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Network abnormalities and interneuron dysfunction in Alzheimer disease

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Abstract

The function of neural circuits and networks can be controlled, in part, by modulating the synchrony of their components' activities. Network hypersynchrony and altered oscillatory rhythmic activity may contribute to cognitive abnormalities in Alzheimer disease (AD). In this condition, network activities that support cognition are altered decades before clinical disease onset, and these alterations predict future pathology and brain atrophy. Although the precise causes and pathophysiological consequences of these network alterations remain to be defined, interneuron dysfunction and network abnormalities have emerged as potential mechanisms of cognitive dysfunction in AD and related disorders. Here, we explore the concept that modulating these mechanisms may help improve brain function in these conditions.

Certain activities of neurons and neuronal networks are associated with the successful encoding of memories and retention of new information, and thus may be necessary for learning and memory. In Alzheimer disease (AD), schizophrenia, epilepsy and other neurological and psychiatric diseases that cause cognitive impairment, network activities supporting cognition are altered, even during preclinical stages[1–5], that is, before symptoms are noticed by the patient or can be detected by neurocognitive exams. These network alterations include activation and deactivation deficits, abnormal oscillatory rhythmic activity and network hypersynchrony. In people at high risk of developing AD, for example, abnormal activation and deactivation of specific networks during memory encoding can be detected decades before the predicted onset of clinical disease[6–9]. As these functional network alterations widely overlap with the brain regions that ultimately develop pathological hallmarks and atrophy in AD, they may be a harbinger and possibly even a cause of clinical disease manifestations.

Robust network alterations are associated with diverse cognitive disorders, but the mechanisms and pathophysiological consequences of the alterations are poorly understood. Do alterations in network activity contribute to cognitive impairment or are they incidental

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by-products of disease-induced cellular dysfunction? Do alterations in network synchrony cause the dysfunction of microcircuits, larger distributed networks, or both? Most importantly, could cognitive alterations be prevented and even reversed by improving the function of cells that promote specific network activities?

Recent findings suggest that altered network activity can indeed contribute to cognitive impairment in AD and that network activities can be experimentally or behaviorally manipulated to improve cognitive functions in patients at risk of AD and related mouse models. In this Review, we explore two main concepts — that network abnormalities and interneuron dysfunction contribute to cognitive deficits in AD and related conditions, and that blocking or counteracting these mechanisms could be of both symptomatic and disease-modifying therapeutic value.

Neuronal synchrony and brain function

Cognitive functions depend on brain states that range from maximal focus and concentration to inattentiveness, drowsiness and sleep. These states probably do not reflect a continuous functional gradient of neuronal activities but rather represent distinct operating modes of brain activity that are closely linked to — and possibly determined by — changes in neuronal synchrony, the degree to which neuronal activities are correlated. Such synchrony fluctuates considerably with behavioural and brain states[10]. The degree of synchrony among neuronal populations (network synchrony) can be determined by measuring and correlating neuronal activities at multiple sites, for example, through electroencephalography (EEG) or the recording of local field potentials (LFPs) with multielectrode arrays. During non-active states, such as slow-wave sleep or quiet wakefulness, cortical neuronal activities at different sites tend to be synchronized and slowly fluctuate at high amplitudes (FIG. 1a). During active behaviours, such as paying attention or learning, this highly synchronized pattern of brain activity abruptly ceases, and neuronal activities at different sites become desynchronized and fluctuate at higher frequencies and smaller amplitudes[11] (FIG. 1a).

The fundamental relationship between the synchrony of neuronal activities and functional states is also evident at the circuit level (FIG. 1b). When mice are resting, adjacent layer 2 pyramidal cells in the somatosensory cortex show synchronous high-amplitude fluctuations in membrane potentials, which result in relatively low signal-to-noise ratios for evoking action potentials relative to ongoing fluctuations; however, with active whisker use, this high-amplitude synchrony of membrane potentials ceases abruptly, and signal-to-noise ratios increase[12,13]. Thus, increasing synchrony among neurons and recruiting them into slow-frequency and high-amplitude fluctuations seem to be basic mechanisms for ‘switching off’ specific brain regions. By contrast, the suppression of high-amplitude fluctuations and desynchronization of neuronal activities increases the ability of neurons to respond to external information-rich inputs[12]. Synchrony and functional states are closely related in many neocortical and hippocampal regions, suggesting that synchrony reflects a fundamental principle of nervous system design. Here, we propose that deficits in synchrony are an important pathogenic mechanism of AD-related cognitive dysfunction.

Amyloid-β and AD pathogenesis

The hypothesis that amyloid-β has a causal role in AD pathogenesis is supported by diverse lines of evidence, including the early accumulation of amyloid-β in the brain in people who go on to develop AD and the ability of mutations in the genes encoding the amyloid precursor protein (APP) or presenilins (PSENs), which alter amyloid-β production, to cause autosomal dominant, early-onset familial AD (FAD)[14]. Amyloid-β peptides are proteolytically released from APP by β-site APP-cleaving enzyme 1 (BACE1; also known as β-secretase) and γ-secretase, and exist in diverse assembly states, including monomers, oligomers, fibrils and amyloid plaques[15]. FAD is caused by *APP* duplications, mutations in *APP* located around the BACE 1 and γ-secretase cleavage sites or within the amyloid-β coding sequence, or by mutations in the genes that encode PSEN1 and PSEN2 (alternative catalytic subunits of the γ-secretase complex). Over 250 genetic alterations have been linked to FAD. Those alterations that have been tested for effects on APP metabolism increase the overall production of amyloid-β or the amyloid-$\beta_{1–42}$/amyloid-$\beta_{1–40}$ ratio[16–19], or promote the accumulation of pathogenic amyloid-β assemblies[20–22]. Conversely, an *APP* mutation (A673T) that reduces the β-secretase-mediated cleavage of APP and, consequently, amyloid-β levels decreases the risk of late-onset sporadic AD[23,24].

Amyloid-β oligomers elicit abnormalities in synaptic and cognitive functions *in vivo* and *in vitro*[15,25–30]. Neuronal expression of FAD-mutant human or humanized APP (with or without co-expression of FAD-mutant PSEN1 or PSEN2) in transgenic mice simulates key aspects of AD, including elevated levels of human amyloid-β, amyloid plaques, neuritic dystrophy, synaptodendritic impairments, astrocytosis, microgliosis, vasculopathy, network dysfunction, cognitive deficits and behavioural alterations[31]. We refer to these models collectively as FAD mice (Supplementary information S1 (table)). An example of such models is highlighted in Supplementary information S2 (table), which lists the AD-like alterations observed in the hAPP-J20 mouse model, which was generated in our laboratory. In combination, the above findings strongly support the amyloid-β hypothesis, which includes the notion that amyloid-β is a critical cause of cognitive decline in AD. Notably, several other factors, including tau accumulation, apolipoprotein E4 (APOE4) and inflammatory mediators, contribute to the complex pathogenesis of AD and can be introduced into FAD models through additional genetic modifications[32–35].

A major unresolved question in the field is which forms of amyloid-β, tau and APOE4 are the most neurotoxic. Lead suspects include soluble amyloid-$\beta_{1–42}$ oligomers[15,30], abnormal assemblies or post-translational modifications of non-fibrillar tau[35–38] and APOE4 fragments[39]. The importance of answering this question is illustrated by the following observations. Approximately 20% of healthy aged individuals, 60% of patients with mild cognitive impairment (MCI) and almost all patients with AD exhibit evidence of amyloid deposition in the cortex, as shown by positron emission tomography (PET) involving radiopharmaceutical ligands that bind to amyloid plaques such as Pittsburgh compound B (PiB)[40]. In healthy aged individuals and patients with MCI, cortical amyloid load correlated inversely with episodic memory performance[40]; this correlation weakened with amyloid accumulation and age and does not exist in AD[40,41]. Discrepancies between amyloid deposition and cognitive dysfunction may be explained, at least in part, by the early plateau

of amyloid burden during disease progression[42] and by dissociations between amyloid burden and the accumulation of soluble amyloid-β oligomers[43]. The latter may be more bioactive than amyloid-β monomers, fibrils and amyloid plaques, and readily elicit neuronal and network dysfunction[26,28,30,43–50]. Notably, patients with FAD who carry a mutation in the amyloid-β sequence that increases amyloid-β oligomerization[49] have prominent cognitive impairments without PiB-positive (PiB^+) amyloid deposition[22], suggesting that AD can be caused by pathogenic assemblies of amyloid-β (probably amyloid-β oligomers) that cannot be detected by PiB imaging.

Notably, amyloid-β oligomers cannot yet be accurately measured in the brain parenchyma of live patients, which has greatly hampered clinical testing of the amyloid-β hypothesis. For example, it is not clear whether amyloid-β oligomer levels were significantly lowered in any of the failed clinical trials of anti-amyloid-β compounds for the treatment of AD. Nor is it clear how much, or by which mechanism, they would have to be lowered to reduce amyloid-β-dependent synaptic and network dysfunction. Anti-amyloid-β treatments that failed to lower amyloid-β oligomer levels in brain also failed to reduce cognitive deficits in hAPP-J20 mice[51,52].

In conclusion, testing the amyloid-β hypothesis in humans will probably require therapeutics that effectively lower or counteract the most pathogenic amyloid-β assemblies as well as better methods to confirm their target engagement in the brain. The above evidence strongly supports the hypothesis that amyloid-β causally contributes to cognitive decline in AD. However, the mechanisms remain to be fully elucidated, and alternative interpretations have been offered[53–56].

Network dysfunction and preclinical AD

Brain activity can be monitored by functional MRI (fMRI), PET, single-photon emission computed tomography (SPECT), EEG or LFP recordings. The corresponding signals emerge from the complex relationships among electrical activity, cerebrovascular hemodynamics, oxygen consumption and the metabolism of neurons and glia[57]. Attention-demanding tasks, such as sensory processing and memory encoding, require the coordinated regulation of many neuronal ensembles. In healthy people, attention-demanding cognitive tasks increase fMRI signals in specific brain regions (for example, the hippocampus during learning) but also cause a profound large-scale deactivation in brain regions that are collectively referred to as the default mode network (DMN)[58,59] (FIG. 2a). This network is most active during inwardly oriented mental activity, such as introspection, daydreaming, mind wandering, wakeful rest, imagination and recalling, and it becomes deactivated during outwardly directed mental tasks such as acquisition and encoding of new information.

The DMN includes the precuneus, posterior cingulate cortex, lateral and inferior parietal cortex, and regions of the temporal and medial prefrontal cortex[59]. A widely overlapping, but not identical, DMN that includes the hippocampus has been revealed by resting-state functional connectivity MRI[60]. Task-induced activation and deactivation of networks correlate well with cognitive performance in young healthy people[61]. Notably, task-induced deactivation of regions of the DMN (for example, the precuneus) can be a better predictor of

good cognitive performance than the activation of regions that have been more extensively studied with regard to their involvement in cognitive functions (for example, the hippocampus)[61]. In fact, task-induced hippocampal activation without adequate DMN deactivation is associated with poor memory formation in healthy people (FIG. 2b), which highlights that proper execution of these complex functions requires well-coordinated regulation of widely distributed networks.

In AD, schizophrenia and other cognitive disorders, deactivation of DMN components is impaired during learning[1–5]. Because synchrony regulates the functional states of networks (FIG. 1), the abnormal activation or deactivation of brain regions during specific tasks raises the possibility that cognitive dysfunction in these disorders results from synchrony deficits. Although AD is increasingly viewed as a heterogeneous, multicausal syndrome, its fMRI signature seems to be remarkably consistent, particularly during the early stages of the disease. Hippocampal hyperactivation and reduced deactivation of DMN components during memory-encoding tasks have been observed in cognitively normal individuals with cerebral amyloid deposits[4] (a potential harbinger of AD), cognitively normal carriers of the *APOE ε*4 allele[6,62–64] (the major genetic risk factor for AD), presymptomatic carriers of FAD-causing mutations[65,66] and patients with MCI[67–69], which often develops into AD. In later stages of AD, the hippocampal formation is hypoactive during memory encoding, whereas the reduced deactivation of the DMN persists[4,9,69,70].

Early hippocampal hyperactivation has been interpreted as a mechanism that may compensate for emerging cognitive decline in early AD[71] and *APOE ε*4 carriers[64]. However, accumulating evidence suggests that this hyperactivation is primarily pathogenic and may impair learning and memory[67,72,73]. In cognitively normal *APOE ε*4 carriers, increased hippocampal activation was associated with reduced grid cell-like representations in the entorhinal cortex during a virtual spatial-memory task[64], suggesting a potential link between entorhinal grid cell dysfunction and hippocampal hyperactivation.

In patients with MCI, hippocampal hyperactivation occurred during a pattern-separation task, which strongly depends on hippocampal functions; treatment with low doses of the antiepileptic drug levetiracetam for 2 weeks reversed the hyperactivation and improved performance on the task[67,73] (FIG. 2c). In FAD mice (lines hAPP-J20 and 3xTg-AD (Supplementary information S1 (table)), levetiracetam suppressed network hyperexcitability, improved cognitive functions[74,75] and reversed excessive neuronal DNA double-strand breaks[76], which may contribute to neurodegeneration[77,78]. Thus, this drug may have both symptomatic and disease-modifying therapeutic potential. Collectively, these studies suggest that network hyperactivity is an early and detrimental alteration in the pathogenesis of AD-related cognitive dysfunction and that preventing or reversing this hyperactivity may be of therapeutic benefit.

Remarkably, there is strong evidence that functional brain alterations begin decades before the clinical onset of AD. The Dominantly Inherited Alzheimer Network (DIAN) consortium revealed that pathophysiological changes in the brain in people carrying autosomal dominant FAD mutations begin at least two decades before the predicted onset of clinical symptoms, including changes in cerebrospinal fluid (CSF) biomarkers, cerebral amyloid deposition, and

brain metabolism[8]. Increased brain activity precedes the diagnosis of AD by 30 years in *PSEN1* mutation carriers[7,9]. Finally, 20–35-year-old asymptomatic carriers of *APOE ε*4 show task-related hippocampal hyperactivation and altered DMN activity on fMRI[6]. Thus, FAD-causing mutations and APOE4 modulate brain function several decades before any clinical manifestations of the disease.

Network activity and amyloid deposits

Impaired deactivation of the DMN in older people with or without AD is closely linked to amyloid deposition in brain regions that make up this network[4,9,70] (FIG. 2d, 3a). Whether the dysfunction of the DMN is a cause or a consequence of amyloid deposition is not known. When studying clinicopathological associations in humans, it is often impossible to conclusively discriminate between detrimental, beneficial and bystander alterations. Transgenic mouse or rat models expressing proteins that are suspected of contributing to the pathogenesis of AD can help to test related hypotheses *in vivo*[31–33,79,80].

In humans and mice, soluble amyloid-β levels in the interstitial fluid of different brain regions fluctuate with the brain state. Amyloid-β levels are higher during wakefulness than sleep[81–83]. In mice, sleep promotes amyloid-β clearance[83], whereas sleep deprivation increases amyloid-β levels and amyloid deposition[82], suggesting that brain states can modulate amyloid deposition. In young FAD mice (line Tg2576) (Supplementary information S1 (table)), interstitial levels of soluble amyloid-β vary markedly in different regions and relate closely to regional differences in metabolic activity[84]. Higher levels of metabolic activity are associated with higher levels of soluble amyloid-β and predict the regional amyloid burden in older mice. Thus, networks with higher metabolic rates may be more prone to amyloid deposition. In addition, experimental increases in neuronal activity by chronic optogenetic activation promote amyloid deposition and trigger epileptiform activity in FAD mice (line APP-A7)[85] (FIG. 3b; see Supplementary information S1 (table)). Thus, the vulnerability of the DMN to amyloid deposition may be related to its relatively high baseline activity and to deactivation deficits that are associated with early stages of AD.

Synaptic functions and amyloid-β

Amyloid-β production and the amyloid-$\beta_{1–42}$/amyloid-$\beta_{1–40}$ ratio, which influence the formation of pathogenic oligomers as well as amyloid deposition, are regulated by neuronal action potential firing and calcium-dependent conformational changes in PSEN1 at presynaptic terminals[86]. Increasing the rates of regular or burst firing enhances amyloid-$\beta_{1–40}$ and amyloid-$\beta_{1–42}$ production in an activity-dependent manner (see also REFS 87,88) (FIG. 3c). Regular firing proportionally increases both amyloid-$\beta_{1–40}$ and amyloid-$\beta_{1–42}$ levels, whereas burst firing, which raises presynaptic calcium concentrations, selectively increases the level of amyloid-$\beta_{1–40}$, reducing the amyloid-$\beta_{1–42}$/amyloid-$\beta_{1–40}$ ratio (FIG. 3c).

Synaptic plasticity is controlled by neurotransmitter release probability and calcium concentrations at presynaptic terminals. Excitatory synapses with a low initial probability of neurotransmitter release typically display greater facilitation during high-frequency

stimulation (potentiation) and act as high-pass filters. Thus, they tend to be unresponsive to infrequent or disorganized action potentials but potentiate their responses to coordinated firing (FIG. 3d). By contrast, excitatory synapses with a high initial release probability respond preferentially to single-spike firing patterns and act as low-pass filters[89,90]. They tend to exhibit depression or reduced potentiation during sequential stimulation (FIG. 3d). In one study, the authors concluded that high-pass-filter synapses with higher calcium loading produce a lower amyloid-$\beta_{1–42}$/amyloid-$\beta_{1–40}$ ratio, whereas low-pass-filter synapses with lower calcium loading produce a higher amyloid-$\beta_{1–42}$/amyloid-$\beta_{1–40}$ ratio[86].

Amyloid-β and other APP metabolites seem to participate in pre- and postsynaptic homeostatic mechanisms that regulate synaptic activity[86,88,91–95]. Amyloid-β may enhance presynaptic facilitation at low concentrations[93] and promote postsynaptic depression at high concentrations[88]. Application of synthetic or recombinant amyloid-$\beta_{1–42}$ oligomers or overexpression of FAD-mutant human APP reduces paired-pulse facilitation — a measure of increased release probability — and impairs long-term potentiation (LTP) at some, but not other, synapses in the mouse hippocampus[91,93,96]. These alterations may shift the filtering properties of the affected synapses from high-pass to low-pass. This shift could enhance the transfer of single action potentials, increase synaptic depression and elevate the amyloid-$\beta_{1–42}$/amyloid-$\beta_{1–40}$ ratio (FIG. 3d), promoting both hyperactivity in vulnerable networks and amyloid deposition. Reducing presynaptic release might counteract these processes. Indeed, levetiracetam, which has beneficial effects on network activity in FAD mice[74,75] and humans with MCI[67,73], reduces presynaptic neurotransmitter release in a use-dependent manner[90,97,98]. Thus, it may counteract amyloid-β-induced alterations in release probability.

In general, it is difficult to extrapolate from the effect that factors exert on specific synapses or neurons to the overall effect they have on microcircuits and complex networks. Indeed, this has been true for APP and amyloid-β. Although early studies suggested that increased neuronal amyloid-β production may be part of a homeostatic feedback loop that primarily reduces neuronal activity[88], we now know that amyloid-β accumulation can also cause neuronal hyperexcitability *in vitro* and *in vivo*[32,96,99–111]. Acute amyloid-β application initially and transiently (10–20 minutes) increases the levels of surface AMPA-type glutamate receptors and GluN2B-containing NMDA-type glutamate receptors (NMDARs)[100,103] and the frequency of spontaneous excitatory postsynaptic currents in primary neuronal cultures[100,103]. In brain slices, amyloid-β application also acutely increases the rate of action potential firing by hippocampal pyramidal cells[99]. FAD mice (lines hAPP-J20, hAPP-J9, APP23xPS45 and APP/PSEN1dE9) (Supplementary information S1 (table)) contain both hyperactive and hypoactive neurons — reflected in abnormally high or low rates of action potential-dependent calcium transients or levels of transcripts for the immediate early genes *Arc* and *Fos* — both before[96,112,113] and after[109,114,115] amyloid deposition becomes detectable.

Neurons exposed to pathologically elevated levels of amyloid-β *in vitro* or *in vivo* show signs of atrophy, including lower dendritic spine density and shorter dendrites[116,117], alterations that can increase intrinsic cellular excitability[118] and may explain the hyperactivity of some excitatory neurons. These morphological and functional effects of amyloid-β may be mediated, at least in part, by neuronal depletion of the DNA repair factor

BRCA1 and the resulting accumulation of activity-induced DNA double-strand breaks[77]. Compensatory increases in inhibitory interneuron activity may account for the hypoactivity of other excitatory neurons[101,109]. Notably, hippocampal neuronal hyperactivity preceded amyloid plaque deposition and neuronal hypoactivity in APP23xPS45 mice and could be induced by local application of amyloid-β in wild-type mice[101], suggesting that it is a very early step in the pathogenic cascade that is triggered by amyloid-β accumulation.

Hypersynchrony in AD and animal models

Besides network activation and deactivation deficits detectable by fMRI (FIG. 2), AD also results in network hypersynchrony (Table 1: see Supplementary information S3 (table)). Unlike normal fluctuations in network synchrony that are associated with physiological changes in behaviour and brain states (FIG. 1), network hypersynchrony is a pathological phenomenon in which aberrant synchronization of neuronal networks results in epileptiform discharges and seizures.

Neuronal expression or overexpression of proteins that accumulate in AD brains or are genetically linked to the disease, such as APP, amyloid-β, tau, APOE4 or α-synuclein, causes network hypersynchrony in transgenic mice[96,119–121]. Spontaneous epileptiform activity has been documented in many FAD models, including hAPP-J20 (REF. 96), APP/PSEN1dE9 (REFS 102,103), Tg2576 (REF. 104), 5xFAD[122], 3xTg-AD[75], APP/TTA-EC[105], APP/TTA-CaMKIIα[106], APP23 (REF. 107) and hAPPJ9/FYN[108] transgenic mice (FIG. 3e; see Supplementary information S1 (table)). Behavioural seizures and lower thresholds for chemically induced seizures have also been described in some of these models[96,103,108,111,123,124]. Interestingly, network hypersynchrony in mouse models of AD and of epilepsy depends on the presence of endogenous, soluble wild-type tau, which seems to enable or promote aberrant synchronization[32,35,110,111,125,126].

In humans, epidemiological studies have consistently shown that AD is a risk factor for epileptic seizures[127,128]. However, the reported incidence of seizures in patients with AD that were detected by observation has ranged from 0.5% to 64%[129,130]. A recent review of 17 clinical studies that assessed epileptic activity in AD reported an average incidence of 15.1% (median: 9.0%)[131]. The incidence of seizures is roughly 7–8-fold higher in individuals with AD than in people without dementia[132,133]. In a recent nationwide study of data from over 140 million hospitalizations, patients with AD were fourfold more likely to be hospitalized for a seizure than for non-seizure-related condition[134]. Moreover, people with early-onset AD (50–65 years old) were more likely to be hospitalized for seizures or epilepsy than those with a later onset of AD (>81 years old)[134]. These new findings are consistent with earlier reports indicating that early-onset AD (<65 years old) is a major risk factor for seizures[129,133,135]. Conversely, patients with amnestic MCI or AD who had seizures or subclinical epileptic activity typically had an earlier onset and faster progression of cognitive decline than those without detectable epilepsy[129,136,258].

Although seizures in AD are widely thought to result from end-stage neurodegeneration, several reports indicate that they can occur early in the disease course and before a neurodegenerative disease diagnosis is made[136,137]. Indeed, in patients who had MCI or

early AD with epilepsy, seizure onset clustered near the onset of cognitive decline[136] or preceded the MCI diagnosis by 4 to 7 years[138]. At the time MCI was diagnosed, the latter group of patients had mild hippocampal atrophy[138]. Seizures in MCI or early AD with epilepsy responded best to the antiepileptic drugs levetiracetam or lamotrigine and least well to phenytoin[136]. The lower relative risk of seizures in patients with late-onset AD may reflect the fact that strokes and other ageing-related comorbidities increase seizure risk in people without dementia. It is also possible that old brains are less susceptible to amyloid-β-induced network hypersynchrony than younger brains and that amyloid-β has a less important role in the pathogenesis of late-onset AD, which may be more multifactorial than early-onset AD.

Epileptic activity is even more prominent in pedigrees of early-onset autosomal dominant FAD[91,139,140]. Seizures have been observed in patients with FAD who carry any of 66 different *PSEN1* mutations[141,142] (Supplementary information S3 (table)), in 31% of patients with AD carrying *PSEN2* mutations[143], and in 58% of patients with *APP* duplications[144,145]. More recently, a multicenter study including 132 patients with FAD showed that 48% of patients harboring an FAD mutation had seizures, including 43% of *PSEN1* mutation carriers ($n = 94$), 43% of *PSEN2* mutation carriers ($n = 7$), 47% of *APP* mutation carriers ($n = 15$), and 81% of *APP* duplication carriers ($n = 16$)[146]. Seizure frequency in patients with FAD seems to be even higher than that observed in most FAD mice (Supplementary information S1 (table)).

In addition, 84% of patients with Down's syndrome who progress to dementia also develop seizures[147]. Interestingly, very early onset of AD (<40 years old) further increases the proportion of FAD pedigrees with epileptic phenotypes (>80%)[148]. Some FAD mutations (for example, *PSEN1* L166P) and *APP* duplications even cause epileptic activity in childhood or adolescence, preceding cognitive decline by many years[145,149]. Thus, network hypersynchrony can be a very early and prominent clinical feature of FAD. Indeed, many FAD-*PSEN1* pedigrees qualify as epileptic syndromes or disorders[140,141]. This intriguing association between AD and epilepsy probably holds important clues about the mechanisms by which amyloid-β, tau, and APOE4 promote the development of AD and about potential entry points for therapeutic intervention.

The power of gamma oscillations

Whereas abnormal neuronal synchrony can result in epileptic activity, normal neuronal synchrony underlies the generation of oscillatory rhythmic activities, or brain rhythms, that promote cognitive functions. Neuronal ensembles coordinate their firing within a range of oscillatory frequencies (0–300 Hz). Within each frequency band, neuronal ensembles can increase or decrease their firing rate and synchrony and thus generate higher or lower oscillatory amplitudes (FIG. 4a), although it should be noted that only a small fraction of the cells contributes to each oscillatory cycle. The amplitude, phase and frequency in each oscillatory band modulate each other and neuronal firing rates in precise ways[150]. For example, the firing of hippocampal pyramidal cells shows phase-coupling with low-frequency oscillations, such as theta (4–8 Hz). Thus, during periods of high theta, the action potential firing rate of pyramidal cells is increased and its timing is synchronized with this

rhythm[151]. By contrast, the firing of several types of interneurons shows phase-coupling with high-frequency oscillations, such as gamma (30–150 Hz)[150–152]. Thus, during periods of high gamma power, action potential firing of interneurons is more prominent and synchronized with the phase of gamma[151] (FIG. 4b,c).

The amplitude (or power) of gamma oscillatory activity increases during sensory processing or memory encoding, and such increases in gamma power predict successful memory formation in humans and mice[153–158]. Encoding during sensory, motor or memory tasks is associated not only with increased power of high-frequency oscillations (gamma) but also with reduced power of lower-frequency oscillations (alpha, beta and theta) in task-related brain regions[57,154,159,160] (FIG. 4d). However, the relationship between gamma power and attention can differ across cortical areas and tasks[161]. Increases in gamma power tend to be localized to networks that are directly involved in the task (task-related networks), whereas reductions in the power of lower-frequency oscillations typically involve multiple cortical regions[162,163]. During sensory encoding, individuals with schizophrenia have reduced increases in gamma power in task-related networks and reduced decreases in the power of lower-frequency oscillations across multiple components of the DMN[164]. It is tempting to speculate that these large-scale deficits of oscillatory activity may be related to the activation and deactivation deficits of fMRI signals in patients with schizophrenia or AD[5] (FIG. 2). Patients with AD also have reductions in gamma power[165]; however, the relationship between task-related deficits in fMRI signals, oscillatory frequencies and the observed prominent memory-encoding problems does not seem to have been directly studied in this disease.

In healthy individuals, the strength of fMRI blood-oxygen-level–dependent (BOLD) signals correlates positively with the power of gamma oscillations[166,167] and negatively with the power of alpha oscillations[168–170]. By contrast, decreases in DMN fMRI BOLD signals are associated with reductions in gamma power[171]. During visual stimulation in monkeys, an increase in oxygen level, which was associated with a rise in fMRI signals, coincided with increases in LFP gamma power in task-related networks (for example, visual area V3), whereas a decrease in oxygen level coincided with prominent decreases in LFP power in all oscillatory frequencies in DMN regions (for example, the posterior cingulate cortex)[57] (FIG. 4d). These findings suggest that fMRI signals may directly reflect changes in oscillatory activity. It should be informative to further explore the relationship between fMRI signals and oscillatory alterations in AD and other cognitive disorders.

Longitudinal video-EEG recordings revealed abnormal behaviour-dependent fluctuations in the power of gamma oscillations in hAPP-J20 mice (FIG. 5a). Notably, spontaneous epileptiform discharges emerged primarily during resting periods in these animals, when the intensity of gamma oscillations was low[172]. In two mouse models of absence epilepsy, pharmacologically induced increases or decreases of gamma power were associated with decreases or increases in epileptic activity, respectively[173]. Thus, network hypersynchrony and reduced gamma power may be mechanistically linked across different conditions, and behaviour-induced increases in gamma oscillatory power may counteract AD-related epileptiform activity by activating task-related brain regions and reducing network synchrony.

These ideas are supported by findings in humans with epilepsy[154] (FIG. 5b). During EEG recordings, individuals were shown a set of images (encoding trials), and their memory of the images was probed 24 hours later (recognition trials). Encoding trials were deemed 'correct' or 'incorrect', depending on whether or not the old images were recognized during the recognition trial. Remarkably, gamma power increased and epileptiform activity reduced only during correct memory encoding.

Overall, these LFP, EEG and fMRI findings suggest that effective memory formation requires, or induces, a pattern of brain activity that increases the power of gamma oscillations and reduces the power of low-frequency oscillations, and that this 'brain state' reduces aberrant network hypersynchrony in humans and mice (FIG. 5c). Social interactions and mental activity may benefit some patients with AD[174], perhaps, at least in part, by promoting this state. Pharmacological interventions that more persistently improve brain rhythms could be of greater therapeutic benefit.

Interneuron impairments in AD

Network synchrony and oscillatory brain rhythms are promoted and controlled by the activity of inhibitory GABAergic interneurons[175]. These cells are highly diverse, and different subtypes form electrically coupled functional networks[176]. Their combined inhibitory synaptic input onto excitatory principal neurons and other interneurons generates precise oscillatory rhythms that in turn coordinate the timing of pyramidal cell firing (see above). Some types of inhibitory interneurons, such as somatostatin-positive ($SOM^{+)}$ or neuropeptide Y-positive (NPY^{+}) cells, tend to fire tonically and independently of brain and behavioural states[177,178]. Others, such as parvalbumin-positive (PV^{+}) or vasoactive intestinal polypeptide-positive (VIP^{+}) cells, fire predominantly during brain states that promote encoding[177,178]. Interneurons and the oscillatory network activities that they regulate are altered in AD, epilepsy, schizophrenia and autism[91,165,172,179–182]. Indeed, interneuron impairment is emerging as a potential common mechanism of brain dysrhythmias and cognitive dysfunction in many neurological and psychiatric disorders[172,179,180,183,184]. What is more, recent findings support the hypothesis that modulating interneuron function may improve brain rhythms and cognitive functions in AD and related disorders[172,182,185,186].

Proper functioning of inhibitory interneurons is required for the generation of high-frequency gamma oscillatory activity, coordination among different oscillatory frequencies (cross-frequency interactions) and regulation of neuronal firing by brain rhythms (frequency-action potential interactions). Several lines of evidence suggest that fast-spiking PV^{+} cells are impaired in disorders associated with hypersynchronous network activity such as schizophrenia and epilepsy[187], and that other types of interneurons — for example, those containing cholecystokinin or NPY — are impaired in mood disorders and anxiety[187–189].

PV^{+} cells constitute ~40% of inhibitory interneurons and are the major source of perisomatic inhibition onto excitatory pyramidal cells. Because PV^{+} cells are electrically coupled by dendritic gap junctions and form an electrically coordinated interneuron network, they are particularly well suited to synchronously modulate the activity of many pyramidal cells[176]. In optogenetic stimulation studies in wild-type mice, increasing the firing rate of PV^{+} cells

increased the power of gamma oscillations but not of other oscillations, whereas increasing the firing rate of pyramidal cells specifically increased the power of low-frequency oscillations[179,190] (FIG. 4c), indicating a causal link between gamma and PV^+ cell function. Increasing gamma power improved the signal-to-noise ratio of pyramidal cell firing, an effect that is likely to enhance neuronal processing[179,190].

In FAD mice (lines hAPP-J20, Tg2576, APP23, *APOE4*-KI, and APP/PSEN1dE9) (Supplementary information S1 (table)), gamma oscillatory activity is altered[107,172,191–193], suggesting that these animals have deficits in interneuron function. hAPP-J20 mice have brief peaks of increased gamma power and long periods of decreased gamma power[172,192]. Similar abnormal fluctuations in gamma power occur in Tg2576 mice[191]. Increased gamma power is associated with behaviour-dependent brain activation, increased firing rate of PV^+ cells[177,194] and the suppression of epileptiform discharges in hAPP-J20 mice[172] and humans with epilepsy[154]. By contrast, gamma power is decreased during resting activity and is associated with reduced firing rate of PV^+ cells[177,194] and increased epileptiform discharges in hAPP-J20 mice[172]. These behaviour-related modulations of gamma oscillations probably differ mechanistically from aberrant increases in gamma power during seizures or hyper-synchronized network activity and from the overall increases in oscillatory power across multiple frequency bands in APP23 and APP/PSEN1dE9 mice[107,193]. In APP23xPS45 mice, hyperactivity of cortical neurons was associated with decreased GABAergic inhibition rather than increased glutamatergic transmission, suggesting impaired inhibitory function[109]. More recently, reduced inhibitory function has been linked to amyloid-β-induced deficits in slow-wave propagation[195,196]. Aberrant increases in gamma power in the auditory cortex during evoked auditory stimulation in patients with AD have also been related to decreased inhibition[197,198]. Overall, however, humans with AD typically show decreases in the power of higher-frequency oscillations and increases in the power of lower-frequency oscillations[199].

APOE4-KI mice (Supplementary information S1 (table)), in which the *Apoe* gene is replaced by knocking in the human *ε4* allele, also have prominent GABAergic dysfunction and show reduced hippocampal power of slow gamma oscillations during sharp-wave ripple activity[200]. Amyloid-β application[99,201] and APP overexpression[202–204] markedly suppress the power of kainate-induced gamma oscillations in neuronal cultures. The mechanisms of gamma degradation by amyloid-β in brain slices are unclear but may involve changes in inhibition–excitation balance and cellular excitability[99]. Amyloid-β treatment increased excitatory and decreased inhibitory postsynaptic currents in pyramidal cells and increased the firing rate of these excitatory neurons[99]. Interestingly, although the mean phase of action potential firing did not change, the temporal firing window of excitatory neurons became wider, suggesting desynchronization of action potential firing[99]. Perhaps, spike-theta phase dysregulation[204] also contributes to the reduced gamma power and the epileptiform activity that are observed in FAD mice. Hippocampal injections of amyloid-β reduced firing rates in rhythmically bursting interneurons (probably PV^+ cells) but not in tonically firing interneurons (probably cholinergic interneurons) in the septum[203].

Across brain regions and behavioural tasks, effective encoding also seems to depend on cross-frequency interactions, particularly the coupling between the phase of theta

oscillations and the power of gamma oscillations (phase–amplitude coupling)[205–209], which is regulated by the synaptic activity of PV^+ cells[210,211]. Recordings from acute brain slices of young FAD mice and *in vivo* recordings from adult FAD mice (lines TgCRND8 and APP/PSEN1dE9, respectively) (Supplementary information S1 (table)) revealed deficits in theta-gamma coupling[193,212], which were associated with cognitive deficits[212] and could result from the kind of PV^+ cell dysfunction that we identified in hAPP-J20 mice. Indeed, by impairing PV^+ cell functions, APP and amyloid-β could disrupt multiple aspects of neuronal coordination.

Single-unit recordings of inhibitory cells in behaving rodents have revealed that behavioural and brain states affect interneuron subtypes differentially[177,178,189,213]. For example, PV^+ and VIP^+ cells drastically increase their action potential firing rate during specific behavioural states (for example, locomotor exploration), whereas NPY^+ and SOM^+ cells show persistent or tonic firing across multiple behavioural states (for example, locomotion, sleep and quiet wakefulness). These findings imply that certain behavioural states may be able to overcome, at least partly and for short periods, PV^+ cell impairments that cause low gamma power, hypersynchronous network activity and cognitive deficits in FAD mice and humans with AD (FIG. 5c). Optogenetically suppressing the activity of interneurons that express the homeobox protein DLX1 in the dentate gyrus impaired learning and acutely suppressed memory retrieval in mice, further highlighting the crucial role of interneurons in cognitive tasks[214]. It is tempting to speculate that fluctuations in interneuron activity may help to explain the fluctuations in cognitive performance of patients with AD that are frequently reported by care takers but have been difficult to document by clinical measurements.

The mechanisms by which interneuron deficits contribute to network and cognitive dysfunction in AD and related conditions remain to be fully elucidated, although much progress has recently been made on this front. Decreased synaptic inhibition and excitation–inhibition imbalances might explain deactivation deficits in the DMN of individuals with MCI or AD[4,67,72], but these hypotheses have not yet been tested experimentally. Impaired inhibition is another potential mechanism for plaque-related neuronal hyperactivity in APP23xPS45 mice[109]. In hAPP-J20 mice, we found that PV^+ cell impairments are caused by the depletion of the voltage-gated sodium channel subunit Nav1.1 and crucially contribute to network and cognitive dysfunctions[172] (FIG. 6a). Voltage-gated sodium channels control intrinsic cellular excitability by modulating action potential firing in specific neuronal subtypes. Nav1.1 is expressed predominantly in interneurons, including PV^+ cells, in both mice[172] and humans[215], and its levels in the parietal cortex are reduced in hAPP-J20 mice and patients with AD[172]. Hypofunction of Nav1.1 has been also described in Tg2576 mice[216] and in transgenic mice overexpressing BACE1 (REF. 217). As indicated earlier, the activity of BACE1, which is expressed at high levels in the brains of patients with AD[218], is required for the release of amyloid-β from APP. Because this enzyme also cleaves the β-subunit of voltage-gated sodium channels, increased BACE1 levels lead to aberrant β-subunit cleavage and reduced transport of Nav1.1 to the membrane, resulting in Nav1.1 hypofunction[216,217]. Neuroblastoma cells expressing the FAD-linked *PSEN1* E280A mutation also had reduced levels of Nav1.1 mRNA and protein levels[219].

APOE4-KI mice also develop spontaneous epileptic activity and seizures[120]. In humans without dementia, hyperventilation induces network hypersynchronization (for example, sharp waves) more frequently in *APOE* ε4 carriers than non-carriers[220]. Although network hypersynchrony has not been directly linked to interneuron dysfunction in *APOE4*-KI mice, these mice lose around 30% of SOM^+ cells in the hilus of the dentate gyrus, and this reduction is associated with learning and memory deficits[221]. Interestingly, chronic treatment with pentobarbital reversed the latter deficits but not the loss of hilar interneurons[221], suggesting that this positive allosteric modulator of GABA type A receptors can compensate for the partial loss of inhibitory input (FIG. 6b).

Synaptic depression and hypersynchrony

Synaptic loss is a pathological hallmark of AD and correlates well with cognitive decline [222,223]. In experimental models, high levels of amyloid-β cause synaptic loss, reduce glutamatergic synaptic transmission and LTP, and increase long-term depression[25,88,94,224–228]. Intriguingly, several proposed mechanisms of amyloid-β-induced synaptic depression might also contribute to network hypersynchrony[229]. For example, amyloid-β blocks neuronal glutamate uptake at synapses, which could result in glutamate spillover around the synaptic cleft[25]. The rise in glutamate may desensitize synaptic NMDARs and aberrantly activate extra- or perisynaptic GluN2B-containing NMDARs and metabotropic glutamate receptors (mGluRs), and both GluN2B-containing NMDARs and mGluRs can promote long-term synaptic depression and spine retraction[25,228,230]. Amyloid-β-induced NMDAR- and mGluR-dependent long-term depression can be prevented by lowering extracellular glutamate[25] and can be mimicked by application of the glutamate reuptake inhibitor thero-β-benzyloxyaspartate (TBOA), which can also trigger epileptiform discharges in wild-type brain slices [231]. Thus, amyloid-β-induced network hypersynchrony may be directly linked to synaptic depression.

Future therapies

The effective therapy of AD will probably require combining treatments targeting the root causes of the disease with therapeutic strategies that can block or counteract the pathogenic processes that these causes trigger[33]. From the evidence reviewed above, we think that brain dysrhythmias caused by aberrant interneuron activity and other mechanisms probably contribute to cognitive deficits and behavioural alterations in AD and related conditions. We further hypothesize that enhancing the function of interneurons in these conditions, particularly of PV^+ and SOM^+ cells, will improve network activities and cognitive performance.

In hAPP-J20 mice, restoring Nav1.1 levels enhanced PV^+ cell-dependent gamma oscillatory power, reduced network hypersynchrony and improved cognitive performance (FIG. 6a), pinpointing Nav1.1- and PV^+ cell-dependent oscillatory rhythms as potential therapeutic targets. Although it is never certain that therapeutic findings obtained in experimental models (or in early clinical trials in humans, for that matter) will hold up in large heterogeneous human populations, Nav1.1 depletion and various other molecular alterations identified in hAPP-J20 mice have been found in people with AD (Supplementary

information S2 (table)). These include depletions of calbindin in the dentate gyrus and of reelin in the entorhinal cortex, increased neuronal production of collagen VI, higher hippocampal levels of activated group IVA phospholipase A2 and increased expression of the adenosine A_{2A} receptor by hippocampal astrocytes[100,172,232–236]. In addition, the anti-epileptic drug levetiracetam, which reduces synaptic, network and cognitive deficits in hAPP-J20 mice[74], also exerts beneficial effects in patients with amnestic MCI[67,73], which is widely viewed as an early stage of AD[237–239].

Manipulating interneuron function to improve brain rhythms is a promising therapeutic strategy for disorders involving interneuron and network dysfunctions, including AD, epilepsy, schizophrenia and autism. But how might these dysfunctions be approached therapeutically? Interneurons have highly specialized functions, electrophysiological properties and molecular profiles. Targeting molecules such as ion channels or receptors that are predominantly expressed in specific types of interneurons might make it possible to improve and harness the function of these cells without impairing other cell types. Indeed, Nav1.1 enhancers that preferentially activate Nav1.1-containing interneurons have been proposed for the treatment of epilepsy, schizophrenia and AD[240]. Because the firing rate of PV^+ cells and gamma power strongly depend on behavioural activity[154,177], behavioural or sensorial interventions that promote brain states associated with increased power ratios in high- to low-frequency oscillations might also be of benefit.

Finally, embryonic interneuron precursors transplanted into adult brains can migrate and integrate into appropriate circuits and mature into fully functional interneurons[182]. Although cell therapy for cognitive disorders may seem to be rather daring and must be approached with appropriate caution, it has already been explored in a small clinical trial in patients with AD[241]. In AD-related mouse models with prominent loss of hilar interneurons, including pilocarpine-treated wild-type mice[185] and untreated *APOE4*-KI mice[186], hippocampal transplants of wild-type interneuron precursors improved behavioural functions. However, it is not known how well such transplants would survive and function in the proteopathic, toxic microenvironment in AD brains[172,203]. Genetic modifications may be required to render interneuron precursors resistant to such conditions. Potentially beneficial modifications include overexpression of proteins that protect against the disease, such as Nav1.1 (REF. 172) in PV^+ cells, or reduction of proteins that promote or enable AD-related pathogenesis, such as tau[110] and APOE4 fragments[242]. These therapeutic opportunities also call for the development of reprogramming strategies to convert skin or blood cells into precursors of specific interneuron subtypes.

Conclusions

Network activities that support cognition are altered decades before the expected onset of clinical signs and symptoms in AD, and the affected networks predict future pathology and brain atrophy. Because neuronal synchrony regulates the functional state of brain circuits and networks, deficits in synchrony, including network hypersynchrony and altered oscillatory rhythmic activity, could contribute to AD-related cognitive dysfunction. Although the precise causes of these synchrony deficits remain to be defined, diverse lines of evidence suggest that interneuron dysfunction and network imbalance may be crucially

involved. Therapeutic strategies that improve the function of interneurons and counteract such abnormalities might improve cognitive functions in AD and related disorders. By preventing excitotoxic overstimulation of neurons and maladaptive compensatory processes, they may also help to prevent or stall disease progression.

Supplementary Material

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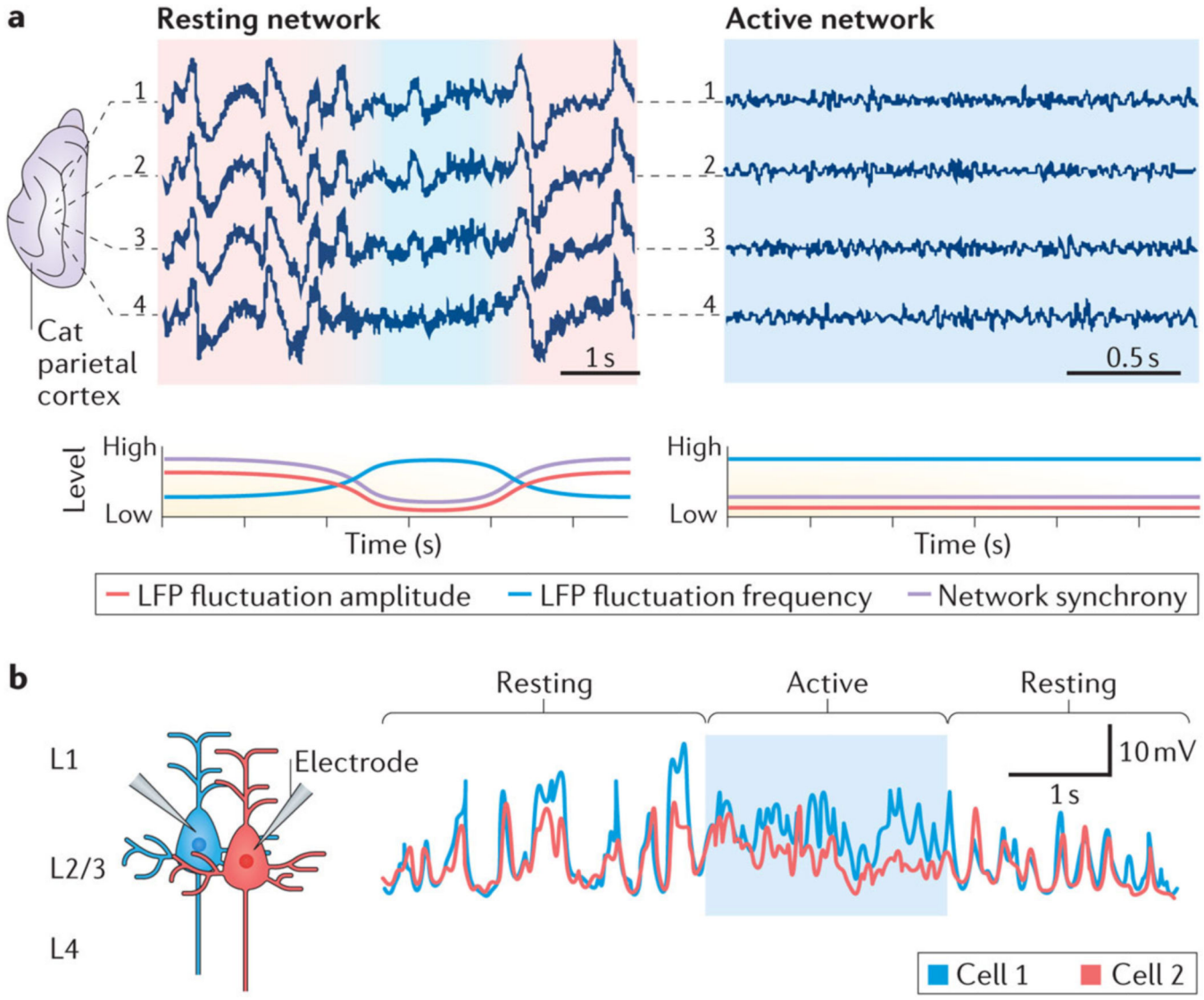

Figure 1 |. Synchrony and functional states of networks.

The degree of correlated neuronal activity (synchrony) reflects the functional state of networks and circuits. **a |** To illustrate this relationship at the network level, the top panels show local field potentials (LFPs) recorded from four electrodes (1–4) inserted 1 mm apart into the cat parietal cortex (suprasylvian gyrus) during sleep (left) and wakefulness (right). Network activity during resting and non-active states is predominantly characterized by synchronized slow-frequency and high-amplitude fluctuations (red shading). By contrast, network activity during active states is characterized by desynchronized fast-frequency and low-amplitude fluctuations (blue shading). The bottom panels show hypothetical representations of the amplitude (red line) and frequency (blue line) of LFP fluctuations and of the associated network synchrony (pink line). **b |** Membrane potential recordings of two layer 2/3 (L2/3) pyramidal neurons from mouse parietal cortex (whisker barrel cortex) during resting and active (whisker use) periods illustrate that neurons desynchronize during active periods. Part **a** is republished with permission of Society for Neuroscience, from

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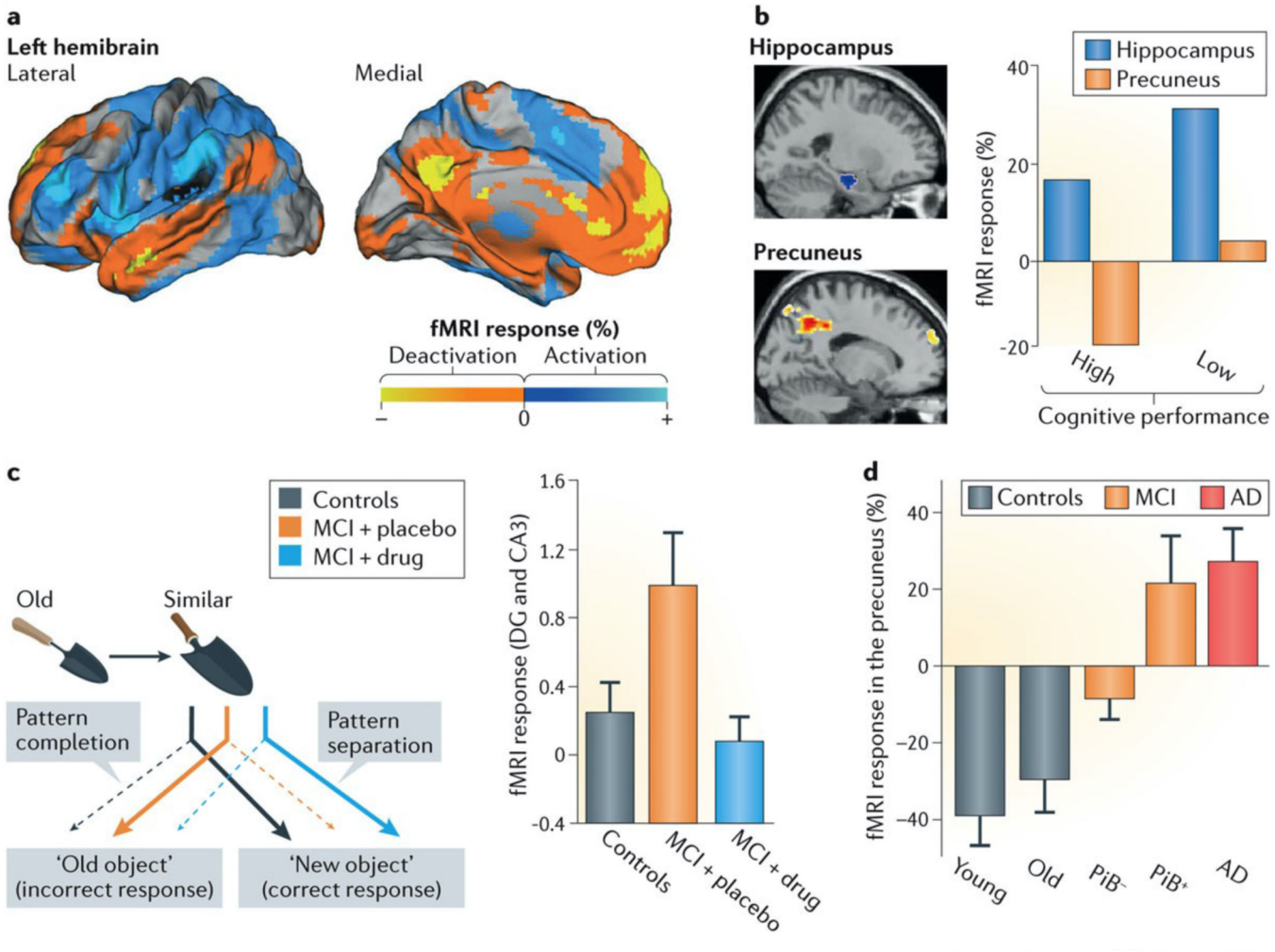

Figure 2 |. Encoding reveals network dysfunction in people with mild cognitive impairment.

Memory encoding causes specific changes in brain activity-related functional MRI (fMRI) signals across different networks. People at increased risk for Alzheimer disease (AD) show early changes in the activation and deactivation of specific networks. **a |** Lateral (left panel) and medial (right panel) views of a healthy left hemibrain. During encoding in healthy people, network activity increases in task-related networks (blue) and decreases in non-task-related networks (yellow/orange). Anti-correlated activity (blue versus yellow/orange) in these two widely distributed and non-overlapping networks is also evident when spontaneous fluctuations of fMRI signals during resting states are examined (not shown). The default mode network (yellow and orange regions) includes brain regions that show decreased fMRI activity during attention-demanding tasks but become active during inwardly oriented mental activity. **b | In** healthy individuals whose brain activity was monitored by fMRI during a cognitive task, a relatively smaller extent of hippocampal activation and a relatively greater extent of precuneal deactivation were associated with better cognitive performance. **c |** Pattern separation and completion are cognitive functions that heavily rely on the hippocampal formation and allow us to discriminate (pattern separation) or merge (pattern completion) similar representations or episodes. In a pattern-

separation task, in which individuals were asked to discriminate between slightly different trowels (left panel), patients with amnestic mild cognitive impairment (MCI) made more pattern-completion errors (that is, they failed to discriminate slightly different trowels) and had aberrant hyperactivation of the dentate gyrus (DG) and CA3 regions of the hippocampus on fMRI (right panel). Treatment with the antiepileptic drug levetiracetam reversed the hippocampal hyperactivation and improved the patients' ability to discriminate between images that were similar but not identical. **d |** During a face–name association task, patients with MCI and amyloid deposits in the brain (as revealed by a Pittsburg compound B-positive (PiB^+) signal on positron emission tomography) and patients with AD showed deactivation deficits in the precuneus. Part **a** is adapted from REF. 58. Part **b** is adapted with permission from REF. 61, Springer. Part **c** is adapted with permission from REF. 67, Cell Press/Elsevier. Part **d** is adapted with permission from REF. 4, Cell Press/Elsevier.

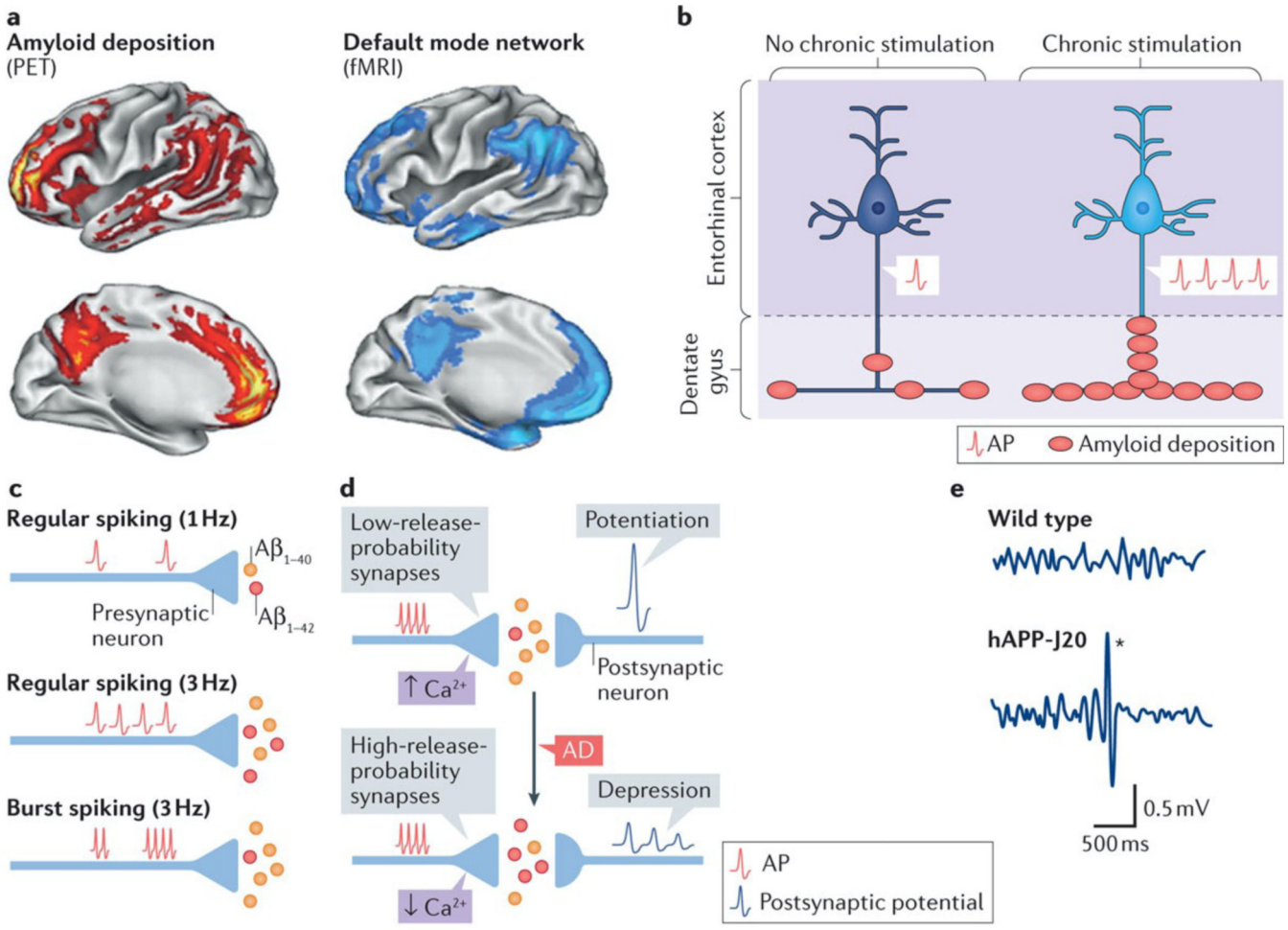

Figure 3 |. Neuronal activity regulates amyloid-β production and deposition.

a | Most patients with Alzheimer disease (AD) and some people without dementia have increased Pittsburg compound B-positive amyloid deposits in the brain[243] (red). Amyloid deposits predominate in brain regions of the default mode network (blue), which shows deactivation deficits in AD (FIG. 2), suggesting a potential link between aberrant neuronal activity and amyloid deposition. **b** | In APP-A7 mice, chronic, optogenetic stimulation of pyramidal cells in the entorhinal cortex triggered epileptiform activity and increased amyloid deposition in the molecular layer of the dentate gyrus, directly supporting the notion that aberrant neuronal activity can promote amyloid deposition *in vivo*. **c** | At the synaptic level, an increase in the frequency of action potentials (APs) proportionally enhances amyloid-$\beta_{1–42}$ ($A\beta_{1–42}$) and amyloid-$\beta_{1–40}$ ($A\beta_{1–40}$) production. Compared with regular firing, burst firing reduces the $A\beta_{1–42}/A\beta_{1–40}$ ratio. **d** | Basal neurotransmitter release determines the 'filter' mode of synapses and regulates synaptic plasticity. The top panel indicates that excitatory synapses with lower release probability (high-pass-filter synapses) have greater presynaptic Ca^{2+} build-up, produce lower $A\beta_{1–42}/A\beta_{1–40}$ ratios, exhibit synaptic facilitation and primarily transfer potentiated responses. The bottom panel depicts synapses with higher release probability (low-pass-filter synapses), which have less presynaptic Ca^{2+} build-up, produce higher $A\beta_{1–42}/A\beta_{1–40}$ ratios and show synaptic depression as well as enhanced

spike transfer. In AD, synapses may shift from high- to low-pass synaptic filtering. **e** | Electroencephalograhy recordings capture the combined electrical output of neuronal ensembles. In such recordings, most familial AD (FAD) mice, including hAPP-J20 (REF. 96), APP/PSEN1dE9 (REFS 102,103), Tg2576 (REF. 104), 5xFAD[122], 3xTg-AD[75], APP/TTA-EC[105], APP/TTA-CaMKIIα[106], and APP23 (REF. 107) mice (Supplementary information S1 (table)), show intermittent large-amplitude epileptiform discharges (denoted by the asterisk in hAPP-J20 mice; bottom panel), which provide evidence of network hypersynchrony. fMRI, functional MRI; PET, positron emission tomography. Part **a** is republished with permission of Society for Neuroscience, from Molecular, structural, and functional characterization of Alzheimer's disease: evidence for a relationship between default activity, amyloid, and memory, Buckner, R. L. *et al.*, 25, 34, 2005; permission conveyed through Copyright Clearance Center, Inc. Part **e** is adapted with permission from REF. 172, Cell Press/Elsevier.

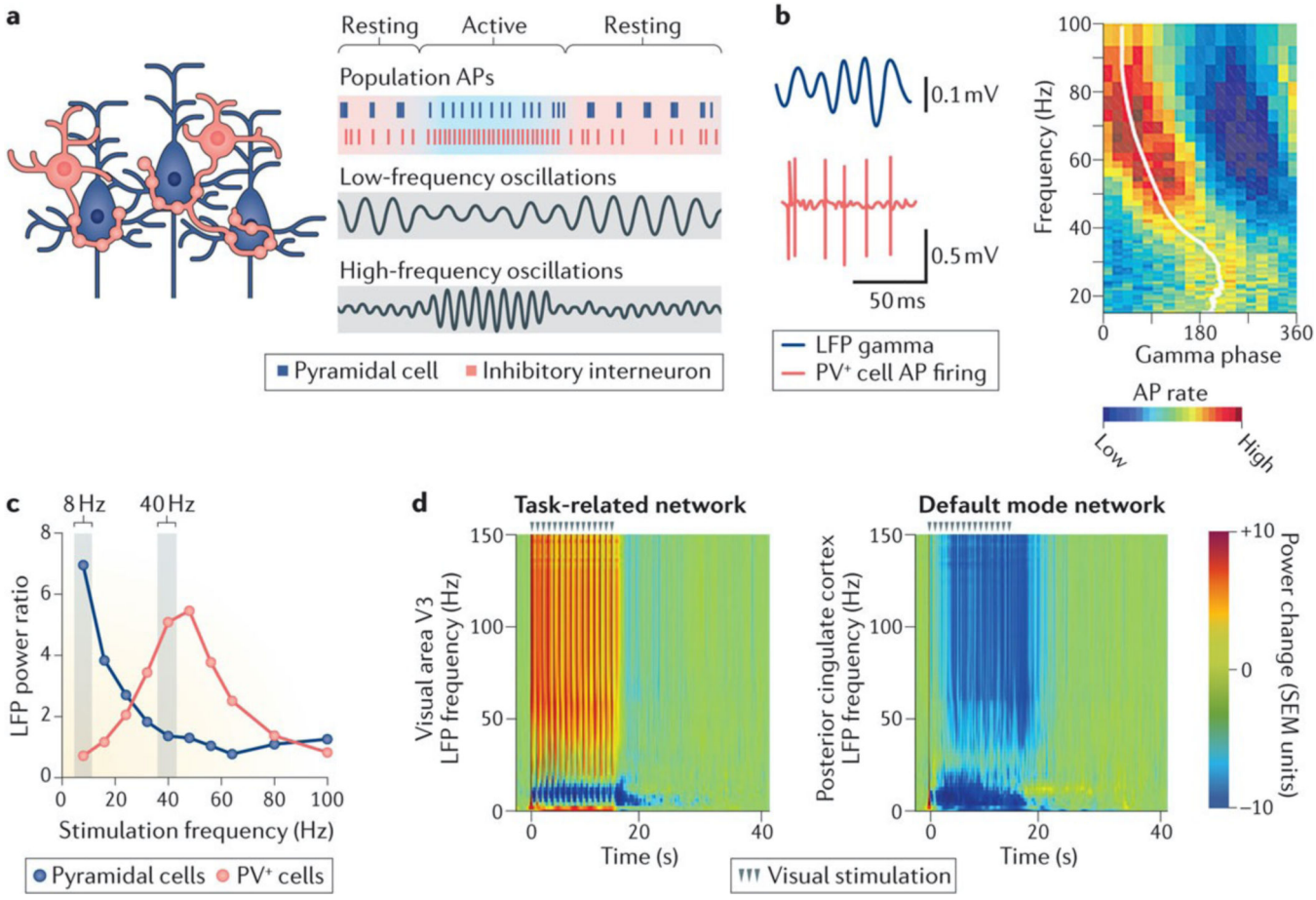

Figure 4 |. Neuronal ensembles generate oscillatory activity patterns.

a | Oscillatory rhythms (grey boxes) emerge from, and control, the activity of neuronal ensembles that are formed by excitatory neurons (blue) and inhibitory interneurons (red). The amplitude, or power, of low-frequency oscillations increases during rest, whereas the amplitude of high-frequency oscillations increases during activity. Action potentials (APs) of excitatory neurons are phase-locked to high-power, lower-frequency oscillations (top grey box), whereas APs of inhibitory cells are phase-locked to high-power, high-frequency oscillations (bottom grey box). **b |** The left panel shows local field potential (LFP) gamma oscillations (blue) and APs (red) for a parvalbumin-positive (PV^+) cell in area CA3, revealing a close association between APs and the phase of gamma oscillations. In the right panel, the AP firing rate (colour coded) is shown as a function of gamma phase for the same PV^+ cell, which prominently fires during the ascending phase of gamma oscillations. **c |** Optogenetic stimulation of PV^+ and pyramidal cells at different frequencies resulted in a cell type- and frequency-specific generation of oscillatory activity. 40-Hz stimulation of PV^+, but not pyramidal, cells increased gamma power, whereas 8-Hz stimulation of pyramidal, but not PV^+, cells increased theta power. **d** | In macaques**,** visual stimulation (15s of dim 1 Hz illumination) increased the power of LFP gamma (30–150 Hz) oscillations in a task-related network (visual area V3; left panel) and decreased LFP power across multiple oscillatory frequencies in a default mode network region (posterior cingulate cortex; right panel). SEM, standard error of the mean. Part **b** is from REF.151, Nature Publishing Group. Part **c** is from

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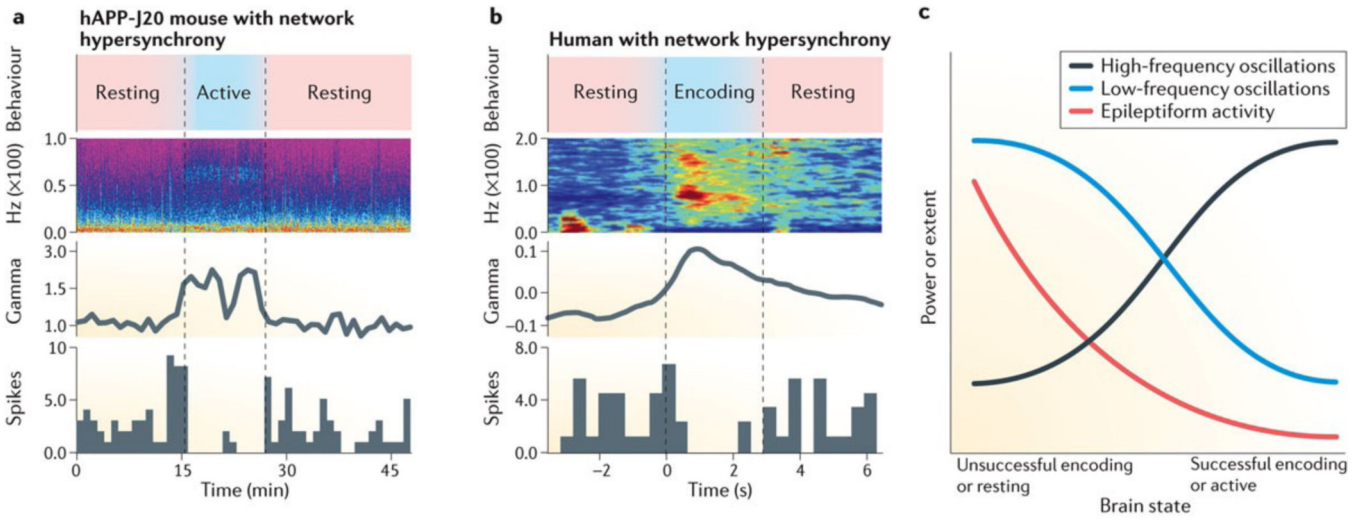

Figure 5 |. Close association between behavioural state, gamma oscillations and epileptiform activity in mice and humans.

a,b | Behavioural activity, full-frequency range spectrograms, gamma oscillatory power, and distribution of epileptic discharges in cortical networks of an hAPP-J20 mouse (part **a**) and a human with epilepsy (part **b**). In mice, exploration (active) of a novel environment robustly increased gamma oscillatory power and reduced epileptiform discharges, suggesting that the brain state modulates brain rhythms and network hypersynchrony. In humans, successful, but not unsuccessful, memory encoding also increased gamma oscillatory power and reduced epileptiform discharges. **c |** In our hypothetical model, memory encoding requires frequency-specific modulation of oscillatory frequencies, which reduces network hypersynchrony. Part **a** is adapted with permission from REF. 172, Cell Press/Elsevier. Part **b** is adapted from Matsumoto, J.Y. *et al.*, Network oscillations modulate interictal epileptiform spike rate during human memory, *Brain*, 2013, **136**, 8, 2444–2456, by permission of Oxford Journals.

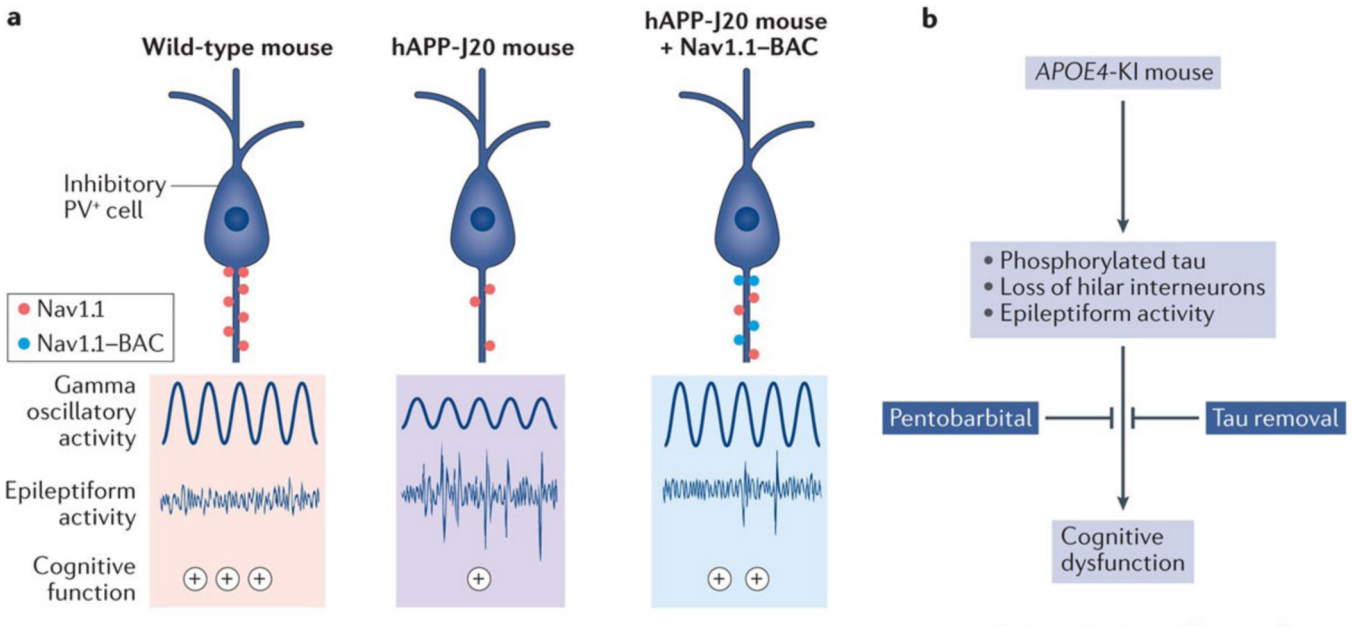

Figure 6 |. Targeting interneurons to improve Alzheimer disease-related network dysfunction.

a | In hAPP-J20 mice (middle panel), reduced levels of the voltage-gated sodium chanel subunit Nav1.1 in parvalbumin-positive (PV^+) cells were associated with reduced gamma power, epileptiform activity and cognitive impairment (the level of cognitive performance is denoted by the plus symbols). Restoring Nav1.1 levels in PV^+ cells with an Nav1.1-BAC (bacterial artificial chromosome) transgene (right panel) reduced all of these deficits. **b |** *APOE4*-KI mice have increased neuronal levels of phosphorylated tau, age-dependent loss of somatostatin-positive interneurons in the hilus of the dentate gyrus, and seizures. Memory deficits in these mice were reduced by pentobarbital treatment[221], tau removal[221] and transplantation of interneuron precursor cells[160]. Part **a** is adapted with permission from REF. 172, Cell Press/Elsevier.

Table 1 |

Network hypersynchrony in humans with FAD caused by mutations used in mouse models.

Affected genes	FAD mutations	Number of patients with seizures (study population percentage)	Age at onset of cognitive deficits, years (mean)	Refs
APP	KM670/671NL	10 (50%)	44–61 (53)	244
APP	V717L, V717G or V717I	11 (40%)	40–67 (51)	245–248
APP	T714I or 714A	6 (85%)	33–55 (NA)	249,250
APP	Duplication	27 (45%)	39–62 (NA)	144,145,251–253
APP; PSEN1	KM670/671NL (*APP*); H163Y (*PSEN1*)	8 (89%)	44–65 (54)	254
PSEN1	M146L	7 (70%)	33–46 (39)	255
PSEN1	M146V	1 (100%)	39 (NA)	256
PSEN1	L286V	7 (64%)	39–56 (48)	257

APP, amyloid precursor protein; FAD, familial Alzheimer's disease; NA, not available; *PSEN1*, presenilin-1.