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Review article

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# Interictal network dysfunction and cognitive impairment in epilepsy

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## Abstract

Epilepsy is diagnosed when neural networks become capable of generating excessive or hypersynchronous activity patterns that result in observable seizures. In many cases, epilepsy is associated with cognitive comorbidities that persist between seizures and negatively impact quality of life. Dysregulation of the coordinated physiological network interactions that are required for cognitive function has been implicated in mediating these enduring symptoms, but the causal mechanisms are often elusive. Here, we provide an overview of neural network abnormalities with the potential to contribute to cognitive dysfunction in epilepsy. We examine these pathological interactions across spatial and temporal scales, additionally highlighting the dynamics that arise in response to the brain's intrinsic capacity for plasticity. Understanding these processes will facilitate development of network-level interventions to address cognitive comorbidities that remain undertreated by currently available epilepsy therapeutics.

## Sections



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## Introduction

Epilepsy is fundamentally a disorder of neural communication. It is characterized by an ongoing predisposition to generate seizures, which are transient epochs of abnormally increased and/or hypersynchronous interactions between neurons. In parallel, epilepsy is associated with more enduring impairments in the ability of neural populations to cooperate physiologically and execute brain functions, leading to sustained cognitive, psychological and social consequences. These comorbid symptoms of epilepsy have been linked to dysfunction of the large-scale, complex neural networks that are required for higher brain functions. The accessibility of these neural networks to direct monitoring across populations of patients with epilepsy has identified some characteristic modes of dysfunction that are common despite divergent underlying aetiologies. Coupled with the ability to invasively and non-invasively manipulate neural network activity, such observations raise the possibility of broadly applicable network-level interventions capable of addressing cognitive comorbidities in epilepsy (Fig. 1).

The simplest definition of a physiological neural network is a population of neurons that together partakes in purposeful communication. The anatomical structure of neural networks can be demarcated by synaptic connectivity, as comprehensively identified by tracing axonal processes[1] or estimated by imaging methods such as diffusion tensor imaging[2]. Although these structural connections provide the underlying architecture for neural interaction, an actively functioning neural network is identified by evidence of ongoing information transfer between regions. At the most fundamental level, such information transfer occurs when action potentials generated in one neuron modify the activity of a synaptically connected downstream neuron, potentially changing synaptic strength[3]. To enable brain functions, synaptic activity should be aligned across a population of neurons capable of performing the required computations and be directionally routed to permit hierarchical processing across brain regions. This alignment and routing are enabled by creation of temporal windows of excitability that regulate the potency of incoming action potentials, thereby providing the means to gate and direct communication. Monitoring the innumerable monosynaptic interactions required for performance of a cognitive task is, of course, impractical. Fortuitously, signatures of activity alignment and routing are accessible directly via electrophysiological monitoring and indirectly through proxies of neural activity such as the blood oxygen level-dependent (BOLD) signal[4–6]. These signatures typically consist of rhythmic or bursty patterns in the local field potential (LFP), representing the concerted synaptic action of a relatively large population of neurons. Oscillations in the LFP are hypothesized to couple excitability between regions that share the frequency and/or phase of the oscillation, providing a sustained spatiotemporal conduit for effective transmission of action potentials[7]. In turn, brief bursts of oscillatory cycles or population transients can provide a strong, concerted input to synaptically connected brain areas, thereby inducing responsive transients or oscillations. Both these communication approaches can be dysregulated in epilepsy, across multiple spatial scales. This dysfunctional communication can result in observable electrophysiological features that facilitate epilepsy diagnosis (such as interictal epileptiform discharges (IEDs) or focal delta band activity). These features also reflect how the network has been disrupted, with implications for association with comorbidities and the most effective treatment approaches.

Here, we review how the neural network activity patterns that are required for cognitive functions are affected by epilepsy, highlighting the abnormalities that persist outside epochs of seizure activity and the immediate post-ictal state. The structure and dynamics of pathological networks responsible for seizure generation have been covered extensively elsewhere[8–12]. We posit that the host of cognitive comorbidities that commonly manifest in patients with epilepsy is a result of the potent ability of abnormalities incited by the epileptic process to overwhelm the mechanisms used for physiological neural communication. At least some of these network-level abnormalities may be convergent, driven by underlying principles of functional network connectivity and therefore expressed in a manner that is independent of the specific epilepsy aetiology and its genetic, molecular and/or cellular mechanisms. For discussion purposes, we separate these mechanisms into those related primarily to coherence of oscillations and those mediated by discrete population transients (such as ripples or IEDs), acknowledging the potential for overlap. Crucially, we also highlight that neural networks are plastic, with activity patterns changing in an experience-dependent manner over time. Adaptation to pathological experience can modify the way the network expresses dysfunction, such that disease course is a critical dimension to identifying driving mechanisms and likelihood of response to various interventions. We synthesize considerations for development of network-level therapeutics capable of targeting these mechanisms, restoring physiological network performance and thus providing an opportunity to ameliorate cognitive comorbidities in a manner that is broadly applicable to patients with shared patterns of network dysfunction.

## Oscillations and coherence

Neural network activity is perpetually dynamic, shifting through different patterns as governed by intrinsic functional connectivity and external stimuli. Expression of transient oscillations is characteristic of the mammalian brain, with examples also identified in birds and reptiles[13]. These oscillations span a wide frequency range (from <1 Hz to hundreds of hertz), although they have been arbitrarily separated into bands for descriptive purposes (delta, 0.5–4 Hz, theta 5–8 Hz, alpha 8–12 Hz, beta 12–30 Hz, gamma 30–100 Hz and ripple >100 Hz). Oscillatory cycles serve as temporal processing windows, facilitating discrete channels of communication between brain regions[3,7]. When oscillations are coherent, windows for optimized synaptic communication are aligned, and the ability to interact over extended anatomic distances is enhanced (Fig. 2a). Slower oscillations in general enable integration across larger anatomic scales, whereas faster oscillations operate more locally[14–16]. Here, we will group oscillations within conventional frequency bands, but with the understanding that the frequency of an oscillation cannot necessarily be assumed to represent a unique mechanism of generation when observed across behaviour states or in different brain structures[17]. Indeed, observation of an oscillation in a given brain region does not necessarily indicate a locally oscillating circuit, as incoming signals from remote oscillating sources can create a similar extracellular signature. Nonetheless, characteristic oscillatory patterns are consistently associated with cognitive processes, and modulation of these patterns can affect cognitive performance, lending credence to their function as biomarkers, despite the fact that their precise generators and underlying mechanisms are often unknown.

Oscillations possess multiple properties aside from frequency that are critical to their effectiveness in mediating communication and information processing. Amplitude can reflect the size of the circuit and neural population contributing to its generation, or the degree of convergence of an upstream oscillatory population to the

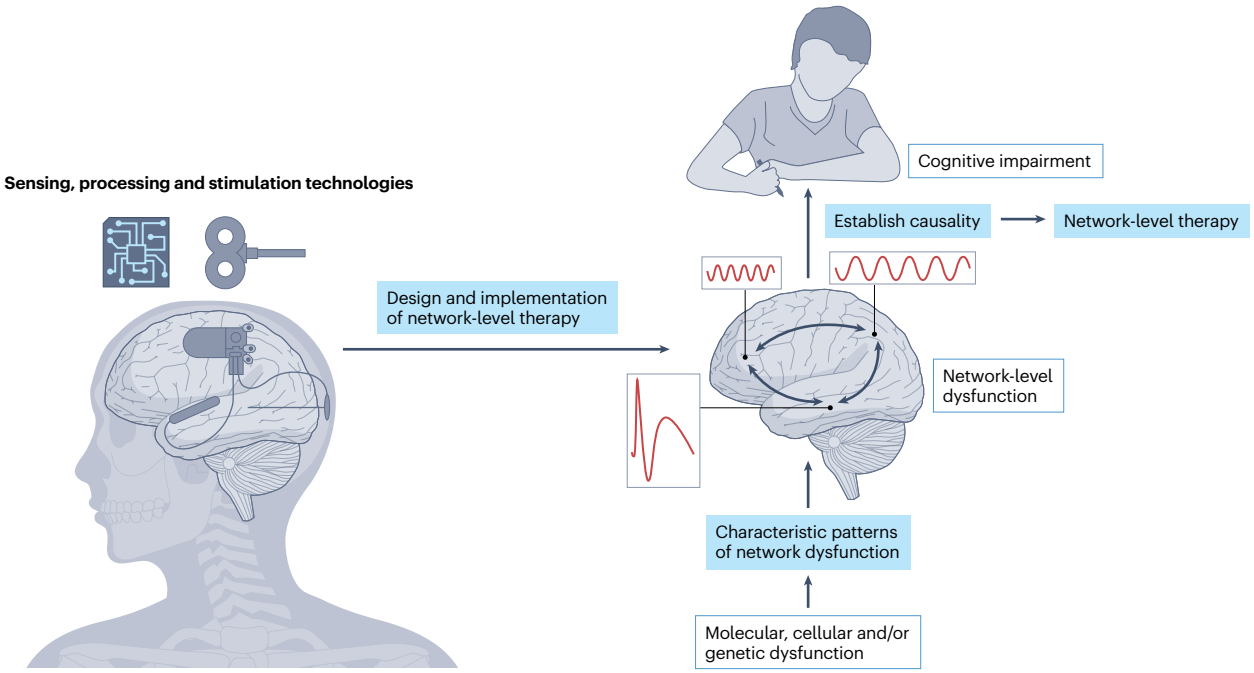


**Fig. 1 | Network-level dysfunction contributing to cognitive impairment in epilepsy.** Heterogeneous molecular, cellular and genetic abnormalities that cause epilepsy can converge into characteristic patterns of interictal network-level dysfunction. The design and implementation of network-level therapy, for example, by using electrical or magnetic stimulation, permit direct manipulation of physiological and pathological activity patterns. Evaluation of therapy outcomes can establish a causal relationship with cognitive impairment. When these criteria have been met, it becomes possible to design and implement network-level therapy with the potential to treat cognitive comorbidities across a diverse patient population.

monitored region. Neural subtypes fire at particular phases of oscillations, regulating the input from different afferent pathways and linking cell assemblies[18,19]. Interaction between oscillations can be expressed through a diversity of coupling mechanisms, including (i) phase–amplitude, (ii) phase–phase, (iii) phase–frequency and (iv) amplitude–amplitude coupling[20,21]. Importantly, the transience of oscillations is a key feature, as persistence of a regular, highly predictable oscillatory regime prevents networks from responding to potentially salient, although weak, incoming stimuli. It is hypothesized that the ability to shift back and forth from a noisy, 'metastable' state to defined oscillatory states is what enables effective sensing of environmental changes and subsequent information processing across spatiotemporal scales[18]. For instance, rodents express a prominent, rhythmic hippocampal theta oscillation during locomotion that aids in experience encoding, which alternates with a desynchronized pattern punctuated by higher frequency oscillations (sharp wave-ripples (SPW-Rs)) associated with replay of relevant experience during subsequent immobility[22]. This oscillation-based capacity for information processing also exhibits a developmental trajectory, with a shift from early oscillations that are loosely correlated and often prominently driven by afferent stimuli to mature oscillations that display spatiotemporal precision and internal organization[23–26]. From such a framework, it is apparent that alterations which either enhance or impair the tendency for neural networks to engage in oscillatory patterns could contribute to brain dysfunction. Thus, a myriad of avenues for oscillatory dysregulation exists, and an extensive assortment has been observed to occur in epilepsy, across various clinical syndromes, brain regions, developmental stages and animal models. Such pathological changes can manifest during epochs without any overt epileptiform activity, implying that the mechanisms set in motion by the epileptic process can simultaneously predispose to sporadic occurrence of seizures and result in more chronic network abnormalities that contribute to epilepsy comorbidities.

## Theta-mediated coherence

Theta (5–8 Hz) is prominently expressed in medial temporal lobe structures, where it is implicated in various memory processes[19]. Within the medial temporal lobe, the hippocampus serves as a key 'node' for episodic memory, receiving highly processed sensory information related to experience and executing computations that prime for long-term storage. Hippocampal patterns contributing to various memory processes have been characterized, providing a platform for understanding network mechanisms of this key cognitive function. Theta oscillations organize spike timing of different neuronal subtypes[27] and allow hippocampal neurons encoding places and events to track and predict spatial trajectories[28–31]. These oscillations arise from the interactions of multiple transmembrane currents, with both extrinsic inputs and local neural properties contributing to appearance and localization of the extracellular dipole, as well as influencing specific functions[32]. Hippocampal neurons can systematically change when they fire action potentials relative to the phase of the theta oscillation during exploration of the environment, providing a means by which neural ensembles may represent the current spatial location and calculate future locations. This phenomenon, known as phase precession, is one of the mechanisms thought to permit formation and segregation of neuronal sequences, generating a coherent representation of experiential

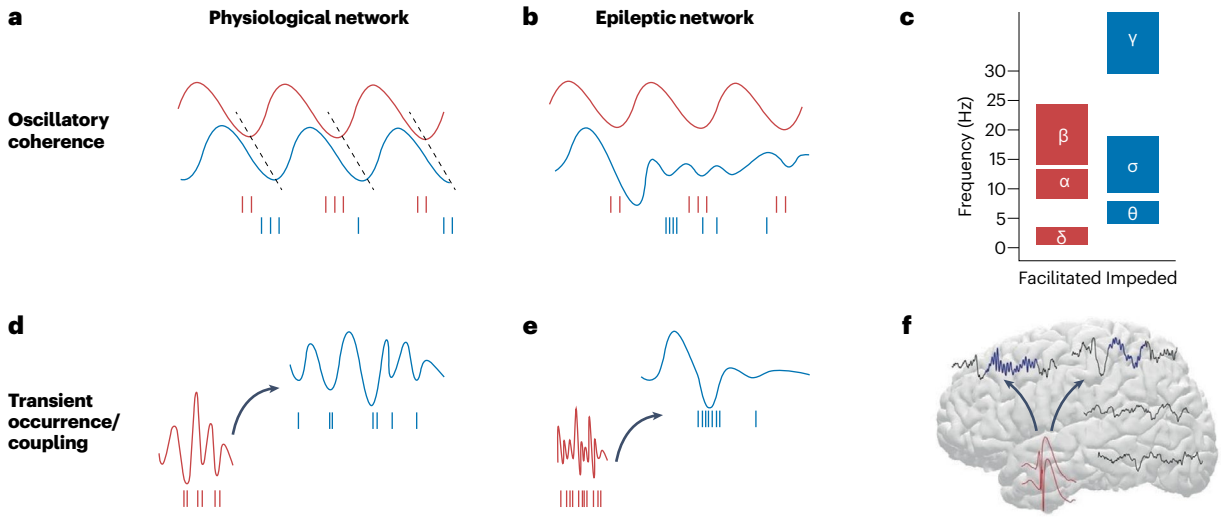


**Fig. 2 | Dysregulation of physiological communication in epileptic networks.** **a**, Physiological networks establish oscillatory coherence between brain regions (represented by blue and red colours) that coordinate action potential occurrence (represented by vertical blue and red lines) for maximal effectiveness of information transmission. **b**, In epileptic networks, oscillatory coherence can be disrupted in various ways. One example, as observed in models of temporal lobe epilepsy[52,53], is illustrated here. Lack of coordinated oscillatory activity in one brain region (blue) decreases the temporal coordination of action potentials (vertical lines) with another brain region (red), thereby impairing coordinated neural spiking and effective information transmission. **c**, This schematic illustrates the tendency for oscillations to be facilitated or impeded in epileptic networks in a frequency-dependent manner, evoking speculation regarding coordinated changes in the physiological system of oscillations mediated by epileptiform activity. **d**, Physiological networks express population transients (red) comprising orderly sequences of action potentials (vertical lines) that can induce coupled population responses (blue) that are crucial for information processing across brain regions. **e**, Epileptic networks facilitate the expression of pathological population transients, comprising excessive and/or disorganized neural spiking, that can induce abnormal population responses in coupled brain regions. **f**, Pathological population transients (such as interictal epileptiform discharges, red) can engage in temporal coupling with spatially distributed oscillations (such as spindles, blue), potentially overriding physiological coupling patterns.

epochs[30,31]. Theta oscillations are observed in rodents and humans and have been linked to various spatial and non-spatial memory tasks[33–35].

Theta power and frequency, as well as phase precession, are altered in models of epilepsy for which the hippocampus forms part of the seizure onset zone[36–39]. Loss of hippocampal theta phase precision has also been observed in patients with epilepsy[40]. Subregion-specific and cell-type-specific cell loss contributes in certain models, but deficiencies of interneuron firing and changes in pyramidal cell responsiveness to different inputs are potential mechanisms in others[41–44]. The degree of theta alteration has been correlated to impaired performance of memory tasks[37,38,45,46]. Thus, epilepsy-associated loss of physiological neural spiking patterns disrupts expression of hippocampal theta, compromising the ability of the network to perform local information processing required for memory.

However, hippocampal theta does not operate in isolation during memory processes. Dynamic theta coherence between entorhinal cortex and hippocampus enables development of ensemble representations and is observed during human episodic memory[47–49]. Similarly, intact working memory requires coherence of theta oscillations between the hippocampus and prefrontal cortex[50,51]. This oscillatory coherence may position sensory inputs for hippocampal processing and subsequently ensure that relevant hippocampal information is available for decision-making.

Altered theta coupling among the medial entorhinal cortex, hippocampus and prefrontal cortex has been observed in hippocampal epilepsy models[52,53], suggesting that local theta deficits can extend to larger-scale network dysfunction (Fig. 2b). Although these multiregional abnormalities can theoretically be tracked back to a local hippocampal mechanism, such as cell loss causing imbalanced connectivity[53], their existence presents additional approaches for restoration of physiological function. For instance, extrinsic stimulation to restore theta rhythmicity or application of pharmacological substances that rebalance theta dipoles can normalize theta expression and rescue associated memory impairment, despite persistence of underlying hippocampal cellular abnormalities[43,54]. Such results suggest the potential efficacy of an inter-regional network intervention to overcome local network deficits and highlight the importance of investigating larger-scale ramifications of local oscillatory dysfunction.

Theta rhythms are a characteristic electrophysiological feature of rapid eye movement (REM) sleep, observed prominently in lower mammals and with a more sporadic and phasic appearance in humans[55]. In animal models, coherence of REM theta among hippocampus, amygdala and cortex increases in a learning-dependent manner, and its disruption using targeted optogenetics impairs memory consolidation[56,57]. Selective pruning and maintenance of new synapses occur during REM, suggesting a mechanism that could underlie behavioural improvements detected after learning[58]. Although focus on theta occurring during REM sleep has been less than that occurring during wakefulness, there is preliminary indication that the coherence of theta between hippocampus and cortex, as well as its coupling with gamma frequencies, is altered in animal models of epilepsy[59,60]. More work remains to clarify the relationship of theta during REM to memory processes and their dysregulation in epilepsy.

### Gamma-mediated coherence

Gamma oscillations are ubiquitous across most hippocampal and cortical regions, typically occurring in brief epochs and strongly implicated in information processing[61,62]. The period of a gamma oscillation is similar to the membrane time constant of pyramidal neurons and the temporal window for synaptic plasticity, suggesting that these oscillations facilitate organization of cell assemblies that encode experience[63]. In neocortical areas, gamma is thought to bind representations determined by disparate cell assemblies into a coherent percept[64]. Several candidate microcircuit motifs have been suggested for generating gamma, including mutual inhibition between inhibitory GABAergic neurons and tight excitation–inhibition interactions between reciprocally connected excitatory and inhibitory neurons[65,66]. The exact cellular mechanisms are likely variable, displaying region and task specificity. For instance, the rodent hippocampus expresses differentiable high-frequency and low-frequency gamma rhythms that are influenced by separate entorhinal pathways and contribute to spatial and object learning tasks, respectively[67]. Importantly, these relatively high-frequency oscillations are often modulated in occurrence and frequency by slower oscillations, as observed in the medial temporal networks in which gamma and theta are strongly coupled[68].

Focal and genetic generalized epilepsies have been associated with decreased gamma power during memory tasks and in response to sensory stimuli[69–71]. By contrast, Angelman syndrome (a genetic disorder with refractory seizures) can manifest increased long-range gamma coherence during sleep[72], and excessive gamma-band response to nerve stimulation is observed in childhood epilepsy related to focal cortical dysplasia[73]. Such studies assay gamma-band activity broadly, limiting mechanistic interpretation. In a rodent temporal lobe epilepsy model, careful examination has revealed selective impairment in fast gamma oscillations in the hippocampal stratum lacunosum moleculare and in the dentate gyrus, with abnormalities in theta–gamma coupling correlated with episodic memory performance[41,42]. These examples notwithstanding, derangements in gamma oscillations are less prominent than those of theta oscillations in well-studied rodent models[36–38,74].

### Alpha-mediated coherence

Alpha is a canonical oscillation of the human brain, easily identified by visual inspection of electroencephalographic (EEG) activity. These oscillations are implicated in cognitive processes including visuospatial attention and short-term memory[75–77]. Evidence also suggests that conscious perception may occur in discrete epochs of a duration comparable to the period of an alpha oscillation[78]. Neurons with sharp phase preferences to the local alpha oscillation have been found in the human brain[79], and although the mechanisms of alpha generation are not yet fully understood, it is hypothesized that alpha oscillations could reflect rhythmic cortical inhibition[80]. In keeping with this notion, higher power of alpha over the posterior brain regions is associated with lower large-scale BOLD signals[81].

Individuals with photosensitive genetic generalized epilepsy exhibit substantially higher alpha power compared with those with other types of epilepsy and control individuals, but these alpha epochs are not associated with the expected decrease in BOLD activity across large-scale networks, which might indicate a lack of functional inhibition. These abnormalities were present in the absence of interictal or ictal epileptic patterns and linked to increased resting state connectivity of thalamic-frontal networks[82,83]. Similar hyperconnectivity through alpha frequency bands has been identified in childhood absence epilepsy[84]. Patients with these types of epilepsy often exhibit impairments in executive control, raising the possibility that the lack of effective alpha-mediated inhibition on frontal networks could be a causal contributor.

### Beta-mediated and spindle-mediated coherence

Bursts of beta oscillations during wakefulness occur across frontal brain regions during working memory and motor planning[85,86]. There is also evidence that beta rhythms mediate synchronization among thalamus, hippocampus and prefrontal cortex to facilitate tasks with mnemonic demand[87]. Although abnormal beta oscillations are a feature of Parkinson disease[88], their role in epilepsy is less well defined. Enhanced frontocentral EEG connectivity in this band has been observed in photosensitive genetic generalized epilepsies, and increased sleep beta power is present in children with SeLECTs, but the functional correlates of these changes remain unknown[89,90].

During non-rapid eye movement (NREM) sleep, thalamocortical spindles emerge, oscillating at 10–20 Hz (ref. 91). Spindles, in concert with hippocampal SPW-Rs and the cortical slow oscillation, are prominently implicated in memory consolidation (the transformation of a labile encoded memory into a more stable, long-lasting representation)[92]. These oscillations are associated with sequential replay of neural firing, and their occurrence is positively correlated with long-term memory[93–95]. The coherent induction of spindles relative to the slow oscillation recruits phase-locked SPW-Rs and improves hippocampus-dependent memory, in keeping with a prominent role of these oscillations in facilitating multiregion communication[96]. Furthermore, the spatial coherence of spindles across cortical regions is variable, with the suggestion that spindles with a larger spatial extent are linked to increased mnemonic demand[97–99].

Reductions in spindle density have been observed across a range of epilepsy syndromes in children and adults, spanning absence epilepsy to medically refractory focal epilepsy[100–103]. The topographic distribution of these spindles may also be altered, with a tendency for deficits in spindle activity proximate to the seizure focus and expanded coherence in anatomically distant but functionally connected regions[102–105]. These changes are correlated with impaired metrics of overall cognitive and executive functions and have been more specifically linked to deficits in memory consolidation of a motor task[100–102,104,106]. Thus, spindles are oscillatory patterns with a strong mechanistic rationale for a role in memory that are commonly disrupted in epilepsy, suggesting capacity to serve as a biomarker for epilepsy-related cognitive impairment and even a therapeutic target.

### Delta-mediated coherence

Delta oscillations are characteristic of NREM sleep, with theoretical and empirical evidence suggesting a role in memory consolidation[92]. These sleep oscillations regulate the occurrence of higher frequency oscillations, including thalamocortical spindles and hippocampal SPW-Rs, which may facilitate integration of information into cortical networks[96,107]. Spectral power in the delta frequency band is often asymmetrically increased during sleep in patients with focal epilepsy, reflecting the location of the putative epileptogenic focus (tissue actively involved in seizure generation)[108–110]. However, this slow wave activity can display abnormalities in the expected features of physiological sleep homeostasis, suggesting a disruption of functional delta oscillations beyond the slowing that can occur related to disrupted white matter connectivity in lesional epilepsy. Such alterations have been linked with cognitive impairment[111]. Because artificial enhancement

of slow wave activity can improve memory (although studies show mixed efficacy)[112–114], the specific network mechanisms resulting in appearance of increased delta power are critical to functional outcome. Modulation approaches that boost slow oscillatory power in phase with ongoing brain activity are most consistently associated with positive cognitive effects[115], indicating high sensitivity to temporal coordination that could be dysregulated by high power epilepsy-related slow waves.

Localized delta activity can also occur during quiet wakefulness in animal models and non-epileptic human cortex, but in this case it may be related to inattentiveness, local sleep and a reflection of use-dependent changes in cortical activity[116–119]. Marked increases in delta power during the awake state are typically related to intracranial pathology and are commonly observed in epilepsy with and without underlying structural brain abnormality[120,121]. Models of post-traumatic epilepsy have revealed that the development of synaptic excitability is accompanied by an increase in slow oscillations that intrude into waking and REM sleep states[122,123], raising the possibility of a compensatory network mechanism to offset excessive neuronal activity. A temporal lobe epilepsy model also revealed enhanced power and coherence between hippocampal and cortical delta[124]. Higher power and coherence of waking delta activity are correlated with decreased indicators of executive function and slower cognitive processing in patients with temporal lobe epilepsy and can furthermore predict expedited deterioration of cognitive test scores in patients with Alzheimer disease and subclinical epileptiform activity[125–127]. Thus, physiological delta oscillations mediate brain state-dependent cognitive effects, whereas epilepsy enhances this activity across brain states in a manner that impairs network function. These findings highlight that changes in power or coherence of oscillatory activity must be taken in context of brain state to understand potential cognitive effects.

### Macroscale oscillatory coherence

Beyond frequency-specific inter-regional oscillatory coherence, macroscale functional networks have also been linked to cognitive functions. The existence of such networks is mostly supported by data derived from non-invasive measures of activity patterns that permit global brain monitoring. Functional network connectivity in these cases is identified by a correlation or covariance in time series activity patterns acquired using electrophysiological methods (typically EEG or magnetoencephalography) or functional MRI (fMRI), operating based on the notion that these relationships indicate joint participation in information processing[128]. Such analyses test for interdependence of activity across brain regions, but are agnostic to underlying mechanisms and directional flow of information. Weighted directionality can be added to these network interactions using statistical modelling or perturbation approaches in concert with knowledge of the structural features of the network[129]. Multiple analytic approaches exist to quantify functional and effective connectivity, without an established gold standard[130]. In some cases, the nature of the activity is identified. For instance, theta coherence is operational at this global scale, supporting functions including internal attention and working memory[131,132]. However, some approaches evaluate functional connectivity across all conventional EEG frequency bands (delta, theta, alpha, beta and gamma), obscuring specific mechanistic interpretation. The neural mechanisms responsible for the fluctuations in BOLD responses as assayed by fMRI are similarly difficult to ascertain, as BOLD exhibits a complex relationship with oscillatory neural activity. Higher LFP power on average is associated with increased BOLD signal, but discrete high power LFP events rather than ongoing oscillatory patterns may drive the majority of the assayed haemodynamic response[133,134]. Thus, although temporal correlation of neural activity appears to be a conserved phenomenon linked to brain function across network scales, it remains unclear to what extent the neural spiking and microcircuit mechanisms supporting local oscillatory coherence underlie the relationships across macroscale networks identified by these non-invasive approaches. However, advances in functional ultrasound have enabled observation of mesoscale brain haemodynamics, demonstrating a correlation with slow fluctuations (<0.3 Hz) in neural spiking and region-specific oscillations in higher frequency bands and suggesting an investigative approach by which these relationships could be clarified[135,136].

Evaluation of macroscale networks in patients with epilepsy can be hampered by patient heterogeneity and variation in methodological approaches. Despite these limitations, there is converging evidence for interictal dysregulation of functional coupling across these networks in epilepsy. Increased correlation is commonly observed between regions involved in generation of epileptic activity, with decreased connectivity and functional disconnection of the seizure onset zone across large-scale networks[137–139]. This disrupted network integration can be associated with neuropsychiatric abnormalities, such as impaired memory and executive function, as well as comorbid depression[140–142]. However, even when considering the most studied macroscale network, the default mode network, only in patients with temporal lobe epilepsy, variable findings are present across different studies[143,144]. These results suggest that observations of oscillatory/functional coherence in epilepsy, from local to macroscale networks, are likely sensitive to factors such as individual patient characteristics, time course of the epileptic process and analytic approaches. To establish causal relationships and move towards therapeutics, studies incorporating interventions that manipulate coherence of activity patterns and evaluate the outcome on brain function will be critical.

### A system of oscillations

Alterations in oscillations and their coherence in epilepsy have been documented across the physiological frequency spectrum. A unified interpretation of why these oscillatory changes arise in epilepsy, if one exists, is lacking. However, emerging theories based on physiological networks provide some grounds for speculation (Fig. 2c). In neocortex, alpha and beta oscillations are observed to be anticorrelated with gamma oscillations[145,146]. Some evidence suggests that these alpha and beta patterns are inhibitory, spatially constraining the gamma power to regions in which they are absent, thereby sculpting epochs of local gamma-mediated information processing[147]. Interestingly, alpha and beta power and coherence are often increased across cortical regions in generalized epilepsies, suggesting that this form of cortical hyperexcitability facilitates inhibitory oscillations[82,83,90]. Delta oscillations, which are associated with decreased neural spiking activity, are also usually enhanced in epilepsy[125]. By contrast, if mesial temporal theta and gamma oscillations are affected, they are typically diminished in some manner, decreasing organization of local neural spiking and its effectiveness in influencing other brain regions in the network. Together, these changes could shift the balance of oscillatory activity towards inhibitory control and dampen capacity for coherent excitation, obstructing the local computations and large-scale communication required for cognitive functions[36,71]. It is therefore possible that the expression of epileptiform activity engages network-level mechanisms that attempt to suppress these hyperexcitable and/or hypersynchronous patterns at the expense of efficient physiological information processing. A similar imbalance

in expression of low-frequency and high-frequency oscillations and their cross-frequency interactions has been suggested to underlie various neuropsychiatric conditions (thalamocortical dysrhythmia[148]). Some evidence of real-time normalization of these dynamics is observable in epileptic networks after resection of the putative epileptogenic focus[149]. Investigation of such hypotheses will require attention to epilepsy-related oscillatory dysregulation across the frequency spectrum and also across disease course.

## Neural spiking and population transients

Oscillatory coherence can be viewed as temporarily opening a valve in the pipes connecting groups of neurons, allowing content to flow in a discrete, regulated manner. Equally important is the content that is flowing, which in this case corresponds to packets of neural spiking. Deciphering the information encoded within these packets remains a major challenge in neuroscience, adding complexity to understanding how they may be dysregulated in epilepsy. Inroads into this issue have been accomplished by focusing on detectable population oscillatory transients that contain a high rate of neural spiking within a compressed temporal epoch. Although bursts of oscillatory cycles may occur at various higher frequencies[150], the best-characterized examples of such physiological transients include hippocampal SPW-Rs, cortical ripples and cortical spindles. Each of these activity patterns is strongly associated with learning and memory, with features that suggest that they participate in compressed transmission of spike content representing environmental experiences (Fig. 2d). Interictal epileptic networks are characterized by their ability to express pathological transients, including IEDs (epileptic sharp waves and spikes) and pathological high-frequency oscillations (HFOs). Thus, an examination of the interplay between these physiological and pathological transients in epilepsy can shed light onto additional mechanisms of network dysfunction that have implications for cognition.

### Hippocampal SPW-Rs and pathological HFOs

The spiking of hippocampal neurons is robustly increased and temporally coordinated during population events known as SPW-Rs, resulting in transiently enhanced excitability in downstream brain regions[151]. These events are characterized by large amplitude deflections in the extracellular field of hippocampal area CA1 stratum radiatum (the sharp wave; not to be conflated with epileptic sharp waves used in the description of human EEG), accompanied by a transient fast oscillation in the CA1 pyramidal layer (100–250 Hz; the ripple). The oscillatory nature of the event is hypothesized to counter its overall high excitatory gain and is generated by periodic, phase-regulated excitatory and inhibitory synaptic potentials[22,152]. The spike content of SPW-Rs is organized and sequential, and critically it consists of a temporally compressed version of firing patterns that occur during waking experience[153–155]. Targeted disruption of SPW-Rs during waking and sleep impairs memory[156,157]. Taken together, these features suggest that SPW-Rs transmit salient information encoded during experience to facilitate integration into long-term memory[158].

Hippocampal SPW-Rs are substantively affected by epilepsies that involve mesial temporal structures. In animal models of epilepsy, occurrence rates of events meeting strict criteria for physiological SPW-Rs are decreased and human hippocampal ripples are transiently suppressed by IEDs[159–161]. However, reductions in excitatory physiological hippocampal transients are accompanied by the appearance of pathological HFOs. These HFOs can manifest a higher oscillatory frequency (250–600 Hz) than SPW-Rs owing to desynchronized neural spiking that disproportionately contributes to the extracellular LFP signal[162,163]. Evidence suggests that pathological HFOs are generated when excitatory pyramidal cell activity is increased and inhibition is compromised[164–166]. Furthermore, pharmacological and surgical manipulations that decrease inhibition or alter spike recruitment can transform SPW-Rs into frank IEDs[167–170]. Thus, the cellular changes that accompany epilepsy may subvert the intrinsic ability of the hippocampus to generate excitatory population transients, diminishing expression of information-rich SPW-Rs and facilitating occurrence of HFOs/IEDs that transmit packets of disorganized neural spiking (Fig. 2e). In keeping with this notion, neurons with significant place coding that participate in pathological HFOs exhibit a decrease in spatial precision and interventions that reinstate neural firing selectivity during hippocampal population transients can improve memory in epileptic rodents[164,165].

### Cortical ripples and pathological HFOs

Neocortex also expresses transient oscillatory activity in and above the ripple frequency range. Cortical ripples (80–200 Hz) are associated with learning and memory processes[171–173], whereas ultrafast (400–600 Hz) oscillations are observed in somatosensory cortices in response to sensory stimuli[174,175]. Although the network mechanisms governing emergence of these events are less well understood than for their hippocampal counterparts, strong excitatory drive to a localized neural population and subsequent pyramidal cell–interneuron dynamics are likely involved[173–176]. Whether cortical ripples contain temporally compressed sequences of experience-relevant neural spiking akin to hippocampal SPW-Rs requires further investigation, but cell ensemble reactivation within packets of high-frequency LFP activity in parietal cortex supports this hypothesis[177].

Pathological HFOs are detected in epileptic cortical networks and have been associated with the seizure onset zone[178]. Whether similar mechanisms are responsible for generation of hippocampal and cortical pathological HFOs remains unclear, and the neural spiking content of cortical pathological HFOs is correspondingly obscure. However, undifferentiated cortical HFOs are linked to impaired memory in patients with epilepsy, suggesting that the emergence of pathological HFOs could disrupt the function of their physiological counterparts[179].

### Interictal epileptiform discharges

IEDs, as characterized on human EEG as 'sharp waves' (waveform duration 70–200 ms) or 'spikes' (waveform duration 20–70 ms), are characteristic, pathological population transients of epilepsy. The ubiquity of IEDs across patients with diverse epilepsy syndromes suggests that they represent a highly conserved network response to diverse molecular and cellular mechanisms that predispose to seizures. Manipulations that artificially induce IEDs have shed light onto their origin and network effects. Intracellular recordings from neurons that participate in IEDs generated by pharmacologically reducing inhibition in a focal area of brain tissue revealed the existence of large depolarization shifts that resulted in these neurons firing high-frequency trains of action potentials[180]. The strongly synchronous synaptic potentials produced by this concerted neural spiking are then implicated in origination of subsequent depolarization shifts[180,181]. The importance of incoming synaptic potentials to IED generation is also supported by experiments demonstrating that external sensory stimuli can drive IEDs in disinhibited cortex involved in processing the sensory signal[181]. Similarly, modulation of synaptic input parameters can transform SPW-Rs into hippocampal IEDs[167–170]. Taken together, these findings suggest that

IEDs could represent a corruption of the physiological capacity of a network to create population transients normally generated to facilitate information processing. However, the extracellular and neural spiking features of IEDs, even within a brain region, are not uniform. IEDs with variable source/sink configurations in the extracellular space have been identified in hippocampus, consistent with coexistence of different IED generators[182,183]. Degree and characteristics of neural spiking modulation associated with IEDs are heterogeneous across individual neurons, with a plethora of firing patterns identified[184]. There is also some indication that structured temporal sequences of neural spiking may be consistently recruited during epileptic activity patterns[185]. Akin to physiological population transients, IEDs therefore seem to be a manifestation of a complex interplay of neural subtypes and microcircuits rather than a uniform hypersynchronous discharge.

It is difficult to ascertain the information content of these pathological population transients, and even the cell types predominantly involved are likely to depend on the nature of the network in which they originate[186–190]. However, in vitro modelling using cell culture supports the notion that bursts of cell firing destroy stimulus-specific information previously presented to the network[191]. If IEDs in a region strongly recruit GABAergic neurons, the resultant large-scale inhibition could also adversely affect ongoing information processing[190]. In keeping with these potential disruptive effects on physiological network communication, occurrence of IEDs in brain regions mediating specific cognitive tasks is correlated with impaired task performance[192–195]. IEDs that can easily propagate through white matter structures and thereby quickly access broader neural populations may also have increased potency to degrade encoding of information[196]. Although IEDs are often most frequent within the seizure onset zone, those that occur outside this area are associated with increased risks of cognitive impairment, indicating a particular sensitivity of putatively more functional tissue to effects of IEDs[197]. IEDs are also observed with substantial prevalence in individuals with neuropsychiatric disorders other than epilepsy (such as attention deficit disorder and Alzheimer disease) and have similarly been linked to cognitive deficits in these cases, implying a conserved pathological neural circuit response to various insults[198–200].

### Temporal coordination of population transients

Although the occurrence of physiological and pathological population transients is therefore altered in epilepsy, these patterns also exert network effects that extend beyond immediate, local modulation. For instance, SPW-Rs result in strong excitatory gain that can depolarize target regions of the hippocampus and are associated with negative BOLD responses in many subcortical structures[201–203]. SPW-Rs also engage in temporal coupling with cortical oscillations (including the cortical slow oscillation, sleep spindles and cortical ripples) such that their oscillatory co-occurrence rate exceeds that predicted by chance[173,204,205]. SPW-Rs also preferentially occur at specific phase of slower oscillations[206,207]. These large-scale interactions are thought to coordinate the directional communication that is necessary for consolidation of information processed by the hippocampus into cortical circuits[158].

Pathological population transients, including IEDs and HFOs, can similarly engage in temporal oscillatory coupling (Fig. 2f). The occurrence of IEDs and HFOs during NREM sleep is biased by the phase of the slow oscillation[108,208,209], but these events are followed by hundreds of milliseconds of global decreased neural spiking[159,210] suggestive of a reset of the slow oscillation phase and a large-scale dampening of activity following a pathological transient. Recovery from this IED-mediated and HFO-mediated inhibition is strongly correlated with time-locked occurrence of sleep spindles outside the epileptic network[105,159,211,212], although locally spindles can be inhibited[103]. Spindles co-occurring with IEDs also displayed altered frequency and duration[212]. Thus, it appears that the network drive that initiates sleep oscillations may at times promote interictal epileptic activity, and in turn, pathological population transients can hijack physiological mechanisms involved in network communication. In keeping with this notion, manipulations that prevent coupling of IEDs and spindles can improve memory consolidation in a temporal lobe epilepsy model[213]. How these pathological oscillatory relationships disrupt cognition at a cellular level requires further investigation, but it is possible that they overwhelm the physiological information being transferred by inserting 'nonsense' information into the system. Reactivation of seizure-related neuronal activity patterns has been detected during sleep in patients with epilepsy, indicating that supraphysiological activity can indeed be 'integrated' into networks. It is possible that even though brief, the frequent, intermittent pathological activity of IEDs could similarly affect networks over extended periods of time.

### Cell-type-specific effects

Oscillations and population transients typically engage multiple cell types across brain regions, emphasizing that the interaction of diverse cellular activities is critical for intact cognitive performance. With the emergence of cell-type-specific manipulations, it has been possible to evaluate the effect of individual cell types on network dynamics and brain function. The degree to which any specific cell type can drive or derange these dynamics is likely variable, dependent on brain regions involved and task complexity. Some evidence suggests that dysregulation of the activity of specific cell types may be uniquely positioned to influence certain cognitive functions. In vitro studies revealed that epilepsy-induced abnormal bursting activity in a subset of dentate granule cells is associated with impaired pattern separation and a deficit in mnemonic discrimination[214]. Suppression of dentate gyrus mossy cell activity could similarly recapitulate the impaired spatial memory of epileptic mice, suggesting a key pathogenic role[215]. The unique vulnerability of certain cell types to epilepsy-related pathology could provide a means by which such cell-type-driven effects arise[216]. However, given the large-scale networks and multiple cell types involved in cognitive processes, it is expected that deficits in other regions and cell types could converge onto a similar behavioural presentation. Determining the necessity of a particular cell-type dysfunction for expression of an epilepsy-related cognitive deficit remains challenging, and it is possible that multiple cell types could be affected across brain regions. Across cell types, it has furthermore been found that cellular morphology and action potential kinetics extracted from resected tissue correlate with functional network integration features in patients with temporal lobe epilepsy[217]. Coordinated transcriptomic shifts in neurons of variable subtype, but likely belonging to the same circuit, have also been identified[218]. Such results suggest that capacity for cognitive performance and its impairment by pathological processes operate simultaneously at multiple scales, with interdependence of individual cellular and macroscale properties.

## Dynamics of dysfunction

The brain is evolutionarily equipped to undergo modification in response to extrinsic and intrinsic inputs. This plasticity can take several forms, including: (i) experience-dependent alterations in synaptic strength, as have been implicated in underlying learning and memory;

(ii) metaplasticity that shapes the subsequent effectiveness of inputs at engaging synaptic plasticity mechanisms; and (iii) homeostatic processes that act over time to counteract changes in activity level or synaptic strength[219–221]. Plasticity is particularly prevalent during neurodevelopment, where it is necessary to tune network sensitivity and establish capability for performing cognitive functions[222]. If ongoing interictal pathology in epilepsy can potently recruit plasticity processes, networks may be fundamentally altered, potentially irreversibly. How network dysfunction in epilepsy is expressed may therefore also change over time, complicating cross-sectional approaches to understanding mechanisms and development of therapeutics (Fig. 3).

Epileptiform discharges appear to engage intracellular pathways that result in long-term potentiation (LTP) and long-term depression (LTD) of synapses. At many glutamatergic synapses, temporal coincidence of glutamate release with postsynaptic depolarization leads to activation of NMDA receptors, which permits intracellular calcium influx and subsequent downstream signalling that result in functional and structural synaptic modifications[223]. In vitro models utilizing hippocampal slices demonstrated that NMDA receptors are similarly required for eliciting a seizure-prone state, although seizures themselves are independent of these receptors[224,225]. The epileptiform activity can also occlude (prevent induction) of LTP and favour induction of LTD, strengthening the notion that it mimics an LTP-like process[225]. In this manner, epileptiform activity patterns may gain access to engage a host of synaptic modifications, including plasticity of GABAergic synapses, the endocannabinoid system and astrocytes, all of which can profoundly affect the ability of the network to respond to experience-dependent stimuli with appropriate induction and/or consolidation of information[226–228].

The expression of synaptic plasticity furthermore determines how easily future inputs can engage the plasticity process, a phenomenon known as metaplasticity. In vitro, synapses that were exposed to epileptiform activity were later unable to express LTD[229]. Properties of hippocampal and lateral amygdala LTP, including magnitude, saturation and polarity, are altered when animals experience epileptiform activity as a result of kindling[230]. In a like vein, spatial learning sufficient to putatively engage long-term synaptic plasticity mechanisms can decrease subsequent generation of in vitro hippocampal LTP in normal animals, but enhance it in chronically epileptic animals[231]. These results suggest that epileptic activity patterns can affect the temporal integration processes that determine how synapses respond to salient incoming signals over time.

Homeostatic plasticity processes that normally keep neuronal activity near a predetermined set point to optimize sensitivity to inputs are also implicated in epilepsy. Because epileptiform patterns comprise excessive and/or hypersynchronous neuronal activity, homeostatic mechanisms should theoretically be engaged to reset physiological excitability levels and promote network stability. Such mechanisms may underpin observations of 'paradoxical' alterations in epilepsy that would be expected to reduce excitability rather than promote a seizure-prone state, such as loss of dendritic spines, increased potassium channel expression and upregulated GABA receptor subunits[232–235]. At the systems level, networks that receive frequent interictal epileptiform activity can downregulate responsiveness to these synaptic inputs, substantially modifying functional connectivity between brain regions[213]. Particular evidence for pathological homeostatic processes exists in the developing brain, where early life epileptiform activity can affect long-term cognitive capacity, even in the absence of ongoing seizures[236–238]. These deficits are paralleled by decreases in dendritic spine density and abnormalities of dendritic morphology[232,239,240]. Epileptiform activity that occurs in sensitive epochs for developmental plasticity can disrupt refinement of cortical circuits[241]. If this interference were to affect association cortices that mediate higher cognitive and social functions, vulnerability to both future seizures and executive, social and communication deficits could be engendered. Such hypotheses are under active investigation to understand the common association of paediatric epilepsy with other neuropsychiatric disorders, such as autism and attention deficit

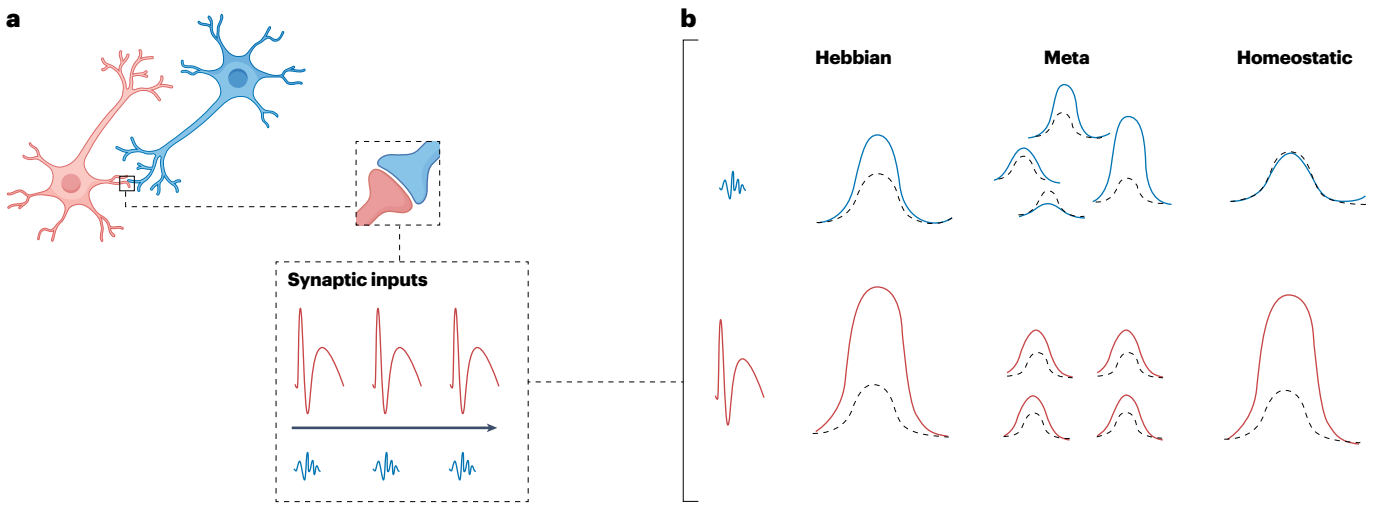


**Fig. 3 | Potential derangements of plasticity processes in epileptic networks.** **a**, Physiological (blue) or pathological (red) activity patterns can serve as repetitive synaptic inputs that engage different plasticity processes. **b**, Repeated association of presynaptic and postsynaptic responses, as could be mediated by coordination through physiological (blue) or pathological (red) population transients, leads to Hebbian synaptic plasticity (left). Metaplasticity results in variability of the plasticity response to the same incoming stimulus (middle). Homeostatic plasticity eventually returns the synaptic response close to a predetermined set point (right). Abnormal plasticity responses can occur with variable strength and polarity at each stage in epileptic networks, leading to chronic dysregulation of response to incoming signals. Dashed lines (black) indicate the baseline response before plasticity induction.

disorder[199,242]. Thus, it is possible that the network attempts to compensate for epileptiform activity by engaging intrinsic homeostatic mechanisms that decrease neuronal activation, but at the expense of capacity for future physiological plasticity[243].

The combination of these processes has the potential to drive a complex, activity-dependent trajectory of network dysfunction, with temporal characteristics that are determined by the balance of epileptic burden and compensatory plasticity. The anatomical localization of pathological activity can further affect this trajectory, with profound shifts in activity patterns when key 'hubs' of a network are involved. These hubs facilitate efficient long-distance connectivity and the formation of hierarchical modules for performing brain functions[244]. It is hypothesized that network pathology initially redirects information flow to hubs with high levels of connectivity to permit continued operations despite limitations in local processing, resulting in metrics indicative of more global processing. However, repeated use of this solution may overload the hub, causing its eventual failure. In this case, brain functions are affected and rerouting through other local connections may be attempted, leading to an enhancement of abnormal local processing with concomitant decreased large-scale processing[245]. Pathological neural hubs have been identified in epilepsy, with spatial scale involving local microcircuits and global networks[246–248]. Thus, network properties across scales, from capacity for in vitro plasticity induction to non-invasive measures of functional connectivity (such as fMRI or EEG), may be highly sensitive to the 'phase' of the epileptic network dysfunction. Biomarkers that robustly identify such phases would enable alignment of disease trajectories across individuals and facilitate understanding of generalizable network mechanisms in epilepsy. Importantly, systems-level therapeutics to address cognitive deficits should be attuned to the dynamics of network dysfunction, as approaches that improve brain function in a particular phase may be ineffective in other phases.

## Modulating networks to ameliorate dysfunction

A major goal of understanding network dysfunction in epilepsy is to open new avenues for treatment. Cognitive comorbidities of epilepsy have no dedicated clinical therapies, despite causing substantial decreases in quality of life[249]. Intrinsic compensatory network responses to the hyperexcitability associated with seizures and interictal activity patterns furthermore have the potential to impair capacity for information processing across global and local circuits over time, emphasizing the importance of identifying approaches that could function in a preventive manner as well as directly targeting active symptoms.

Optimally and simplistically, a treatment for epilepsy-associated cognitive impairment would address the root causative pathological mechanism at the most fundamental scale. For instance, if a genetic mutation results in seizures and cognitive disturbance, a genetic therapy that corrects the mutation would conceptually be the most effective treatment[250]. However, this type of approach is unfortunately often limited in real-world applicability for several reasons. In the vast majority of epilepsies, a specific cellular or molecular causative mechanism cannot be identified, or multiple mechanisms interact to produce the constellation of symptoms. A root cause may also be irreversible, such as a brain injury that leads to neural damage and/or loss. Even when a key mechanism is known, it may induce plasticity processes that chronically alter multiple facets of the network, rendering correction of the inciting mechanism insufficient to address the dysfunction[251–253]. Therapies capable of targeting cellular/molecular mechanisms can also require the introduction of viral vectors, stem cells or genetic material, raising restrictions related to safety and cost.

Attempts to modulate neural networks in a manner that addresses both seizures and cognitive comorbidity have been made using pharmacological and surgical approaches. Certain antiseizure medications can decrease interictal epileptiform activity, with potential improvement in IED-mediated functional impairment[254]. Because these agents primarily operate by dampening overall network excitability, they can concomitantly slow cognitive processing and even impair maturation of physiological circuits when administered in childhood[255,256]. Titrating antiseizure medications to resolution of IEDs is therefore clinically controversial and is typically used only in specific epilepsy syndromes (such as epileptic encephalopathy with spike-wave activation in sleep) where interictal burden is extremely high and cognitive deficits are profound[257] (Fig. 4a,b, left). For patients undergoing resective surgery for epilepsy, rates of seizure freedom may be improved when areas exhibiting a high occurrence rate of pathological population transients (such as IEDs and HFOs) or increased pathological functional connectivity are included in the resection[258,259]. The direct effects of using such metrics to influence surgical decision-making are difficult to evaluate, and the cognitive consequences remain unclear[260]. Surgical procedures are only clinically indicated in a subset of patients with epilepsy, and enlarging resection areas is often limited by proximity to eloquent cortex and risk of neurological morbidity[261] (Fig. 4a,b, right).

However, some evidence suggests that it may be possible to design effective therapeutics that instead directly target network-level phenomena that mediate cognition, bypassing the need to manipulate lower-level neural processes or resect tissue[262–264]. The rationale behind these approaches is that artificially bolstering the network 'infrastructure' required for physiological information processing would naturally recruit local cellular and/or molecular mechanisms that are currently inaccessible to direct manipulation (Fig. 4c). Support for the ability of network-level interventions to appropriately engage cellular and molecular mechanisms and affect cognition is most evident in animal models, in which application of spatiotemporally targeted electrical or optogenetic stimulation that boosts physiological oscillations recruits neural spiking relevant to behaviour and enhances memory[262–264]. Networks appear to be capable of responding to a broad range of artificial oscillatory frequencies, with functional impairments observed only when the paced frequency substantially differs from the spontaneous physiological frequency[265,266]. Preliminary efficacy of this type of intervention for improving cognition in normal subjects and psychiatric symptoms in patients with depression has also been demonstrated[267,268]. Task-specific memory modulation via electrical stimulation is also possible in patients with epilepsy, although the underlying mechanisms remain obscure[269–272]. In epileptic networks, approaches that shift patterns of neural spiking or manipulate firing of a cell-type-specific population (particularly interneurons) can abort seizures[273–276], providing support for the notion that network-level interventions may similarly be able to target interictal activity, including IEDs and pathological HFOs.

Because oscillatory coherence and emergent population transients contribute to network dysfunction in epilepsy, they are key targets for modulation. Non-invasive methodologies such as transcranial magnetic stimulation and sleep-based auditory stimulation have shown promise in altering oscillatory coherence in epilepsy[277,278] and invasive electrical stimulation can be leveraged to stimulate or suppress population transients[156,279,280]. At a more fundamental level, interneuron grafts have been proposed to correct local network hyperexcitability

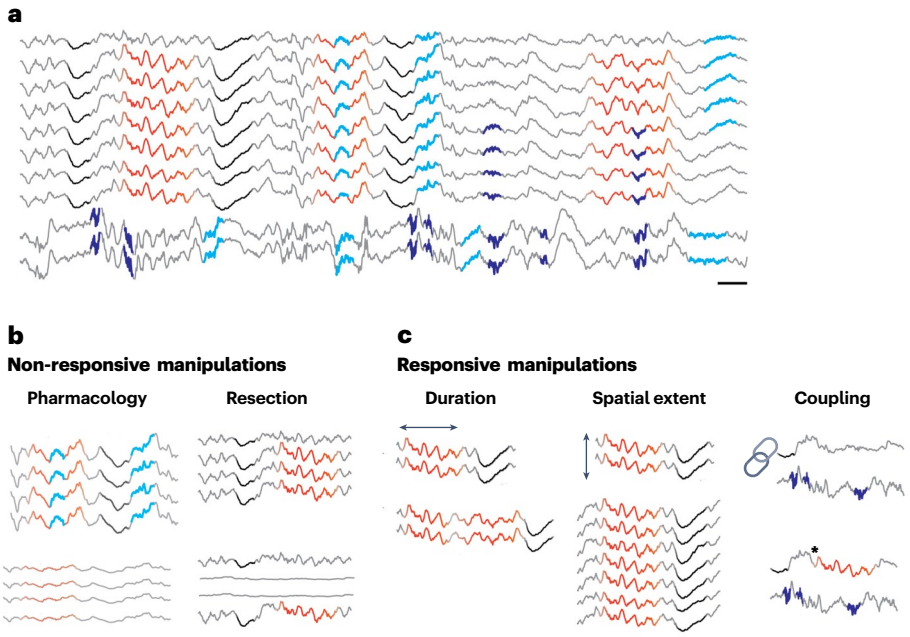


**Fig. 4 | Approaches to network-level interventions aimed at ameliorating cognitive dysfunction in epilepsy. a**, Sample local field potential traces demonstrating physiological variability in frequency (colours) and spatial extent of oscillations. Scale bar, 200 ms. **b**, Non-responsive manipulations are limited in their ability to effectively target cognitive dysfunction in epilepsy. Systemic administration of pharmacological agents (left) broadly affects physiological and epileptic networks without temporal specificity. Resection of tissue (right) can eliminate pathological activity, but can be limited in spatial extent and does not preserve potential physiological tissue function that may exist outside pathological epochs. **c**, Responsive manipulations can be used in a spatiotemporally specific manner to modify various properties of oscillations and population transients, including duration, spatial extent and temporal coupling.

and are currently undergoing phase I/II study in patients with refractory epilepsy[281]. Critically, network-level biomarkers can be conserved despite highly variable underlying epilepsy aetiologies, offering the possibility of treatments that could be more broadly applicable than those based on a single cellular or genetic cause. Modulation that occurs at a network level may also engage intrinsic plasticity processes at the cellular and/or molecular level that slowly decrease the likelihood of expressing pathological activity patterns and potentially decreasing the occurrence of network states that lead to seizures. Evidence for such effects is emerging for clinical responsive neurostimulation protocols currently used to reduce seizure occurrence in patients with refractory epilepsy[282].

Of course, network-level modifications come with their own challenges. A key issue is determining which network biomarkers are amenable to neuromodulation and whether the planned manipulation is capable of substantially improving brain function. For instance, early febrile seizures in an animal model result in alteration of oscillatory dynamics in the hippocampus, but although biologically plausible as a mechanism for hippocampus-dependent memory impairment, such issues were not identified in the animals[283]. Thus, it is critical to test proposed network-level interventions for a causal relationship with cognitive symptoms, identifying mechanistic links whenever possible. This step is particularly critical owing to the potential for competition between artificial stimulation and physiological oscillations, impairing cellular processes required for function[266]. It is also conceivable that chronic neuromodulation could engage plasticity processes that adversely affect different network processes in the long term, leading to unanticipated side effects. Longitudinal monitoring of network response and outcome measures are therefore necessary when considering feasibility and safety of such interventions. Additionally, most network-level interventions will require spatiotemporal specificity for optimized efficacy[284]. Current devices capable of responsive neuromodulation are limited by mechanical, signal processing and data management constraints[285]. For example, monitoring the large-scale neural networks involved in cognitive processes at a resolution sufficient to assess efficacy of modulation at the level of neurons will require materials innovations that increase the efficiency of miniaturized electrodes without compromising biocompatibility[285,286]. It is also likely that effective stimulation of neural networks will be best accomplished by arbitrary waveforms that more closely resemble physiological signals than the conventionally used square wave pulses, necessitating alternative circuit designs for stimulation components of neuromodulation devices[287]. Computational architectures, as well as power and data handling, will need to be optimized to enable the complex operations for accurate detection of dynamic brain signals within the physical constraints of an implanted device[288,289]. Thus, implementation of network-level monitoring and stimulation protocols capable of affecting cognition is likely to need next-generation devices that leverage novel materials and approaches to electronic circuit design[290].

## Conclusion

The shift to conceptualizing epilepsy as a network disorder is a key advance that has facilitated clinical diagnosis and treatment, as well as providing a framework for basic research. In this article, we provide a unifying perspective on how epilepsy results in dysfunction of physiological networks, suggesting convergent mechanisms by which cognitive impairment can arise in these patients. Brains capable of generating seizures tend to manifest convergent abnormalities in network activity: changes in (i) oscillatory coherence across the physiological frequency spectrum and (ii) capacity for transmission of population transients. These alterations, which can deviate from normality in either direction, disrupt the communication between neural populations required for information processing and thereby can potently interfere with cognitive functions, which rely on spatiotemporally precise interactions across regions. Critically, network dysfunction in epilepsy is dynamic, engaging a multitude of plasticity processes that may aim to stabilize one aspect of performance over

time (for example, decreasing likelihood of seizure) at the expense of another (for example, speed or accuracy of computation). Evaluation of interictal epileptic networks would therefore benefit from assessment across multiple spatial and temporal scales. Such assessments come with substantial potential benefit, as evidence is emerging that interventions which facilitate physiological neural communication can lead to improved cognitive function, even when the underlying root cause of the epileptic state is not known or cannot be directly modified. Novel experimental and analytic tools will facilitate large-scale monitoring of brain activity in concert with execution of cognitive tasks and ensure that identified network patterns are actively modulating behaviour. Fostering discovery of such network-level biomarkers will permit design of therapeutics that counteract characteristic patterns of dysfunction, offering opportunities to address the currently untreated cognitive comorbidities of epilepsy.

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**This study details conceptual and technical advances required to implement spatiotemporally targeted manipulation of neural networks involved in cognitive processes.**



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## Author contributions
J.N.G. and D.K. performed the literature review, discussed article content, and wrote and revised the manuscript.

## Competing interests
The authors declare no competing interests.

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