on microglial function: immune metabolic and endocrine perspectives. *Cells*. 2021;10:1584.
120. Baufeld C, Osterloh A, Prokop S, Miller KR, Heppner FL. High-fat diet-induced brain region-specific phenotypic spectrum of CNS resident microglia. *Acta Neuropathol*. 2016;132:361-375.
121. Li J, Tang Y, Cai D. IKKβ/NF-κB disrupts adult hypothalamic neural stem cells to mediate a neurodegenerative mechanism of dietary obesity and pre-diabetes. *Nat Cell Biol*. 2012;14:999-1012.
122. McNay DE, Briançon N, Kokoeva MV, Maratos-Flier E, Flier JS. Remodeling of the arcuate nucleus energy-balance circuit is inhibited in obese mice. *J Clin Invest*. 2012;122:142-152.
123. Puig J, Blasco G, Daunis-i-Estadella J, et al. Hypothalamic damage is associated with inflammatory markers and worse cognitive performance in obese subjects. *J Clin Endocrinol Metab*. 2015;100:E276-E281.
124. Baik SH, Kang S, Lee W, et al. A breakdown in metabolic reprogramming causes microglia dysfunction in Alzheimer's disease. *Cell Metab*. 2019;30:493-507.e496.
125. Johnson ECB, Dammer EB, Duong DM, et al. Large-scale proteomic analysis of Alzheimer's disease brain and cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and astrocyte activation. *Nat Med*. 2020;26:769-780.
126. Ulland TK, Song WM, Huang SCC, et al. TREM2 maintains microglial metabolic fitness in Alzheimer's disease. *Cell*. 2017;170:649-663 e613.
127. Vogt NM, Kerby RL, Dill-McFarland KA, et al. Gut microbiome alterations in Alzheimer's disease. *Sci Rep*. 2017;7:13537.
128. Sun MF, Shen YQ. Dysbiosis of gut microbiota and microbial metabolites in Parkinson's disease. *Ageing Res Rev*. 2018;45:53-61.
129. Cattaneo A, Cattane N, Galluzzi S, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiol Aging*. 2017;49:60-68.
130. Wang X, Sun G, Feng T, et al. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. *Cell Res*. 2019;29:787-803.
131. Kim S, Kwon SH, Kam TI, et al. Transneuronal propagation of pathologic α-synuclein from the gut to the brain models Parkinson's disease. *Neuron*. 2019;103:627-641.e627.
132. Berti V, Walters M, Sterling J, et al. Mediterranean diet and 3-year Alzheimer brain biomarker changes in middle-aged adults. *Neurology*. 2018;90:e1789-e1798.
133. Kashiwaya Y, Bergman C, Lee JH, et al. A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease. *Neurobiol Aging*. 2013;34:1530-1539.
134. Brownlow ML, Benner L, D'Agostino D, Gordon MN, Morgan D. Ketogenic diet improves motor performance but not

cognition in two mouse models of Alzheimer's pathology. *PloS One*. 2013;8:e75713.
135. Aso E, Semakova J, Joda L, et al. Triheptanoin supplementation to ketogenic diet curbs cognitive impairment in APP/PS1 mice used as a model of familial Alzheimer's disease. *Curr Alzheimer Res*. 2013;10:290-297.
136. Galea I, Bechmann I, Perry VH. What is immune privilege (not)? *Trends Immunol*. 2007;28:12-18.
137. Kettenmann H, Hanisch U-K, Noda M, Verkhratsky A. Physiology of microglia. *Physiol Rev*. 2011;91:461-553.
138. Kierdorf K, Masuda T, Jordão MJC, Prinz M. Macrophages at CNS interfaces: ontogeny and function in health and disease. *Nat Rev Neurosci*. 2019;20:547-562.
139. von Bartheld CS, Bahney J, Herculano-Houzel S. The search for true numbers of neurons and glial cells in the human brain: a review of 150 years of cell counting. *J Comp Neurol*. 2016;524:3865-3895.
140. Bradl M, Lassmann H. Oligodendrocytes: biology and pathology. *Acta Neuropathol*. 2010;119:37-53.
141. Simons M, Trajkovic K. Neuron-glia communication in the control of oligodendrocyte function and myelin biogenesis. *J Cell Sci*. 2006;119:4381-4389.
142. Barres BA. The mystery and magic of glia: a perspective on their roles in health and disease. *Neuron*. 2008;60:430-440.
143. Thorburne SK, Juurlink BH. Low glutathione and high iron govern the susceptibility of oligodendroglial precursors to oxidative stress. *J Neurochem*. 1996;67:1014-1022.
144. Kohler S, Winkler U, Hirrlinger J. Heterogeneity of astrocytes in Grey and White matter. *Neurochem Res*. 2021;46:3-14.
145. Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathol*. 2010;119:7-35.
146. Hickman S, Izzy S, Sen P, Morsett L, El Khoury J. Microglia in neurodegeneration. *Nat Neurosci*. 2018;21:1359-1369.
147. Keren-Shaul H, Spinrad A, Weiner A, et al. A unique microglia type associated with restricting development of Alzheimer's disease. *Cell*. 2017;169:1276-1290 e1217.
148. Masuda T, Sankowski R, Staszewski O, et al. Spatial and temporal heterogeneity of mouse and human microglia at single-cell resolution. *Nature*. 2019;566:388-392.
149. Masuda T, Sankowski R, Staszewski O, Prinz M. Microglia heterogeneity in the single-cell era. *Cell Rep*. 2020;30:1271-1281.
150. Olah M, Menon V, Habib N, et al. Single cell RNA sequencing of human microglia uncovers a subset associated with Alzheimer's disease. *Nat Commun*. 2020;11:6129.
151. Prinz M, Erny D, Hagemeyer N. Ontogeny and homeostasis of CNS myeloid cells. *Nat Immunol*. 2017;18:385-392.
152. Prinz M, Priller J. The role of peripheral immune cells in the CNS in steady state and disease. *Nat Neurosci*. 2017;20:136-144.
153. Sofroniew MV. Astrogliosis. *Cold Spring Harb Perspect Biol*. 2014;7:a020420.
154. Condello C, Yuan P, Schain A, Grutzendler J. Microglia constitute a barrier that prevents neurotoxic protofibrillar Aβ42 hotspots around plaques. *Nat Commun*. 2015;6:1-14.
155. Escartin C, Galea E, Lakatos A, et al. Reactive astrocyte nomenclature, definitions, and future directions. *Nat Neurosci*. 2021;24:312-325.
156. Sams EC. Oligodendrocytes in the aging brain. *Neuronal Signal*. 2021;5:NS20210008.
157. El Khoury J, Toft M, Hickman SE, et al. Ccr2 deficiency impairs microglial accumulation and accelerates progression of Alzheimer-like disease. *Nat Med*. 2007;13:432-438.
158. Ulland TK, Colonna M. TREM2—a key player in microglial biology and Alzheimer disease. *Nat Rev Neurol*. 2018;14:667-675.
159. Cruchaga C, Kauwe JS, Harari O, et al. GWAS of cerebrospinal fluid tau levels identifies risk variants for Alzheimer's disease. *Neuron*. 2013;78:256-268.
160. Bennett RE, DeVos SL, Dujardin S, et al. Enhanced tau aggregation in the presence of amyloid beta. *Am J Pathol*. 2017;187:1601-1612.
161. Lee SH, Meilandt WJ, Xie L, et al. Trem2 restrains the enhancement of tau accumulation and neurodegeneration by beta-amyloid pathology. *Neuron*. 2021;109:1283-1301.e6.
162. Heneka MT, Kummer MP, Stutz A, et al. NLRP3 is activated in Alzheimer's disease and contributes to pathology in APP/PS1 mice. *Nature*. 2013;493:674-678.
163. Matt SM, Johnson RW. Neuro-immune dysfunction during brain aging: new insights in microglial cell regulation. *Curr Opin Pharmacol*. 2016;26:96-101.
164. Block ML, Calderon-Garciduenas L. Air pollution: mechanisms of neuroinflammation and CNS disease. *Trends Neurosci*. 2009;32:506-516.
165. Huat TJ, Camats-Perna J, Newcombe EA, Valmas N, Kitazawa M, Medeiros R. Metal toxicity links to Alzheimer's disease and neuroinflammation. *J Mol Biol*. 2019;431:1843-1868.
166. Fgaier H, Mustafa IH, Awad AA, Elkamel A. Modeling the interaction between beta-amyloid aggregates and choline acetyltransferase activity and its relation with cholinergic dysfunction through two-enzyme/two-compartment model. *Comput Math Methods Med*. 2015;2015:923762.
167. Rosenthal J, Belfort G, Isaacson D. Early treatment critical: bexarotene reduces amyloid-Beta burden in silico. *PLoS One*. 2016;11:e0153150.
168. van Maanen EMT, van Steeg TJ, Ahsman MJ, et al. Extending a systems model of the APP pathway: separation of beta- and gamma-secretase sequential cleavage steps of APP. *J Pharmacol Exp Ther*. 2018;365:507-518.
169. Karelina T, Demin O, Nicholas T, Lu Y, Duvvuri S, Barton HA. A translational systems pharmacology model for Abeta kinetics in mouse, monkey, and human. *CPT Pharmacometrics Syst Pharmacol*. 2017;6:666-675.
170. Karelina T, Demin O Jr, Demin O, Duvvuri S, Nicholas T. Studying the progression of amyloid pathology and its therapy using translational longitudinal model of accumulation and distribution of amyloid Beta. *CPT Pharmacometrics Syst Pharmacol*. 2017;6:676-685.
171. Stepanov A, Karelina T, Markevich N, Demin O, Nicholas T. A mathematical model of multisite phosphorylation of tau protein. *PLoS One*. 2018;13:e0192519.
172. Madrasi K, das R, Mohmmadabdul H, et al. Systematic in silico analysis of clinically tested drugs for reducing amyloid-beta plaque accumulation in Alzheimer's disease. *Alzheimers Dement*. 2021;17:1487-1498.
173. Lin L, Hua F, Salinas C, et al. Quantitative systems pharmacology model for Alzheimer's disease to predict the effect of aducanumab on brain amyloid. *CPT Pharmacometrics Syst Pharmacol*. 2022;11:362-372.
174. Clausznitzer D, Pichardo-Almarza C, Relo AL, et al. Quantitative systems pharmacology model for Alzheimer disease indicates

targeting sphingolipid dysregulation as potential treatment option. *CPT Pharmacometrics Syst Pharmacol*. 2018;7:759-770.
175. Ranjan B, Chong KH, Zheng J. Composite mathematical modeling of calcium signaling behind neuronal cell death in Alzheimer's disease. *BMC Syst Biol*. 2018;12:10.
176. Geerts H, Spiros A, Roberts P. Impact of amyloid-beta changes on cognitive outcomes in Alzheimer's disease: analysis of clinical trials using a quantitative systems pharmacology model. *Alzheimers Res Ther*. 2018;10:14.
177. Geerts H, Spiros A. Learning from amyloid trials in Alzheimer's disease. A virtual patient analysis using a quantitative systems pharmacology approach. *Alzheimers Dement*. 2020;16:862-872.
178. Diem AK, Tan M, Bressloff NW, et al. A simulation model of periarterial clearance of amyloid-beta from the brain. *Front Aging Neurosci*. 2016;8:18.
179. Fornari S, Schafer A, Jucker M, Goriely A, Kuhl E. Prion-like spreading of Alzheimer's disease within the brain's connectome. *J R Soc Interface*. 2019;16:20190356.
180. Kunze T, Hunold A, Haueisen J, Jirsa V, Spiegler A. Transcranial direct current stimulation changes resting state functional connectivity: a large-scale brain network modeling study. *Neuroimage*. 2016;140:174-187.
181. Iturria-Medina Y, Carbonell FM, Sotero RC, Chouinard-Decorte F, Evans AC, Alzheimer's Disease Neuroimaging Initiative. Multifactorial causal model of brain (dis)organization and therapeutic intervention: application to Alzheimer's disease. *Neuroimage*. 2017;152:60-77.
182. Bakshi S, Chelliah V, Chen C, van der Graaf PH. Mathematical biology models of Parkinson's disease. *CPT Pharmacometrics Syst Pharmacol*. 2019;8:77-86.
183. Savageau MA. Biochemical systems analysis: I. some mathematical properties of the rate law for the component enzymatic reactions. *J Theor Biol*. 1969;25:365-369.
184. de la Fuente-Fernandez R, Schulzer M, Mak E, Calne DB, Stoessl AJ. Presynaptic mechanisms of motor fluctuations in Parkinson's disease: a probabilistic model. *Brain*. 2004;127:888-899.
185. Qi Z, Miller GW, Voit EO. Computational systems analysis of dopamine metabolism. *PLoS One*. 2008;3:e2444.
186. Qi Z, Miller GW, Voit EO. Computational analysis of determinants of dopamine (DA) dysfunction in DA nerve terminals. *Synapse*. 2009;63:1133-1142.
187. Sass MB, Lorenz AN, Green RL, Coleman RA. A pragmatic approach to biochemical systems theory applied to an alpha-synuclein-based model of Parkinson's disease. *J Neurosci Methods*. 2009;178:366-377.
188. Braatz EM, Coleman RA. A mathematical model of insulin resistance in Parkinson's disease. *Comput Biol Chem*. 2015;56:84-97.
189. Spiros A, Roberts P, Geerts H. A quantitative systems pharmacology computer model for schizophrenia efficacy and extrapyramidal side effects. *Drug Dev Res*. 2012;73:196-213.
190. Spiros A, Carr R, Geerts H. Not all partial dopamine D2 receptor agonists are the same in treating schizophrenia. Exploring the effects of bifeprunox and aripiprazole using a computer model of a primate striatal dopaminergic synapse. *Neuropsychiatr Dis Treat*. 2010;6:589.
191. Spiros A, Roberts P, Geerts H. Phenotypic screening of the Prestwick library for treatment of Parkinson's tremor symptoms using a humanized quantitative systems pharmacology platform. *J Parkinsons Dis*. 2013;3:569-580.
192. Roberts P, Spiros A, Geerts H. A humanized clinically calibrated quantitative systems pharmacology model for hypokinetic motor symptoms in parkinson's disease. *Front Pharmacol*. 2016;7:6.
193. Yousif N, Bain PG, Nandi D, Borisyuk R. A population model of deep brain stimulation in movement disorders from circuits to cells. *Front Hum Neurosci*. 2020;14:55.
194. Yousif N, Mace M, Pavese N, Borisyuk R, Nandi D, Bain P. A network model of local field potential activity in essential tremor and the impact of deep brain stimulation. *PLoS Comput Biol*. 2017;13:e1005326.
195. Merrison-Hort R, Yousif N, Njap F, Hofmann UG, Burylko O, Borisyuk R. An interactive channel model of the basal ganglia: bifurcation analysis under healthy and parkinsonian conditions. *J Math Neurosci*. 2013;3:14.
196. Veronneau-Veilleux F, Robaey P, Ursino M, Nekka F. An integrative model of Parkinson's disease treatment including levodopa pharmacokinetics, dopamine kinetics, basal ganglia neurotransmission and motor action throughout disease progression. *J Pharmacokinet Pharmacodyn*. 2021;48:133-148.
197. Francis F, Garcia MR, Middleton RH. A single compartment model of pacemaking in dissasociated substantia nigra neurons: stability and energy analysis. *J Comput Neurosci*. 2013;35:295-316.
198. Shao H, He Y, Li KC, Zhou X. A system mathematical model of a cell–cell communication network in amyotrophic lateral sclerosis. *Mol Biosyst*. 2013;9:398-406.
199. Pei F, Li H, Henderson MJ, et al. Connecting neuronal cell protective pathways and drug combinations in a Huntington's disease model through the application of quantitative systems pharmacology. *Sci Rep*. 2017;7:17803.
200. Cobanoglu MC, Liu C, Hu F, Oltvai ZN, Bahar I. Predicting drug–target interactions using probabilistic matrix factorization. *J Chem Inf Model*. 2013;53:3399-3409.
201. Cobanoglu MC, Oltvai ZN, Taylor DL, Bahar I. BalestraWeb: efficient online evaluation of drug–target interactions. *Bioinformatics*. 2015;31:131-133.
202. Li J, Shui X, Sun R, et al. Microglial phenotypic transition: signaling pathways and influencing modulators involved in regulation in central nervous system diseases. *Front Cell Neurosci*. 2021;15:736310.
203. Twohig D, Nielsen HM. Alpha-synuclein in the pathophysiology of Alzheimer's disease. *Mol Neurodegener*. 2019;14:23.
204. Wittig U, Rey M, Kania R, et al. Challenges for an enzymatic reaction kinetics database. *FEBS J*. 2014;281:572-582.
205. Raj A, Kuceyeski A, Weiner M. A network diffusion model of disease progression in dementia. *Neuron*. 2012;73:1204-1215.
206. Beudel M, Little S, Pogosyan A, et al. Tremor reduction by deep brain stimulation is associated with gamma power suppression in Parkinson's disease. *Neuromodulation*. 2015;18:349-354.
207. Little S, Pogosyan A, Neal S, et al. Adaptive deep brain stimulation in advanced Parkinson disease. *Ann Neurol*. 2013;74:449-457.
208. Durstewitz D, Seamans JK, Sejnowski TJ. Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. *J Neurophysiol*. 2000;83:1733-1750.
209. Geerts H, Roberts P, Spiros A. A quantitative system pharmacology computer model for cognitive deficits in schizophrenia. *CPT Pharmacometrics Syst Pharmacol*. 2013;2:e36.

210. Bouteiller JC, Mergenthal AR, Hu E, Berger TW. Pathogenic processes underlying Alzheimer's disease: modeling the effects of amyloid Beta on synaptic transmission. *Annu Int Conf IEEE Eng Med Biol Soc*. 2019;2019:1956-1959.
211. Sotero RC, Trujillo-Barreto NJ. Biophysical model for integrating neuronal activity, EEG, fMRI and metabolism. *Neuroimage*. 2008;39:290-309.
212. Geerts H, Roberts P, Spiros A. Exploring the relation between BOLD fMRI and cognitive performance using a computer-based quantitative systems pharmacology model: applications to the COMTVAL158MET genotype and ketamine. *Eur Neuropsychopharmacol*. 2021;50:12-22.
213. Hines ML, Carnevale NT. The NEURON simulation environment. *Neural Comput*. 1997;9:1179-1209.
214. Cummings J. Lessons learned from Alzheimer disease: clinical trials with negative outcomes. *Clin Transl Sci*. 2018;11:147-152.
215. Schirner M, Domide L, Perdikis D, et al. Brain simulation as a cloud service: the virtual brain on EBRAINS. *Neuroimage*. 2022;251:118973.
216. Erdemir A, Mulugeta L, Ku JP, et al. Credible practice of modeling and simulation in healthcare: ten rules from a multidisciplinary perspective. *J Transl Med*. 2020;18:369.

How to cite this article: Bloomingdale P, Karelina T, Ramakrishnan V, et al. Hallmarks of neurodegenerative disease: A systems pharmacology perspective. *CPT Pharmacometrics Syst Pharmacol*. 2022;11:1399-1429. doi:10.1002/psp4.12852