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Review

Functional Neurophysiological Biomarkers of Early-Stage Alzheimer's Disease: A Perspective of Network Hyperexcitability in Disease Progression

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Abstract. Network hyperexcitability (NH) has recently been suggested as a potential neurophysiological indicator of Alzheimer's disease (AD), as new, more accurate biomarkers of AD are sought. NH has generated interest as a potential indicator of certain stages in the disease trajectory and even as a disease mechanism by which network dysfunction could be modulated. NH has been demonstrated in several animal models of AD pathology and multiple lines of evidence point to the existence of NH in patients with AD, strongly supporting the physiological and clinical relevance of this readout. Several hypotheses have been put forward to explain the prevalence of NH in animal models through neurophysiological, biochemical, and imaging techniques. However, some of these hypotheses have been built on animal models with limitations and caveats that may have derived NH through other mechanisms or mechanisms without translational validity to sporadic AD patients, potentially leading to an erroneous conclusion of the underlying cause of NH occurring in patients with AD. In this review, we discuss the substantiation for NH in animal models of AD pathology and in human patients, as well as some of the hypotheses considering recently developed animal models that challenge existing hypotheses and mechanisms of NH. In addition, we provide a preclinical perspective on how the development of animal models incorporating AD-specific NH could provide physiologically relevant translational experimental data that may potentially aid the discovery and development of novel therapies for AD.

Keywords: Alzheimer's disease, amyloid, biomarkers, epilepsy, hippocampus, hyperexcitability, laboratory animal models, tau proteins, translational research

INTRODUCTION

Network overexcitability or hyperexcitability (NH), a state in which neural networks exhibit an increased likelihood to be excited or activated, is a mainstay in several forms of epilepsy and seizure-related disorders. One possible cellular basis for this state of hyperexcitability originates from the excitability of excitatory neurons [1], and may stem from factors intrinsic to the neuron, such as the availability of synaptic neurotransmitter receptors, or extrinsic factors such as disinhibition from inhibitory interneuron activity [2] or astrocytic clearance of

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Table 1
List of neurodegenerative disorders linked to network hyperexcitability

Disorder	Cognitive and physiological symptoms	Regions of hyper-excitability	Reference
Alzheimer's disease	Intellectual impairment, memory and attention deficits, language impairment, visuospatial deficits, learning deficits, gait disturbances, seizures, sleep disorders.	Cortical regions, temporal lobes, default mode network, motor cortex	[22, 70, 77, 242–245]
Amyotrophic lateral sclerosis	Muscle weakness, twitches, cramps, spasticity, slurred speech, difficulty in fine motor control.	Motor cortex, peripheral motor neurons	[246, 247]
Epilepsy syndrome	Seizures, loss of muscle control, loss of consciousness, memory and attention deficits, language deficits, deficits in mental acuity, learning deficits, sleep disorders.	Temporal lobes, cortical regions	[29, 248–252]
Fragile X Syndrome	Intellectual impairment, memory impairments, deficits in spatial visualization, visuo-motor coordination, language deficits, seizures, attention deficits, hyperactivity, low muscle tone, hypersensitivity.	Neocortical regions	[46, 253, 254]
Parkinson's Disease	Bradykinesia, increased muscle tone, tremors, fine motor control deficits, balance and gait impairments, speech deficits, visuospatial deficits.	Motor cortex, cerebellum	[255–258]
Rett Syndrome	Cognitive impairment, speech impairments, loss of movement and coordination, seizures, breathing disturbances.	Motor cortex, cortical regions	[259–262]
Spinal cord injury	Enhanced pain transmission, neuropathic pain.	Spinal cord	[263]
Traumatic brain injury	Cognitive impairment, attention, memory and executive function deficits, speech impairments, speech deficits, loss of consciousness, sleep disorders, loss of balance and coordination, seizures.	Variable, depending on site of trauma	[264–266]

neurotransmitters [3]. While NH has been generally associated with epilepsy and the development of seizures, it also occurs in many other neurological disorders (Table 1), indicating a strong relationship between hyperexcitability and brain dysfunction. While hyperexcitability across all these disorders is unlikely to share the same etiology, the presence of hyperexcitability in these disorders implies a more mechanistic role through which associated behavioral and cognitive symptoms can manifest.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder without effective treatment at present. Current symptomatic treatment options for AD partially alleviate cognitive and physiological deficits, but do not significantly alter the pathology progression or prolong the lifespan of the patient [4]. The current, repeated failures of clinical trials serve to underscore the complex, multifactorial nature of AD, indicating an incomplete understanding of the pathological mechanisms underlying this progressive disease [5]. These failures have been ascribed to reasons such as the validity of the available animal models, the validity of the tests for translational assays, the subjectivity of (early) clinical diagnoses as well as the lack of valid and precise biomarkers, e.g., for patient selection in clinical trials [5, 6]. The timing of therapeutic intervention has also been highlighted as a key factor influencing ineffectiveness in clinical trials [7], due to the extensive neurodegeneration likely present at the point of a confirmed diagnosis. Following this line of thinking, attention has turned to finding newer and more valid biomarkers of AD that allow for therapeutic intervention at an earlier stage of the disease, potentially allowing for halting or slowing of the disease [8].

Currently, the most accepted pathological features of AD are the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles [9], chronic neuroinflammation [10], and neurodegeneration [11]. In addition to the molecular characteristics of AD, neurophysiological characteristics of increased network activity [13], epileptic activity [14], slowing of neural oscillations [15] and reductions in waveform complexity [16] have also been reported in some patients.

Several observations point to NH in patients with AD, even before incipient pathology, suggesting that hyperexcitability may be a prodromal feature of AD [17]. Consistent with these findings, indications of NH have been noted in animal models of pathology

associated with AD [18–20]. Therefore, NH has been posited as a potential indication of dysfunctional neural networks thought to occur in the prodromal stages of AD, linked to soluble amyloid-β species and accumulating AD-related proteins and peptides [21], with links to cognitive dysfunction [22] and progression of pathology [23]. Here, we discuss the consequences of NH on network function, assess the evidence for NH in animal models and human patients, as well as address some of the gaps pertaining to the hypothesis of hyperexcitability in AD. Lastly, we provide a perspective on the development of animal models that proposes the application of NH as a measure of construct validity, as well as approaches to improve experimental design by incorporating the assessment of NH that are crucial for adequate translational validity.

Implications of altered excitability for network function

It has been established that the proper functioning of neurons is necessary for the development and the continued survival of the organism, as shown by the debilitating phenotypes associated with perturbances to neuronal function [24–26]. Neuronal excitability is one such property that governs a broad range of neuronal functions, ranging from, but not limited to: neuronal development, functional integration, and even cell death [27, 28]. The factors that determine the excitability of a neuron arise from elements related to the generation of action potentials and can be broadly classified into factors intrinsic and extrinsic to the neuron. Intrinsic factors such as the density of receptors at a synapse, the properties of ion channels, or the phosphorylation state of certain proteins in the cell can all affect the excitability of a neuron [29]. For example, a mutation in voltage-gated sodium channels that results in the reduction of the sodium channel voltage activation threshold, subsequently requiring less depolarization to open the ion channel and initiate an action potential, could increase neuronal excitability [1]. Factors extrinsic to the neuron affecting its excitability would be associated with other determinants such as interactions with other inhibitory or excitatory neurons, the availability of extracellular neurotransmitters, the concentrations of surrounding extracellular ions, the presence of extracellular ligands which alter the membrane potential [29], or neuroinflammation [30]. An example of such an extrinsic factor would be inhibitory interneurons [2].

Functional organization and network hyperexcitability-associated perturbations

The activity of a neuron does not only depend on its excitability but also on the activity of other neurons to which it is connected within the network. One of the properties that emerges from the complex interaction of neurons in networks is neural oscillations, the high amplitude oscillations detectable from local extracellular field potentials to scalp recordings [31]. The intrinsically complex dynamics of single neurons that allow them to resonate and oscillate at multiple frequencies are a key feature believed to facilitate the emergence of large-scale oscillations that span multiple brain regions [32]. Neuronal oscillations have been classified into various bands in the frequency range from 0.05 to 500 Hz, with different functional or behavioral correlates putatively ascribed to each of the frequency bands. However, definitions of the frequency bands may somewhat differ between researchers and between species investigated (e.g., [31, 33–35], the frequency bands of delta (< 4 Hz), theta (4–8 Hz), alpha (8–15 Hz), beta (16–31 Hz), gamma (> 30 Hz)).

At the cellular level, the interaction between excitatory and inhibitory neuronal activity is known to be responsible for the generation of synchronous rhythms [36, 37]. Alterations in oscillatory rhythms have been implicated in some of the neurological disorders that exhibit hyperexcitability, such as epilepsy [38–40], AD [41–43], and Fragile X syndrome [44–46] as well as Parkinson's disease [47].

However, the relationship between different forms of hyperexcitability and the development of abnormal neuronal rhythms remains to be fully understood. One study observed marked increases in gamma band power and decreased phase-locking properties in patients with fragile X syndrome, which appears to be related to the observation of hyperexcitability [48]. NH has also been shown to be linked to the development of high-frequency oscillations (80–500 Hz), a potential biomarker of epilepsy [38, 49], with the presence of hyperexcitable mechanisms linked to these oscillations [50].

In the context of AD, a multitude of oscillatory changes have been documented in the literature [51]. Indications of altered gamma activity [52–55] and slow-wave activity in animal models [56] are just some examples that have been reported. In AD patients, reports of altered theta, delta oscillation power [57], gamma, delta, and alpha power and amplitudes [58–60] in resting-state EEG as well as a

"slowing" of oscillations [16] have been reported. However, studies exploring the potential causal link(s) between altered oscillatory activity and NH in AD are sparse [53, 61].

Another way in which NH may have large-scale implications is in terms of structural changes that may impact the function of the network. An important structural change associated with the development of seizures and epilepsy associated with the temporal lobe is the axonal sprouting of mossy fibers in the hippocampus [62]. Mossy fibers are the excitatory outputs of granule cells in the hippocampus, and the main excitatory output of granule cell layer, projecting toward the Cornu Ammonis region 3 in the hippocampus under physiologically normal conditions [63]. In response to injury and/or damage, as in repeated seizures, the mossy fibers of the granule cells redirect to the supragranular layer of the dentate gyrus [62]. Depending on the projections of this redirection toward the dendrites of other granule cells, or inhibitory interneurons, the resulting net effect on the hippocampal network could be excitatory or inhibitory, respectively [62, 64–67]. Therefore, this resulting structural change could further alter the balance of excitation and inhibition.

Considering the wide range of disturbances and brain disorders associated with NH as well as the structural and functional implications briefly covered above, the therapeutic management of this phenomenon in neurological disorders could modify the course of the disease or even contribute to recovery. Recently, NH has emerged as a potential neurophysiological readout of network dysfunction in AD and prognostic indicator of disease. However, what is the evidence that NH is a key feature of AD? In the next section, the evidence for NH as a neurophysiological indicator of AD is reviewed and evaluated.

NETWORK HYPEREXCITABILITY IN AD PATIENTS

In humans, direct evidence for NH in patients with AD is sparse, due to ethical and practical considerations that would preclude a definitive evaluation of NH. Such a definitive evaluation would theoretically consist of exact placement of invasive recording electrodes or advanced magnetoencephalography (MEG) approaches, which are presently limited. Numerous other indirect indications suggest the existence of NH in patients with AD, such as the presence of hippocampal hyperactivity [22, 68, 69], cortical hyperexcitability measured by transcranial magnetic stimulation [70], increased risk of seizure and epileptic-like symptoms [14], and alterations in default mode network (DMN) inactivation [71, 72]. These alterations in brain function have been noted in subjects through techniques such as functional magnetic resonance imaging (fMRI) [13, 22], MEG [15], and transcranial magnetic stimulation (TMS) studies [73]. In this section, we discuss the past and recent observations supporting the presence of hyperexcitability in humans.

Hippocampal hyperactivity

Hippocampal hyperactivity is an important feature of AD during the prodromal stages of the disease [69, 74–76] and may reflect an observable manifestation of underlying NH in the early stages of the disease. The temporal progression of hippocampal activity has been reported to be increased during amnestic mild cognitive impairment (aMCI) and the preclinical phase of early AD and progresses to reduced activity relative to baseline in the later phases of AD [71, 77], when the diagnosis is confirmed. This observation of hippocampal hyperactivity has gained interest as a potential biomarker and functional indicator of the disease state for the development of therapeutic interventions [22, 78], and that may help to disentangle the multiple AD genotypes and phenotypes and their heterogeneous underlying clinicopathology. The evaluation of hippocampal hyperactivity has been carried out using various modalities such as fMRI, MEG, or positron emission tomography (PET). One such PET study has reported an increase in hippocampal glucose metabolism, where global-hippocampal connectivity decreases resulted in increased intrahippocampal glucose metabolism [79]. The increased glucose metabolism has been suggested to imply an increase in intrahippocampal activity, providing some evidence for the presence of hippocampal hyperactivity as well.

Hippocampal hyperactivity was initially proposed as a compensatory mechanism to support memory function [80] and has also subsequently been suggested to be maladaptive instead [22, 68, 81]. One study supporting the idea of a compensatory function examined blood oxygenation level brain response in nondemented participants with or without the apolipoprotein E (*APOE*) ε4 allele, a major risk factor for the development of AD [80]. Blood oxygen level dependent (BOLD) activity levels in *APOE* ε4 subjects were increased to a greater extent during learning of new images compared to control subjects,

distributed in the precuneus, frontal, temporal, and cingulate gyri regions of the brain. This increase in activation during the learning task has been interpreted as a compensatory increase in cognitive effort to achieve comparable levels of episodic memory encoding.

Opposing this compensatory activation hypothesis, a study by Bakker and colleagues showed an improvement in cognitive function by reducing hyperactivity of the hippocampus using levetiracetam [22]. This reduced hippocampal activity was observed through fMRI readouts. The rationale proposed by Bakker and colleagues was that if hyperactivation was indeed beneficially compensatory, attenuation of hyperactivation would result in a reduction in cognitive function. However, the reduction of hyperactivity resulted in an improvement in cognitive function, suggesting that this hyperactivity was detrimental to cognitive function instead of a beneficial compensation.

These studies illustrate a seemingly dichotomous relationship between compensation and maladaptive phenomena in terms of hippocampal hyperactivity. While the words "compensatory" and "maladaptive" may initially appear to be mutually exclusive and dichotomous, it is possible compensatory mechanisms may lead to the development of detrimental states, such as in the case of maladaptive plasticity [82]. While it is not certain that the increased hippocampal activity reflects a compensatory or maladaptive state, it bears noting that these two concepts are not mutually exclusive.

There is an ongoing debate regarding the cause and timing of this hippocampal hyperactivity, with indications that implicate both amyloid and tau pathology as some of the responsible factors involved. PET has been employed to detect the pathology of amyloid plaques and more recently, the pathology of tau as well [83]. Prior to the application of PET scanning as a measure of the amount of amyloid and tau pathology, the extent of the pathology could only be quantified in postmortem tissue, precluding any definitive correlation between pathological load, hippocampal activity, and cognitive function while the patient was alive. Several studies have applied PET in conjunction with fMRI readouts to estimate the contribution of AD pathology to hippocampal hyperactivity [84–86]. Several studies carried out investigating the effects of amyloid-β using PET imaging have reported both contrary increases [85, 87, 88] and decreases in brain activation [84, 89]. A recent article proposed that tau accumulation was associated with hippocampal hyperactivity, as opposed to amyloid-β [86]. In this study, it was proposed that the emergence of hyperactivity occurs in the later stages of preclinical AD and leads to discrepancies in the correlation between amyloid-β levels and hippocampal hyperactivity.

Default mode network alterations

Another observation that could also be related to underlying hyperexcitability is the deficiencies observed in the DMN of AD patients [90, 91].

The DMN is an inter-regional brain network believed to be associated with introspective thinking, planning, and remembering the past [92]. The regions that comprise the DMN are the posterior cingulate cortex, precuneus, dorsal and ventral medial prefrontal, lateral (mainly inferior) parietal cortices, and medial temporal lobes [90]. DMN network activity is characterized by a consistent reduction in activity while performing goal-directed tasks and is activated during states of quiet rest [92]. Based on this characteristic of the DMN, one could conceptualize the deactivation and activation of the DMN as states of externally-directed focus and internally-directed thinking respectively [93]. It is believed that the proper activation and deactivation of the DMN is necessary for the retrieval of stored memories as well as the encoding and acquisition of new memories [94, 95]. Studies have shown that lower DMN activity during stimulus-driven goal-directed cognitive tasks is associated with more successful performance [96–98].

In the context of AD, the DMN has been characterized by reductions in resting state functional connectivity and activity [13, 72, 99–101] and is associated with the progression and severity of the disease [102–104]. In addition, the compromised integrity of the DMN system has been related to the progression of the disease [102, 103]. In the context of task-related DMN activation, decreased levels of DMN task-related deactivation in aMCI and AD patients, as well as *APOE4* carriers [71, 72, 105, 106] have been reported. However, in contrast to the decreased resting state functional connectivity, other studies have shown increased levels of functional connectivity, suggested to be compensatory [99, 104, 107]. One study has reported disrupted medial-parietal and medial-temporal lobe dysconnectivity has resulted in increased intrinsic medial-temporal lobe local functional connectivity [108] and subsequent increase in intrinsic activity.

While evidence points toward an overall decrease in DMN functional connectivity and activity, especially in the later stages of the disease [71], a possible indication whereby hyperexcitability may exist is the decreased deactivation of the DMN. The decreased DMN deactivation indicates a possible inability to properly deactivate DMN or inappropriate DMN activation during these tasks [91, 106]. NH could be one such mechanism that may explain the inability to appropriately deactivate the DMN which has been ascribed to the deficits associated with levels of GABA [109], suggesting that inhibitory deficits could be contributing to the reduced deactivation, and indicate a shift toward a more excitable network state. This decrease in deactivation has also been associated with the presence of amyloid pathology [110]. It is not clear if this reduced deactivation reflects a maladaptive mechanism, functional reorganization to reflect compensatory mechanisms in order to sustain cognitive functions, or both. Lastly, a link between alterations in the DMN and depression, a common comorbidity in AD has been suggested [111, 112], including ruminations-related electroencephalography (EEG) changes [113], which emphasizes the potential clinical importance of hyperexcitability beyond epilepsy per se.

These observations of decreased DMN deactivation might reflect underlying hyperexcitability in the earlier stages of the disease [72, 105]. However, it also bears noting that multiple reports have indicated overall DMN activity reduction [71]. A better understanding of how decreased DMN deactivation might be related to NH could provide a better insight into translational indications of AD or eventually even of AD patient stratification.

Cortical hyperexcitability

Another form of hyperexcitability suggested comes from studies involving TMS of the motor cortex in patients with AD [70, 73, 114, 115]. These studies involve the stimulation of the motor cortex using a TMS paradigm and measurement of the evoked motor potential. The minimum stimulation threshold necessary to evoke a motor threshold in AD patients has been reported to be lower than that healthy controls, suggesting an "increased" motor cortex excitability [114]. This increased excitability of the motor cortex is suggested to be a compensatory mechanism to facilitate voluntary movements [70]. Current discussion has attributed this alteration in excitability to dysfunction of cholinergic and glutamatergic signaling [70].

There is evidence for the deterioration of the cholinergic signaling system in AD throughout the disease, generally stemming from the neurodegeneration of cholinergic neurons in the Nucleus basalis of Meynert, in the basal forebrain [116]. This region harbors neurons rich in the acetylcholine neurotransmitter and projects extensively into cortical regions (for a review of the cholinergic system, see Mesulam, 2013 [117]). The motor cortex has muscarinic and cholinergic terminals and receives a large input from the Nucleus basalis of Meynert [118], believed to be inhibitory [119, 120]. The neurodegeneration of these cholinergic neurons in AD would lead to a reduction in inhibition based on this hypothesis and could contribute to cortical hyperexcitability.

Risk of seizures and epilepsy

Epilepsy is considered to be strongly related to NH, with its myriad of etiology generally ascribed to the imbalance of excitation and inhibition and the development and onset of seizures [121].

Patients with AD have been reported to have an increased risk of developing seizures over the course of the disease [14, 122]. The prevalence of seizures appears to increase with the duration of AD, with studies correlating onset of seizures with the later stages of AD [123–125]. This observation has been hypothesized to be due to the progressive severity of neurodegeneration or the increased accuracy of the diagnosis of AD [122]. Other studies have observed an increased rate of seizure occurrence in younger patients with AD [126, 127], attributed to the higher prevalence of patients with familial AD, which has been associated with higher rates of seizures or more aggressive progression of AD [122].

Seizures are believed to arise from the hypersynchronous state of neuronal populations, characterized by heterogeneity of neuronal firing and temporal evolution of synchronization [128]. Physiological evidence for abnormal neuronal synchronicity has been reported in animal models of AD pathology [18, 20, 129, 130], highlighting a possible mechanistic explanation for epileptogenesis in patients with AD. Although the clear causative factor underlying the development of seizure-like activity in AD is not fully understood, animal studies have attributed the presence of amyloid and tau pathology, as well as interneuron dysfunction to epileptogenesis. Due to

the difficulty of detecting seizures, particularly of the nonconvulsive form, characterizing the prevalence of seizures in patients with prodromal AD is extremely challenging [131]. It is not clear which form(s) of epilepsy is (are) engendered in AD or if it can be classified into a single type. Due to the numerous forms of epilepsies, the presence of epilepsy-like and seizure-like symptoms in AD patients may even differ from hitherto known forms of epilepsy such as temporal lobe epilepsy. Studies investigating the types of seizures in patients with AD have reported generalized convulsive seizures [132], complex partial seizures [133], as well as nonconvulsive seizures [131], indicating some extent of seizure heterogeneity in patients with AD. Other indications point to similarities between the seizure activity observed in patients with AD and those with focal hippocampal seizures [14]. However, certain limitations and inaccuracies in seizure reporting could also preclude an accurate assessment of seizure prevalence in AD patients [134].

Correlational studies have shown that the incidence of seizure activity in patients with AD is related to faster cognitive decline compared to AD patients with no reported incidence of seizures [135]. One possibility suggests that the severity of the pathology may determine the rate of seizure prevalence. Another possibility suggests that the presence of seizures could exacerbate the rate of disease progression. Better characterization of epilepsy and seizure phenotypes in patients with AD could provide a better insight into how epilepsy-associated phenomena contribute to AD pathogenesis or even serve as a predictive indicator of disease progression for therapeutic intervention (for a recent review see Toniolo et al. [77]). In their first retrospective studies by Vossel et al. examining the incidence of seizures in 233 MCI subjects and 1,024 probable AD subjects, the incidence rate of repeated seizures in MCI and probable AD patients was 5% and 3.4% respectively [136], while in their prospective follow-up study, this prevalence rate reached 42% in patients with AD [137]. This indicates that not all patients develop seizures, suggesting an incomplete penetrance of this phenotype, and that NH in the form of seizures may potentially only be present in a subpopulation of AD patients, emphasizing the heterogeneity of the AD patient population [21].

The presence of increased network activity and the prevalence of epileptiform activity in patients with AD suggests hyperexcitability occurring throughout the disease. Although the full spectrum of molecular and cellular correlates of NH has not been elucidated, several reports have identified factors leading to the development of NH. In the next section, we review some of the putative pathological mechanisms of NH from studies primarily conducted in animals.

PRECLINICAL STUDIES OF AD-RELATED NETWORK HYPEREXCITABILITY

Evidence in AD patients points toward the possibility of NH, most likely correlating with increased activation of several regions of the brain, such as the DMN and the hippocampus. However, the determination of molecular pathological correlates as well as the localization of hyperexcitability directly in humans would require some form of invasive electrode implantation for measurement of electrophysiological changes associated with hyperexcitability. This has led to studies attempting to elucidate the molecular and cellular correlates of NH in animal models exhibiting AD-associated pathology. It should be noted that differences in techniques used for the experimental qualification of hyperexcitability in humans as compared to in animal models, could preclude a direct translational comparison. In this regard, it is possible that the exact nature of hyperexcitability in animal models may differ from that in human patients.

Unlike techniques used in human studies to evaluate neurophysiology, preclinical studies of hyperexcitability involve techniques such as intracranial EEG [19, 52], calcium imaging [129, 138], and patch clamping of *ex vivo* slices [18, 139] carried out in animal models of AD pathology. Hence, a closer look at animal studies associated with the incipience of NH, as well as a critical evaluation of the evidence for the pathological bases of NH will be presented next.

Glutamate dysfunction as a molecular mechanism underlying network hyperexcitability

The glutamate hypothesis of AD, initially proposed decades ago, was based on postmortem evidence indicating reduced aspartate binding as well as a loss of other putative markers of glutamatergic activity [140]. The observation of increased glutamate concentrations around neurons and synapses, attributed to deficits in the glutamatergic processing pathway is at the heart of this hypothesis [141]. Glutamate, being the main excitatory neurotransmitter in the brain, could be a main molecular effector of inducing NH.

Glutamate receptors can be classified into ionotropic and metabotropic glutamate receptors, both of which have been suggested to be implicated in hyperexcitability and excitotoxicity [142, 143]. Of the two groups, metabotropic glutamate receptors (mGluRs) have been shown to interact with AD pathology, such as extracellular oligomeric amyloid-β species, resulting in LTD induction [144], synaptotoxicity [145], among other effects [146]. It has also been shown that the interaction of amyloid-β with a particular mGluR subtype, mGlu1, results in a dramatic and lasting depolarization of membrane potential [147]. This depolarization could very likely contribute to a transition to a state of hyperexcitability. However, the activation of mGlu1 has also been associated with the proteolytic processing of amyloid-β protein precursor (AβPP), increasing the production of the neuroprotective sAβPPα fragment, and a decrease in amyloid-β production [148], potentially serving as a sensor of extracellular amyloid-β levels. *In vitro* application of amyloid-β fragments in slice culture have shown increased glutamate concentrations [149], potentially through augmenting glutamate release [150] or by inhibiting the uptake of glutamate by astrocytes [151, 152]. A recent *in vivo* report also appears to be in line with the *in vitro* findings, reporting increased neuronal activity being attributed to glutamate accumulation as a result of amyloid-β [143].

The role of glutamate has also been implicated in the process of glutamate-mediated excitotoxicity, the process by which neurons succumb to damage or die as a result of overstimulation by glutamate [153]. It has been suggested that the neurodegeneration seen in AD could be the result of this form of excitotoxicity [153, 154]. This excitotoxicity is believed to be mediated by an increased influx of calcium, primarily through NMDA receptors [155, 156]. The hyperexcitability seen in AD could also imply ensuing excitotoxicity.

Inhibitory signaling dysfunction as a cellular basis of network hyperexcitability

Based on the hyperexcitability model resulting from an excitation and inhibition imbalance, inhibitory signaling represents a major player in this balance. Inhibitory signaling is a product of both the inhibitory presynaptic neuron and receptors on the postsynaptic neuron. Interneurons are a major source of inhibitory input to neurons, generally facilitated by the action of neurotransmitters such as the GABA neurotransmitter [157].

Several indications of interneuron dysfunction appear to be present in AD, primarily from preclinical studies [52, 53, 158] but have yet to be well studied and characterized in human observations. These preclinical studies identified alterations suggested to be attributed to parvalbumin-expressing cells [52] and hippocampal perisomatic GABAergic synapses [159]. In addition, the restoration of these interneuron cell populations appears to attenuate effects of hyperexcitability [160] as well as the restoration of deficits in oscillatory brain rhythms [53].

Neurophysiological changes in interneurons associated with AD pathology appear to be evident in multiple mouse models of AD pathology, with functional implications for the network [52, 53]. One of these functional consequences concerns the alteration of oscillatory rhythms. Interneuron activity contributes greatly to the presence of gamma oscillations in the brain [161], and are believed to contribute to the temporal coordination of neuronal activity at the network level, facilitating aspects of cognition and neuronal computation [162–164]. Along with putative changes in interneurons, the properties of gamma oscillations have also been noted to be altered in several mouse models of AD pathology [54, 165, 166], correlating the neurophysiological changes with functional changes.

Although some direct evidence for the presence of interneuron deficits in AD patients is present [52], indirect evidence also supports this hypothesis. Oscillatory activity is impaired in patients with AD, in particular gamma oscillations [167–169]. A recent study involving the application of light stimulation at the gamma frequency range to entrain interneurons has been reported to clear amyloid plaque build-up [170], suggesting that external neuromodulation of interneuron function may be capable of altering pathology.

In addition to changes in oscillatory activity, interneuron deficits have also been correlated with the presence of epileptic and seizure phenomenon [171, 172]. One such study has reported reductions in network hypersynchrony facilitated by modified interneuron transplants in a mouse model of AD pathology [53]. While network synchrony was shown to be reduced in this study, it should be noted that it does not imply that interneuron dysfunction might not be the cause of this of form of hypersynchrony but instead only attenuates it.

Interneuron deficits present itself as a potential cellular candidate for explaining the presence of NH in animal models and patients with AD. Expanding

our understanding of interneuron deficits (e.g., subtypes of interneuron affected, receptor expression properties, interneuron quantity) should provide better insight into the development of animal model on a cellular basis of NH.

Amyloid-associated network hyperexcitability in animal studies

Several animal models of amyloid pathology showcase hyperexcitability-related behavior in the form of their propensity to exhibit unprovoked seizures [19], increased susceptibility to pharmacologically [173] and audiogenic seizures [18] as well as epileptiform-like activity [130, 174]. This effect also does not appear to be limited to a single amyloid animal model but appears to be a common trait across multiple amyloid pathology models [18, 173–175], indicating a phenotype strongly associated with amyloid-related alterations in these mice. Studies associated with NH and amyloid are summarized in Table 2.

The hyperexcitability associated with amyloid-β also appears to be dose-dependent, as suggested by the presence of tonic-hyperexcitability proportionate to the amount of amyloid plaque burden [138, 176]. However, it has been suggested that the molecular correlate of this hyperexcitability is likely to be the oligomeric species of amyloid-β [143], rather than the amyloid plaques as suggested by experiments involving *ex vivo* application of amyloid-β species described in the following section.

Ex vivo experiments involving the application and incubation of amyloid-β species have demonstrated that these oligomeric species possess the ability to depolarize the membrane potential and shift the network to a more excitable state [19, 177]. However, the excitability of the network already appears to be permanently altered as evidenced by *ex vivo* slice experiments on these mouse models of amyloid pathology [18, 178]. This suggests the possibility that chronic exposure of neurons to extracellular amyloid-β could already induce permanent changes in the network, providing a possible explanation for the lack of clear effects seen in amyloid clearance-related therapies. Alternatively, the development of the organism could be altered under the influence of the transgenic expression of proteins responsible for AD pathology, resulting in an already abnormal baseline state.

Accompanying the *ex vivo* experiments involving the application of amyloid-β to brain slices, one *in vivo* experiment involving the application of amyloid species appear to elicit similar results as visualized by calcium imaging [143]. Paradoxically, this only had an effect when amyloid-β was applied in wild-type mice as opposed to mice with amyloid phenotypes. This suggests some sort of alteration of the network already present in response to the presence of transgenic manipulations associated with amyloid.

Neuronal activity has also been shown to affect AβPP processing and the release of amyloid-β species [23, 179]. It is suggested that the increase in neuronal activity leads to an increase in amyloid-β secretion and aggregation into oligomers which could be part of a positive feedback loop driving each other reciprocally.

The functional consequences of amyloid-associated hyperexcitability still lacks sufficient understanding. Apart from the suggested role of amyloid-β associated hyperexcitability prompting subsequent epileptogenesis [19], in a functional context, one other study has reported that progressive deterioration of neuronal tuning for visual stimuli occurs in relation to amyloid load. In particular, this was noted only in hyperactive neurons during spontaneous activity [180]. In the context of amyloid-β associated hyperexcitability and its purported role in excitotoxicity [181], animal models bearing amyloid-associated transgenic manipulations generally do not show overt neurodegeneration or cell loss [182], even in the presence of high amounts of amyloid plaque load and seizures. This implies that neurodegeneration in AD may not be linked solely to the presence of amyloid-driven hyperexcitability and excitotoxicity. However, amyloid-associated hyperexcitability may indirectly facilitate the development of amyloid plaques, which may drive the propagation of tau pathology and subsequent tau-pathology-associated neurodegeneration [23, 179, 183]. Moreover, specific proteins and AD-related peptides (e.g., sAβPPα or Aη) are increasingly being identified for their specific role in circuit excitability dynamics, hypothesizing the mediating effects of amyloid as well as tau to hyper- and hypoexcitability [21].

Tau-associated network hyperexcitability in animal studies

In addition to the studies of NH focusing on amyloid pathology in AD, the other main hallmark of AD, the tau protein, has been shown to be related to hyperexcitability [184–188]. Tau is a

Table 2
Animal studies of amyloid-related hyperexcitability

In vivo			
Experimental paradigm	Animal model(s)	Main finding and conclusion	Reference
Two-photon calcium imaging	APPswe/PS1G384A	Early hyperactivity of hippocampal neurons in predepositing transgenic mice. Soluble Aβ induces neuronal hyperactivity in wild-type mice.	[176]
	APPswe/PS1G384A, APPswe and PS1G384A, PS45 mice	Neuronal hyperactivity in absence of plaque or neuroinflammation pathology. Hyperactivity of cortical neurons is significantly enhanced by AD-related mutations in presenilins.	[267]
	APP23xPS45 mice	Hyperactive neurons found near amyloid plaques.	[138]
	Wild-type mice	Application of soluble synthetic Aβ induced a massive increase in activity.	[143]
	Tg 2576 mice	Anti-Aβ antibody 3D6 reduces amyloid pathology but increases neuronal hyperactivity.	[129]
Local field potential stimulation and recording under urethane anesthesia	3xTgAD mouse model	Increased synaptic facilitation in the 3xTgAD model. Significant differences in fEPSP amplitudes generated in 17–18 months of age 3xTgAD mice.	[268]
In vivo patch clamp and local field potential recordings under isoflurane anesthesia	APPswe/PS1dE9 model	Hyperexcitability on the cellular and network levels in APP/PS1 mice *in vivo*.	[178]
Freely moving subdural EEG recordings	hAPPJ20, hAPPJ20xFVB/N amyloid mouse model	Network hypersynchrony emerges during reduced gamma activity in hAPPJ20 mice. Presence of epileptiform spike activity in hAPPJ20 mice.	[52]
	hAPP-J20 amyloid mouse model	Hyperexcitability and unprovoked nonconvulsive seizure activity in hAPP-J20 mice.	[20]
	APP/TTA mice	Overproduction of Aβ is not sufficient to generate EEG abnormalities in double knock-in APP/PS1 mice. AβPP overexpression alters the excitatory to inhibitory balance in the cortex. Suppression of AβPP overexpression during postnatal development delays the onset of EEG abnormalities in APP/TTA mice.	[215]
	hAPP J20, APP-KI_$^{NL-F}$ mice	J20 mice exhibit frequent inter-ictal spikes but $APP^{NL/F}$ mice do not.	
Freely moving cortical screw EEG recordings	APPswe/PS1dE9 amyloid model	Increased prevalence of unprovoked seizures based on video-EEG recordings.	[19]
	Tg2576 mouse model	Tg2576 mice exhibit spontaneous epileptiform activity as young as 1.5 months of age.	[269]
Freely moving epidural EEG recordings	hAPP-I5, hAPP-J20, APP^{NL-G-F}	Non-convulsive epileptiform activity present across all mice.	[130]
Freely moving subcortical local field potential recordings	Tg2576 mouse model	Interictal-like spikes are present in 5-week-old Tg2576 mice during REM sleep. Interictal-like spikes increase with age and emerge in additional behavioral states besides REM sleep.	[175]
Seizure induction – pharmacological /chemical	Tg2576 mouse model	Tg2576 mice show higher susceptibility to pharmacologically induced seizures from early age.	[269]
	hAPP-J20, J9, ARC48, I5, N8, J9/FYN, hAPP-J20/Tau–/– amyloid mouse models	Increased seizure activity after PTZ administration in hAPP-J20 mice.	[20]

(*Continued*)

Table 2
(*Continued*)

In vivo			
Experimental paradigm	Animal model(s)	Main finding and conclusion	Reference
	APP/TTA mice	Increased susceptibility to chemically induced seizures is not attenuated by diminishing spontaneous hyperactivity.	[215]
Seizure induction - audiogenic	3xTgAD mouse model	Young 3xTg-AD mice are highly susceptible to audiogenic seizures.	[18]
Ex vivo			
Brain-slice extracellular field potential recordings	hAPP-J20, J9, ARC48, I5, N8, J9/FYN, hAPP-J20/Tau–/– amyloid mouse models	Increased inhibition in granule cells of hAPP-J20 mice. Short- and long-term plasticity impairments in the dentate gyrus of hAPP-J20 mice	[20]
	APPswe/PS1dE9 model	Impaired short-term synaptic plasticity in aged APdE9 mice.	[270]
	APPswe/PS1dE9 model	Age-dependent Aβ relationship with membrane depolarization that enhances the excitability of pyramidal cells.	[19]
Whole-cell patch clamp recordings	APPswe/PS1dE9 and WT mice	Membrane depolarization was exclusively found after application of (proto-)fibrillar Aβ1–42 to L2/3 pyramidal cells in cell-attached recordings Short- and long-term plasticity impairments in the dentate gyrus of hAPP-J20 mice APdE9 mice exhibited decreased action potential threshold and burst firing of pyramidal cells.	[19]
	APPswe/PS1dE9 model	Decreased action potential generation probability of interneurons in aged APdE9 mice.	[270]
	Xenopus Laevis	Aβ oligomers elicit inward currents in NR1/NR2A and NR1/NR2B-injected Xenopus oocytes.	[139]
	C57-BL6/J Mice	Aβ treatment resulted in the hyperpolarization of the action potential threshold. Aβ treatment depressed the after-hyperpolarization that followed action potentials.	[177]
	APPswe/PS1dE9 model	Increased intrinsic excitability of CA1 pyramidal neurons of APP/PS1 mice.	[178]
	hAPPJ20, hAPPJ20xFVB/N amyloid mouse model	Inhibitory synaptic impairments and parvalbumin cell Dysfunction in hAPPJ20 mice.	[52]
Intracellular current clamp recording	3xTgAD mouse model	Young 3xTg-AD mice exhibit hyperexcitability of the hippocampal CA3 neuronal network. Spontaneous epileptiform discharges elicited by the application of bicuculline on hippocampal slices in 3xTg-AD mice.	[18]
Voltage-sensitive dye imaging	APPswe/PS1dE9 model	Hippocampal circuit hyperexcitability in the dentate gyrus of APPswe/PS1dE9 mice.	[270]
In vitro			
Experimental paradigm	Animal model(s)/ *In vitro* model(s)	Main finding and conclusion	Reference
Primary neuronal cell culture calcium imaging	Sprague-Dawley rats	Aβ oligomers induce Ca^{2+} influx into cortical neurons in culture by activating preferably NMDA receptors lacking NR2B subunit.	[139]
Cell culture electrophysiological recording	HEK293 cells	Sodium currents are reduced in APP knockdown HEK293 Nav1.6 cells.	[271]

microtubule-associated protein that is involved in the assembly or disassembly of microtubules [189].

Several reports have indicated that levels of tau modulate NH, with reductions of endogenous tau protein levels ameliorating hyperexcitability [185, 190, 191] and overexpression exacerbating hyperexcitability [192, 193]. These findings suggest that levels of tau proportionately facilitate NH.

Moreover, contrary evidence has suggested that increase in tau is capable of silencing neurons and contributing towards a state of reduced excitability [188, 194, 195]. A summary of reports involving tau-associated NH can be seen in Table 3. There may be several mechanisms by which tau dysfunction may elicit a phenotype of hyperexcitability or even the opposite. Activation of synaptic and extrasynaptic NMDA receptors has been shown to correlate with an increased expression of tau [196, 197]. In addition to this, at least one type of NMDAR activation, Fyn-mediated NMDAR activation, has been reported to be associated with tau [198]. As previously discussed, amyloid-β has also been indicated to interact with NMDA receptors [139]. This relationship between amyloid-β, NMDAR interaction, and tau-mediated NMDA activation may be one mechanistic explanation for the presence of increased neuronal activation in AD. Another factor that may contribute to increased levels of tau expression could be increased levels of extracellular glutamate also interacting with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NMDA receptors [142, 199].

However, the effect of tau reduction in an animal model without amyloid-related mutations (e.g., in Kcna1 +/–Tau+/– *C57BL/6 mice*) shows that the reduction of levels of tau results in the attenuation of hyperexcitability in this model [185]. This suggests that there may not be a preference of tau to a specific cause of hyperexcitability and that tau is a general regulator of intrinsic neuronal excitability and alters the excitation/inhibition balance without any particular preference for amyloid [200].

However, conflicting evidence for the effects of tau pathology on the effects of neuronal activity is present. One study reported the silencing of hyperactive neurons observed in amyloid-bearing APP/PS1 animals when crossed with inducible tau-expressing rTg4510 and rTg21221 mice [188]. These mice bear the mutated form of the human tau protein, the P301L mutation that confers a risk for developing frontotemporal dementia in humans [201]. This suggests that in this case, an increase in mutant tau expression could silence the increased activity associated with the APP/PS1 mouse strain as evaluated by calcium imaging.

In addition, other reports of mutated and soluble tau protein species has been shown to reduce the transient frequency of calcium in cortical neurons in layers 2/3 of P301S mice, independent of neurofibrillary entanglement [194]. Moreover, the high-frequency ripple oscillations of local field potentials in the CA1 hippocampal area are considerably reduced in young rTg4510 mice, and even more deteriorated in old rTg4510 mice [195]. In addition, diminished neuronal activity with tau pathology in aged EC-tau mice [202], as well as reduced raw theta power in mice models of tauopathies [203], have been reported. One other study has suggest that entorhinal cortex neuronal hyperactivity is associated with the human amyloid precursor protein (hAPP) or Aβ, instead of tau in a combined tau-amyloid mouse model [204]. These reports have indicated evidence for tau being capable of reducing neuronal activity and highlight a role in neuronal silencing.

The phosphorylation of tau, a main factor thought to lead up to the formation of neurofibrillary tangles, appears to exhibit a role in attenuating hyperexcitability as well. Several reports have shown that tau hyperphosphorylation is associated with reductions in hippocampal CA1 neuron excitability [205, 206] as well as decreased synaptic AMPA receptor expression due to mislocalization of tau as a result of hyperphosphorylation [207]. At least one study has suggested that phosphorylation of tau at a specific site is protective against amyloid-β mediated excitotoxicity [187], suggesting that phosphorylation of tau may attenuate hyperexcitability. These findings suggest that phosphorylation of tau could be a possible response to hyperexcitability, in order to silence and counteract the increase in excitability [187, 208]. In contrast to the pathological role currently thought to be associated with tau, there appears to be some evidence indicating a beneficial or compensatory role for the existence of this mechanism, at least in the attenuation of hyperexcitability. Assuming this relationship between tau phosphorylation and NH holds true, increasing tau phosphorylation to counteract NH as a therapeutic strategy is unlikely to be a viable option due to the exacerbation of tau pathology and its associated detrimental effects.

These studies have highlighted some examples of how tau and tau-associated pathology may be related to NH. It does not appear to paint a clear picture whether tau contributes to or attenuates neuronal

Table 3
Animal studies of tau-associated hyperexcitability

In vivo			
Experimental paradigm	Animal model(s)	Main finding and conclusion	Reference
Two-photon calcium imaging	APP/PS1, Tg4510, APP/PS1-rTg4510, APP/PS1-rTg21221	Tau-dependent suppression of activity and neuronal silencing.	[188]
	P301S mice	Strong reduction of calcium transient frequency in layer 2/3 cortical neurons of P301S mice, independent of neurofibrillary tangle presence.	[194]
Anaesthetized EEG amperometry	P301L mice	The amplitude of KCl-evoked glutamate release was 4 and 7 times larger in TauP301L mice.	[193]
Freely moving subdural EEG recordings	hAPP/Tau+/+, hAPP/Tau+/–, hAPP/Tau–/–, TASD41/Fyn/Tau, SOD1G93A mice, amyloid-tau mouse models	Tau reduction alters spontaneous epileptic activity from convulsive to nonconvulsive activity in hAPPJ9/Fyn mice. Tau reduction prevents EEG abnormalities and spontaneous seizures in hAPPJ20 mice.	[191]
	rTg4510	High-frequency ripple oscillations of local field potentials in the hippocampal CA1 area are significantly reduced in young rTg4510 mice, and even further deteriorated in old rTg4510 mice.	[195]
Freely moving subcortical EEG recordings	Kcna1 +/–Tau+/– *C57BL/6 mice*	Decreasing tau reduces hyperexcitability and spontaneous seizures in Kv1.1-deficient mice.	[185]
	APP23/p38 $\gamma^{-/-}$ mice	Reducing tau phosphorylation via depletion of postsynaptic p38γ exacerbates excitotoxicity and deficits in APP transgenic mice.	[187]
	EC-Tau mice	Reduced grid cell firing and periodicity in the dorsal MEC of aged EC-Tau mice.	[202]
	EC-Tau/hAPP mice	Tau has no impact on overall firing rate but diminishes the rate of narrow spiking single units in EC-Tau mice with amyloid.	[204]
	rTg4510 mice	Diminished raw power and peak theta frequency in tau Tg4510 mice.	[203]
Seizure induction – pharmacological/chemical	hAPP/Tau+/+, hAPP/Tau+/–, hAPP/Tau–/– amyloid-tau mouse models	Tau attenuation results in seizure reduction induced by PTZ administration.	[190]
	C57BL/6J	Reducing tau mRNA and protein protects against PTZ and PTX-induced seizures.	[200]
	hAPP/Tau+/+, hAPP/Tau+/–, hAPP/Tau–/–, TASD41/Fyn/Tau, SOD1G93A mice, amyloid-tau mouse models	Tau attenuation results in seizure reduction induced by PTZ administration in hAPPJ9/Fyn and hAPPJ20 mice.	[191]
	hTau A152T	The A152T variant enhances hTau-induced network hyperexcitability as measured by PTZ challenge.	[192]

(*Continued*)

Table 3
(*Continued*)

In vivo			
Experimental paradigm	Animal model(s)	Main finding and conclusion	Reference
Seizure induction – physical	*Drosophila melanogaster* (*eas, kcc*) strains	Reducing tau decreases hyperexcitability in bang-sensitive Drosophila mutants.	[185]
Ex vivo			
Slice extracellular field potential recordings	Kcna1 + /–Tau+/– *C57BL/6 mice*	Tau loss decreases network hyperexcitability in Kcna1–/– hippocampal slices exposed to increased extracellular K + levels.	[185]
	hAPP/Tau+/+, hAPP/Tau+/–, hAPP/Tau–/–, TASD41/Fyn/Tau, SOD1G93A mice, amyloid-tau mouse models	Tau reduction prevents epileptiform bursting in hippocampal slices.	[191]
	hTau-A152T mice	hTau accumulation increases synaptic transmission strength and reduces paired-pulse facilitation.	[192]
Whole-cell patch clamp recordings	hAPP/Tau+/+, hAPP/Tau+/–, hAPP/Tau–/–, TASD41/Fyn/Tau, SOD1G93A mice, amyloid-tau mouse models	Tau reduction prevents abnormalities in miniature postsynaptic potentials in dentate granule cells of hAPPJ20 mice. Tau reduction prevents excitation–inhibition imbalance in dentate granule cells of hAPPJ20 mice. Tau reduction prevents abnormalities in synaptic transmission and plasticity in hAPPJ20 mice.	[191]
	rTg4510, pR5 tau mouse models	Depolarized action potential initiation and reduced firing in CA1 neurons of two P301L tau transgenic mouse models. Reduced firing in rTg4510 mice occurs in the presence of hyperphosphorylated tau prior to neurodegeneration.	[205]
	pR5 tau mouse model	Reported decreased firing threshold and reduced LTP behavior	[206]
In vitro			
Primary neuronal culture electro-physiological recording	rTg4510, pR5 tau mouse models	Pseudo-hyperphosphorylated tau reduces firing in primary neuronal cultures.	[205]
Organotypic cell culture calcium imaging	hTauAT mice	Expression of hTauAT elevates intracellular Ca^{2+} concentrations in CA3 neurons at resting state and after membrane depolarization through NR2B-containing NMDA receptors. The hTauAT mutation enhances synaptic transmission and susceptibility for epileptiform activity in area CA3 without affecting synaptic plasticity.	[272]

excitability, as the absence of tau has been shown to reduce excitability and increased expression of mutant tau and phosphorylated tau also appears capable of silencing neurons, reducing activity.

It should be noted that several animal models previously used for the development of treatments, and which form the bases for some NH hypotheses, have limitations which diminish their translational validity. In the next section some of the limitations and caveats of the respective animal models that should be considered or controlled as part of the experimental design are addressed.

A TRANSLATIONAL PERSPECTIVE ON NETWORK HYPEREXCITABILITY IN AD

Limitations and caveats

The development of several mouse models with amyloid pathology generally involves the overexpressions of hAPP [209]. Current amyloid mouse models are based on introducing hAPP, in which even overexpression of wild-type hAPP is already associated with neurophysiological effects [210]. In addition to this, the introduction of hAPP compounds the amount of endogenous mouse AβPP already being expressed in the neurons [211]. The presence of high levels of AβPP would also mean that higher levels of AβPP-associated fragments such as sAβPPα, sAβPPβ, amyloid protein fragment eta, and amyloid intracellular domain, would also be elevated in these mouse models. These fragments have been shown to affect synaptic activity [212, 213] as well as amyloidogenesis [214] nontrivially, raising the issue of these fragments confounding some of these interpretations claimed to be derived from amyloid-β solely.

A study addressing these confounds by incorporating an inducible switch of AβPP expression in mice demonstrated that by halting AβPP expression, it was able to slow and attenuate the presence of epileptiform-like activity in these mice [215], suggesting the presence of the NH phenotype to be associated with AβPP and other AβPP fragments rather than amyloid-β. In concordance with this, a study to reduce amyloid-β mediated hyperexcitability by immunotherapy in mice produced the exact opposite effect [129]. These findings suggest that AβPP, rather than amyloid-β, might be the causative factor for NH in these animal models. Another primary argument against the application of AβPP-associated mutations in animal models is the fact that these mutations only represent a small fraction of the population of AD patients. Patients with AD can be divided into two main categories: those with sporadic AD, which account for approximately 94–99% of all cases, and those with familial AD, the remaining 6-1% [216]. The mutations used to induce amyloid pathology in animal models stem from the mutations associated with familial AD and might not or might at least be only partly representative of sporadic AD cases, limiting direct translational potential to many AD patients. Besides the overexpression of proteins, animal models develop under these conditions from the embryonic stage, altering the development of the animal. If a putative neurophysiological effect arising from the pathology was detected in such an animal, it could be possible that the effect could be due to a different baseline due to the development under these genetic conditions rather than the pathology at that point of time itself. Approaches incorporating the temporal control of the expression of pathology-associated genes, such as the regulatable rTg4510 tau mice could provide a more physiological approach to study pathological mechanisms and subsequent neurophysiological changes.

As with the generation of amyloid pathology models of AD, mouse models with tau pathology also suffer from some of these caveats and limitations. The tau mutation(s) required to elicit part of the tau pathology reminiscent of AD pathology, are more commonly associated with frontotemporal dementia (FTD) rather than AD [209, 217]. Given the heterogeneity of tauopathies, tau pathology associated with FTD may have differential effects on hyperexcitability compared to pathological tau associated with AD [218]. In addition, certain manipulations that involve the phosphorylation state of tau, such as the application of okadaic acid to elicit an increase in tau phosphorylation state [219], can lead to the phosphorylation of other substrates that could alter neuronal excitability. The specificity of some phosphate-related manipulations limits some of the relationships between tau phosphorylation and its effects on hyperexcitability that can be concluded from some of these experiments.

Another unintended effect and confound related to the generation of transgenic animals also involves the incorporation of the transgene construct into the genome of the animal. In a recent example, behavioral and molecular phenotypes originally thought to be associated with tau pathology in the rTg4510 mouse model were instead associated with gene disruption due to construct insertion [220].

These caveats and their associated research implications provide a critical angle to some of the studies associated with NH in preclinical models of AD and challenge some of the underlying assumptions regarding the origin of NH in AD. Being cognizant of these caveats and potential confounding factors should prevent misleading conclusions from being made.

The studies presented above showcase strong evidence for the presence of NH in animal models, and to a lesser extent, human patients as well as the implications for the disease. However, due to some of the caveats and limitations associated with animal models, can we be certain that the hyperexcitability

seen in animal models of pathology faithfully mimics that of the human condition? Here, we present a perspective on evaluating the presence of NH in animal models of AD, as well as providing some insight into preclinical research tools that should address the uncertainty regarding the validity of NH in preclinical studies in the next section.

Network hyperexcitability as a marker of AD pathology model validity

The failure of clinical trials of drugs for AD has highlighted an incomplete understanding of the disease. This could be due to inaccurate animal models that may only superficially resemble the pathological traits of AD but not the underlying etiology or dysfunction. Perhaps a deeper understanding of the effects of the functional changes associated with pathology, such as NH are necessary. The neurophysiological indication of NH in AD may be a factor that links the 'form' of pathology and 'function' (or dysfunction) of neurons in AD. However, since many types of neurological disorders can result in NH, it is key that aspects of hyperexcitability in animal models are relevant to the disease.

As mentioned above, indirect evidence for NH may be present in human patients in the form of cortical hyperexcitability, hippocampal hyperactivity, and deficits in DMN deactivation. Based on these premises, experiments investigating the presence of NH in animal models of AD pathology should consider the relevant spatial localization of the NH (i.e., investigating hippocampal hyperactivity in animal models) in conjunction with the presence or absence of AD-associated pathology to evaluate the validity of the model representing AD-relevant NH. Secondly, the temporal aspects of network activity should also be a feature capitulated by animal models. While it remains to be ascertained that the increase in brain activity in the prodromal phase reflects the phenomenon of NH, this could be an indirect indication. Working on this premise, animal models of AD-associated pathology that exhibit NH should also consider the temporal onset and progression of NH in relation to overall network activity. By matching not only pathological, but also the neurophysiological change timelines to the temporal progression currently understood from clinical reports, model validity can be reinforced.

The presence of epileptiform and seizure-like activity in AD is a tantalizing possibility for evaluating the presence of AD-relevant NH in animal models. However, given the myriad forms of epilepsies and seizures, caution should be exercised in making definitive conclusions regarding seizures, epilepsy, and AD. Further electrophysiological characterization of the seizure type(s) associated with human AD patients in both sporadic and familial forms is suggested before any definitive claims of model validity are made on the basis of seizure-like phenomena. Nonetheless, once validated in humans, this aspect of NH is expected to be one of the most definitive and promising indications of NH in animal models.

Cellular and molecular indications of hyperexcitability such as interneuron deficits and dysfunction of glutamate metabolism may also provide an indication of an abnormal state of excitability. Characterization of cellular subtypes and biomolecular assays of brain homogenates, gene expression levels from both AD patients and animal models may lead to more solid basis of increased excitability from a molecular and cellular perspective.

These proposed indications form the initial framework for the evaluation of NH in animal models. As more research on the electrophysiological nature of NH emerges, these proposals will become more refined and specific to the human condition.

Further preclinical opportunities for optimizing/validating NH as an early AD indicator

The caveats and limitations presented in the previous section in animal models illustrate some potential confounding factors that might preclude a direct translational comparison between current animal models and clinical studies of AD in terms of NH. By reducing these confounds, certainty regarding the origins of NH can be elucidated and compared to human observations for a better measure of model validity.

In the cases of animal models of amyloid and tau pathology, the overexpression of the transgenic proteins is the main driving factor of the pathogenesis of the respective pathologies. However, this leads to uncertainty regarding the source of dysfunctions, whether it be due to the pathology itself or the side effects of the transgenic manipulations themselves. Recent developments in animal models of both amyloid and tau pathology may be able to resolve and mitigate this confound to a large extent.

The generation of knock-in variants of mouse models of amyloid pathology, termed, the APP-KI mice [221], replaces the mouse APP gene with a humanized form and incorporate familial Alzheimer's disease mutations associated with the development of amyloid pathology, such as the Swedish (KM670/671NL) or Iberian (I716F) mutations. These mice develop robust amyloid pathology but exhibit similar amounts of the AβPP compared to wild-type mice, eliminating most of the confounding factors associated with the overproduction of AβPP-associated fragments and AβPP itself. In addition, generation of multiple mouse models combining individual APP mutations (e.g., Swedish or Arctic) such as the APP^{NL-F} or APP^{NL-G-F} mice, increases the amount of C terminal β (CTF-β) fragments in a gene-dose response (i.e., APP^{NL-G-F} mice produce more amyloid-β fragments than APP^{NL-F} mice). This allows for the study of the dose response effects of amyloid-β in these mice when comparing APP^{NL-G-F} and APP^{NL-F} to $APP^{NL/NL}$ mice for example. In a recent study by Johnson and colleagues [130] investigating the differential effects of AβPP overexpression, mouse models exhibiting AβPP overexpression were compared to APP-KI animals to evaluate the effects of AβPP overexpression. The outcomes noted were that while all models exhibited NH in the form of nonconvulsive seizures, reduction of amyloid-β levels in J20 mice overexpressing AβPP did not ameliorate epileptiform activity. This suggests that the presence of NH phenotypes in these mouse models may not be related solely to amyloid-β levels but to a confluence of factors involving AβPP overexpression and AβPP processing, which can only be investigated using newer animal models controlling for these factors. However, other reports argue against changes in neuronal activity in APP-KI models in terms of network hyperactivity. Multi-tetrode recordings of entorhinal cortex and hippocampus, revealed equivalent firing frequencies in APP KI mice relative to age-matched wild-type mice [222], while diminished power and phase amplitude-coupling was found in this mouse model [54, 223]. Moreover, the incidence of network hyperexcitability in the form of interictal spikes did not differ between APP-KI^{NL-F} mice and wild-type controls [224]. Following from the discussion above regarding the protein overexpression and NH, the evidence stemming from these studies of APP-KI animals does indeed suggest NH to be driven by AβPP overexpression rather than by amyloid-β.

In a similar vein, the generation of mouse models of tau pathology requires the overexpression of the humanized form of the mutant MAPT gene encoding for the tau protein. The mutation which allows the development of tau pathology is derived from the mutation observed in FTD, such as the P301S [225] or P301L [226] mutation. Similar to the APP-KI mice, humanized tau knock-in mice were also produced [227], with the murine MAPT gene replaced by the humanized wild-type MAPT gene. These modifications should reduce confounds of protein overexpression. These mice were reported to be similar to wild-type mice containing murine tau in terms of amyloid-β levels, neuronal death, or brain atrophy, suggesting no clear detrimental effects of replacing murine tau with human tau [227]. It should be noted that these mice do not contain any mutations that promote the development of tau pathology, but rather mimic the properties of endogenous human tau without overexpression.

Alternatively, another method of inducing tau pathology exploits the prion-like nature of the pathological form of the protein [228] in tandem with or without transgenic approaches for the induction tau pathology. This method grants to some extent, both temporal and spatial control over where and when tau pathology may be induced, allowing for a more controlled study of the local effects, and spreading of tau pathology. This process, called seeding, involves the injection of tau fragments that promote the aggregation of the tau protein into the pathological form and subsequently propagate it across the brain [8, 229–231]. However, a prerequisite for this seeding process is the expression of transgenic humanized tau containing mutations (e.g., P301S) that confer a predisposition to develop pathology. Several recent reports have investigated the neurophysiological outcomes of this seeding method in various mouse models associated with tau [230, 231]. Recent developments in tau seeding have enabled the induction of tau pathology in mice that do not have a mutant human tau genotype such as wild-type mice [232]. This opens the possibility for more closely mimicking cases of sporadic AD, which do not have direct genetic bases for developing tau pathology and eliminate the confound of altered development, transgenic insertion artefacts, and protein overexpression. Further strengthening this approach is the source from which these seeds are derived. The seeding method described in [232] is directly derived from brain samples taken from patients with AD, thus theoretically resembling the

tau pathology more closely associated with AD rather than FTD.

These approaches seem to represent a more accurate proxy of combined amyloid and tau pathologies in AD, allowing the field to step closer to discerning the etiology of NH in AD.

Translational limitations and opportunities for clinical detection of network hyperexcitability

As briefly described above, conclusively detecting NH in a clinical setting remains elusive, generally due to the requirement for invasive electrodes to be implanted local to the source of NH. Noninvasive neurophysiological methods such as BOLD fMRI offer insight into indications of network activity, but may suffer from issues such as source localization accuracy, spatial and temporal resolution, as well as difficulty in measuring deeper brain structures [233]. Other methods such as PET involve exposure to doses of radiation and limits the numbers of scans that can be safely performed [233]. Other limitations come in the form of practical methodological challenges relating to measuring hyperexcitability in certain vigilance states, such as sleep, which has been suggested to contain more epileptiform activity [14].

However, which methods are the best suited for the detection of hyperexcitability with minimal discomfort to the patient? Both EEG and MEG are promising techniques for the detection of hyperexcitable phenomena due to the direct measurement of electrical activity generated from network activity. However, depending on the recording montage and recording paradigms, MEG, and purely scalp-based EEG may not be able to identify with sufficient spatial resolution, the source(s) of hyperexcitable activity, especially in deeper brain structures [234, 235]. Several approaches attempting to address the issue of deep source localization in both MEG and EEG have been developed to study deeper brain regions. Some of these include MEG virtual electrodes [236] and high-density scalp EEG recordings [237]. While there is debate regarding which method offers a higher spatial and temporal resolution, MEG-based methods have been reported to outperform EEG-based measures in detecting subclinical epileptiform activity in AD patients [77], as well as predict the conversion from MCI to AD [238, 239].

While both methods have inherent limitations in terms of source localization, the combination of both methods is able to yield better source localization than the usage of a single modality [240]. This combined modality approach has also been successfully applied in the field of epilepsy evaluation [241] and could be an underdeveloped opportunity for the detection of NH in AD patients.

CONCLUSIONS AND PERSPECTIVE

NH is a pathological feature shared among multiple neuropathological disorders with implications for cognitive function and possibly for neurodegenerative disease progression. Accumulating evidence points to the presence of NH in patients with AD, hypothesized to impair cognitive, motor, and behavioral function. The links between NH and amyloid, tau, glutamatergic and interneuron functions have shown multiple pathways by which these pathologies interact, even synergistically, to result in dysfunction. Clinical studies have shown cortical hyperexcitability, alterations in hippocampal activity, increased predisposition to seizure-like activity in AD as well as changes in inactivation of the DMN which may indicate NH.

Indications of NH in animal models of AD pathology are emerging as features of model validity. However, studies using animal models of AD pathology have generally involved the application of protein overexpression to induce pathology, which could have NH as a side effect, confounding the interpretation of the relationship between pathology and NH observed in humans and animal models. Recent improvements in model development and molecular approaches to studying AD pathology alleviate some of these confounds associated with protein overexpression and provide a clearer picture of the source of NH. In addition, care should be exercised when generalizing preclinical outcomes of NH phenotypes when using animal models that primarily model the familial form of AD or FTD rather than sporadic AD. It is possible that the NH phenotypes in AD may even differ between familial and sporadic instances of the disease.

NH is a very promising indicator of network dysfunction in patients of AD and may serve as a prodromal indicator of AD pathogenesis. By understanding and aligning the source of NH in patients and in animal models, we can obtain a key biomarker of AD progression that correlates with cognitive dysfunction and pathology.

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