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CRITICAL REVIEW

Putative roles for homeostatic plasticity in epileptogenesis

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Abstract

Homeostatic plasticity allows neural circuits to maintain an average activity level while preserving the ability to learn new associations and efficiently transmit information. This dynamic process usually protects the brain from excessive activity, like seizures. However, in certain contexts, homeostatic plasticity might produce seizures, either in response to an acute provocation or more chronically as a driver of epileptogenesis. Here, we review three seizure conditions in which homeostatic plasticity likely plays an important role: acute drug withdrawal seizures, posttraumatic or disconnection epilepsy, and cyclic seizures. Identifying the homeostatic mechanisms active at different stages of development and in different circuits could allow better targeting of therapies, including determining when neuromodulation might be most effective, proposing ways to prevent epileptogenesis, and determining how to disrupt the cycle of recurring seizure clusters.

KEYWORDS

cyclic seizures, mechanisms of epileptogenesis, posttraumatic epilepsy

Why the brain experiences seizures in some situations is unknown. Epileptogenesis is the cryptic process by which brain regions become prone to seizures. Here, we explore one possible mechanism of epileptogenesis for localization-related epilepsy, specifically, maladaptive homeostatic plasticity. Homeostatic plasticity has been well described in the basic science literature, but its potential role in epileptogenesis and epilepsy therapy is underappreciated in the clinical world.

1 | HOMEOSTATIC PLASTICITY IN NORMAL PHYSIOLOGY

Homeostatic plasticity is a term first used by Gina Turrigiano and colleagues in the 1990s[1,2] to describe the cellular and circuit changes that maintain a certain level of neuronal activity averaged over time. The now classic experiments that introduced the concept of homeostatic plasticity were performed in neuronal cultures.[3] Cortical pyramidal neurons were bathed for 2 days in solutions that altered their activity, and the changes to neuronal excitability were measured over time. When neuronal activity was increased using bicuculline to inhibit γ-aminobutyric acid type A ($GABA_A$) receptors, miniature excitatory postsynaptic currents (mEPSCs; these are postsynaptic responses thought to be elicited by the presynaptic release of individual synaptic vesicles) slowly decreased in size such that postsynaptic neuronal firing rates eventually decreased to the same firing rates as before bicuculline was applied. Conversely, when neuronal activity was

suppressed using tetrodotoxin (TTX), mEPSCs slowly increased in size. Similar phenomena have been reported in vivo. For example, in the dark, neurons in the visual cortex fire only rarely; however, if visual deprivation is prolonged, the firing rates of these neurons slowly increase despite the continued lack of visual input.[4] There are, therefore, homeostatic mechanisms that keep neuronal activity near a set level; prolonged excitation is countered by a reduction in a neuron's sensitivity to inputs, whereas prolonged inhibition is countered by an increase in a neuron's sensitivity.

The need for such plasticity can be understood in the context of learning and information encoding. C. E. Shannon, in work to understand how to best encode information within a communication system, introduced the notion that the rate of information transmission is related to the variability, or entropy, in the encoded message. A simple demonstration of this is the transmission of a message within an electric circuit. If the message is encoded in such a way that the circuit is nearly always open (i.e., no current flowing), then the rate of information transfer is low. Similarly, if the circuit is nearly always closed (i.e., usually has current flowing), the rate of information transfer is also low.[5] These are low-entropy conditions in which the recipient of the signal has a good guess as to what state the circuit would be in at the next time point, because the state of the circuit rarely changes. The most efficient state for transmitting information is when the circuit can be either open or closed with equal probability; the recipient would be surprised by either state the circuit was in, so would be receiving information by either state all the time. Similarly, a neuron cannot efficiently process or transmit information if it is depolarized rarely or nearly continuously; in the absence of variation, the neuron would be contributing little meaningful information to its neuronal network.[6] Homeostatic plasticity could optimize the responses of a neuron to inputs, reducing a neuron's sensitivity to inputs when they are constantly firing and increasing its sensitivity when input action potentials are rare.

Homeostatic plasticity also plays a role in learning. D. O. Hebb postulated that information can be stored in synapses through a process that strengthens or weakens synapses based on correlated activity.[7] When presynaptic inputs are consistently correlated with postsynaptic activity, synapses between the inputs and the neuron are strengthened. For example, a neuron that responds to your grandmother's face is activated by her image, but her voice is also present when her face is seen, so the synapses from the auditory inputs that encode her voice are strengthened. This allows neurons to store correlations in inputs as changes in synaptic strength, and this kind of learning is called Hebbian plasticity. Long-term potentiation (LTP) is the best-studied process by which correlated activity affects synaptic strengths and is the quintessential example of Hebbian plasticity. Postsynaptic N-methyl-D-aspartate (NMDA) receptors act as coincidence detectors and play a central role in correlation-based strengthening of synapsis with LTP.[8] Hebbian plasticity therefore acts on a local scale to strengthen individual synapses in a way that encodes correlations in inputs, like the correlation between a person's face and voice. However, Hebbian plasticity has a potential fatal flaw; unchecked correlation-based potentiation would lead to a positive feedback loop and maximal strengthening of even weakly correlated inputs.[9–11] Homeostatic plasticity differs from Hebbian plasticity in changing neuronal responses based on the overall activity levels, regardless of the correlations of the inputs. For example, if a neuron is firing less than expected, a fraction of the inhibitory receptors everywhere on the neuron might be internalized, increasing the average activity of the neuron. Homeostatic plasticity is thought to limit the positive feedback loop that would destroy Hebbian learning, and if working properly, would maintain information in correlation-based synaptic weights.[12,13]

Key Points

- Homeostatic plasticity is the process of keeping brain activity levels within a useful range
- In certain situations, homeostatic plasticity might result in seizure activity developing
- Homeostatic plasticity might play a role in generating seizures in three situations: acute drug withdrawal seizures, posttraumatic or disconnection epilepsy, and cyclic seizures
- The time course of homeostatic plasticity could set the periodicity of cyclic seizures

2 | HOMEOSTATIC PLASTICITY IN EPILEPSY

Homeostatic plasticity can potentially contribute to epileptogenesis in multiple ways. In a recent review Lignani et al.[14] nicely laid out a model of how seizures could develop in an abnormal patch of cerebral cortex in which homeostatic mechanisms fail to maintain a physiological set point. They propose that the area in which homeostatic mechanisms fail could succumb to unregulated activity, becoming a seizure onset zone with propagation outward into normal tissue. In this model, gene therapies or novel medications are suggested as possible routes to boosting the homeostatic ability of the abnormal tissue to reestablish the activity set point.

Here, we review an additional mechanism by which homeostatic regulation could contribute to epileptogenesis, specifically that seizure activity can develop through normal homeostatic plasticity in an abnormal environment. Reduced activity in normal tissue, perhaps due to ischemic damage of inputs, disruption of incoming white matter tracts by tumors, or other causes, drives homeostatic mechanisms to increase local neuronal activity. In a study analogous to the original work of the Turrigiano group, Trasande and Ramirez showed that activity deprivation in hippocampal slices strengthens synaptic connections (synaptic scaling) and, through network changes, results in seizurelike activity.[15] That a mechanism thought to optimize cerebral function might instead produce seizures is, on its face, counterintuitive. Other modulators of seizure likelihood (e.g., hormone levels or state-dependent changes) are independent of the recent activity levels of the brain. However, homeostatic plasticity provides a rubric for predicting how seizure likelihood might depend on the brain's own recent activity history. Implementing the concept of a homeostatic set point could give us insight into the activity-dependent dynamics of seizures: why the recent history of brain activity can affect seizure likelihood, why seizures often come in cycles, and how seizure likelihood might be modulated exogenously.

The homeostatic changes that occur in the brain can be broadly classified as those that alter the intrinsic firing rate of neurons and those that change the pattern of neuronal connectivity. The mechanisms that alter firing rate are typically cell autonomous, for example increasing the effectiveness of excitatory receptors or reducing the effectiveness of inhibitory receptors, whereas changes in neuronal connectivity adjust activity through a network effect, for example, by increasing the number of connections from remaining inputs. Ultimately, the homeostatic mechanisms increase the excitability of the tissue, potentially making seizures more likely.

Although homeostatic plasticity might increase the activity level of quiescent tissue, by itself that should not trigger seizures. The drive to reach a physiological set point of activity should optimize for information processing rather than push the network into pathological bursting. However, the increased sensitivity in the neuronal population could prime the tissue to experience seizures under specific conditions. We examine two conditions in which homeostatic changes in firing rate could affect seizure risk: (1) the sudden reduction in global inhibition that occurs with alcohol withdrawal after chronic use and (2) the development of cyclicality in seizure likelihood through the action of two homeostatic mechanisms with opposite effects and different time courses. We then review the homeostatic changes in neuronal connectivity that result from traumatic brain injuries and predispose to posttraumatic epilepsy (PTE).

3 | ALCOHOL WITHDRAWAL SEIZURES AS PROTOTYPICAL HOMEOSTATIC SEIZURES

Seizures induced by alcohol withdrawal, like other types of GABA-agonist withdrawal (e.g., benzodiazepine or phenobarbital withdrawal), might be the prototypical seizures associated with homeostatic plasticity, and are an example of seizures that result from a sudden reduction in global inhibition.[16,17] Lovinger and Abrahao note that there has long been evidence for homeostatic changes in synaptic activity with chronic alcohol exposure, and that with acute alcohol withdrawal, "what is initially homeostatic may well become pathological."[17] Clinically, withdrawal seizures can develop in subjects who drink daily but then stop their alcohol intake abruptly. The mechanism by which seizures occur has been well studied. Ethanol acts both as an agonist of $GABA_A$ receptors[18,19] and as an antagonist of NMDA glutamate receptors.[20] The effect of daily drinking is therefore chronic inhibition of neural circuits in the brain. In line with the goal of preserving an average level of activity in a circuit, homeostatic mechanisms reduce the number of $GABA_A$ receptors[21] and increase the number of NMDA receptors.[22] This restores circuit activity to near baseline levels even in the presence of ethanol. However, abrupt withdrawal of alcohol then leaves the brain with less $GABA_A$ receptor activity and more NMDA receptors than at prealcohol baseline, so neural circuits become hyperactive and tend to produce a seizure.

Different homeostatic mechanisms likely govern changes in activity during the withdrawal period. Upon removal of alcohol's effect on $GABA_A$ and NMDA receptors, an excess of neural activity develops. This rebound in activity would drive homeostatic mechanisms to reduce neuronal firing, resulting in resolution of withdrawal symptoms. Particularly large excesses of neuronal activity, seizures for example, might encourage the recovery process by giving a large push to the homeostatic mechanisms, assuming the patient survives the acute withdrawal process.

A simple model of brain activity that incorporates homeostatic plasticity illustrates how prolonged alcohol intake can lead to withdrawal seizures (Figure 1). The model assumes cortical circuits have a set point activity level created by a balance of excitation and inhibition. During normal functioning, the activity level sits around the set point. With brief exposures to alcohol (Figure 1A), cortical activity is inhibited for a short time, allowing homeostatic plasticity to proceed only for that period, and no seizure occurs. With prolonged exposure, cortical activity is inhibited, and homeostatic mechanisms work over the full period of exposure, nearly completely reestablishing set-point activity

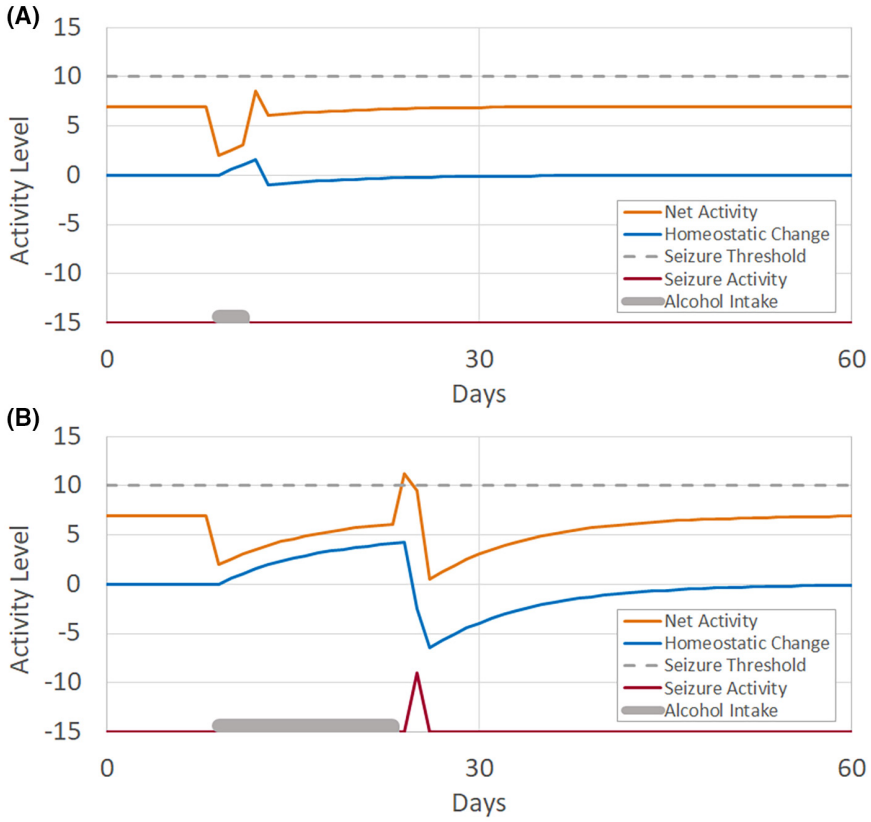

FIGURE 1 Alcohol withdrawal seizures as a result of homeostatic plasticity. In a model of alcohol withdrawal seizures, the endogenous excitatory and inhibitory tone (constants; not shown) sum to produce the net activity of the brain (orange line). Homeostatic plasticity (HP; blue line) works to maintain the net activity of the brain near its baseline and is produced by a fast inhibitory homeostatic mechanism (time constant $\tau_{inh} = .63$ days) that is active when brain activity is above a set point, and a slow excitatory homeostatic mechanism (time constant $\tau_{exc} = 8.8$ days) that is active when brain activity is below a set point. (A) With 2 days of alcohol intake, the slow excitatory homeostatic mechanism slightly increases the endogenous activity in an attempt to counterbalance the inhibition from alcohol. Once alcohol intake is stopped, there is a small rebound increase in the net brain activity, but it does not reach the seizure threshold (dashed line). (B) With prolonged alcohol intake of 2 weeks, the excitatory homeostatic mechanism has longer to act, so excitation has nearly matched the inhibition from alcohol exposure. When the alcohol is abruptly stopped, there is a sudden jump in net activity that now exceeds the seizure threshold, resulting in alcohol withdrawal seizures. The figures were produced by a model implemented in Microsoft Excel as a time series with time steps t. Net Activity(t) = Excitation$_{tonic}$ + Inhibition$_{tonic}$ + Inhibition$_{alcohol}(t)$ + Seizure(t) + HP(t), in which HP(t) = (Set Point − Net Activity$[t-1]$)/(τ); τ was either τ_{inh} or τ_{exc}, based on whether Net Activity$(t-1)$ was larger or smaller than the set point. Seizure activity was added if Net Activity$(t-1)$ exceeded a threshold. Model parameters were selected to illustrate the concept without reference to any measured physiological parameters.

even in the presence of alcohol (Figure 1B). After abrupt cessation of alcohol, the cortex becomes hyperexcitable and goes into a seizure. The combination of long-duration inhibition and a slow homeostatic mechanism causes the brain to experience seizures with chronic, but not acute, alcohol use and cessation.

4 | CYCLIC SEIZURES AS A MANIFESTATION OF HOMEOSTATIC PLASTICITY?

Cyclic seizures occur with a relatively fixed periodicity. Several seizure periodicities, including circadian and multidien, have been identified from seizure reports and chronic recordings in patients and animals with epilepsy.[23–26] Karoly et al.[27] reviewed these findings and suggested that seizures can be entrained to both exogenous and endogenous cyclic patterns. The mystery, however, is why such cyclic patterns would affect the activity of neural circuits. There is the suggestion that hormonal cycles change the sensitivity of ion channels over weeks[28,29] and that the increased oscillatory synchrony during certain stages of sleep promotes seizures,[30,31] but for many factors associated with seizure cycles, like the varying wake/sleep patterns with a 7-day work week or increased oscillatory activity in slow-wave sleep, the associations are only correlational and do not provide a

mechanism for changing seizure likelihood. Here, we propose that homeostatic processes could work in parallel with previously identified potential drivers to affect the cycling of seizure likelihood.

Rigorous theoretical treatments of electroencephalographic (EEG) dynamics suggest that the combination of oscillators, damping forces, and random fluctuations can describe many observed complex patterns.[32] In an oversimplification of these concepts, we consider how the cyclicality of seizures might be modeled by an oscillator, like a pendulum. The initial impetus is a deprivation of activity that triggers a slow homeostatic process of increasing the connectivity to or sensitivity of the deprived tissue, therefore augmenting activity within it. If this were a "damped oscillator," the activity in the system might initially overshoot the intended set point, then homeostasis would bring the sensitivity down again, and over a few cycles of overshoot and correction, the activity within the system would settle down at the intended set point. The behavior of the neural system likely differs from that of an ideal pendulum; with a pendulum, the force that brings it to the bottom point of its swing is the same on either side of the nadir, but the processes that regulate neural activity can be different depending on whether neural activity is below the set point or above the set point. In some cases, the neural system could even receive an extra "push" to restart the process; if, at the height of system sensitivity, the network crosses a seizure threshold (perhaps due to random fluctuations in activity or external stimuli), an extreme amount of activity would be generated by the seizure all at once. This would provide a strong signal to the system that the activity level must be brought down, and strong homeostatic regulation would be put in place. This would quickly suppress network activity, potentially halting a seizure cluster. In addition, however, the strong suppression of activity could again trigger the process of slowly increasing network sensitivity, beginning another seizure cycle (Figure 2).

If the time course of homeostatic plasticity determines the periodicity of cyclic seizures, then there must be multiple different homeostatic mechanisms, each with its own time course to account for the variety of periodicities. The first homeostatic mechanisms identified by Turrigiano and coworkers (described in the section "Homeostatic Plasticity in Normal Physiology") took days to have an effect (Table 1).[3] Subsequent theoretical studies, eventually experimentally validated, suggested that homeostatic mechanisms must also function over shorter time scales.[33,34] Table 1 shows examples of homeostatic mechanisms with a range of time scales (see reviews[11,33]). The basic building blocks for cyclic seizure dynamics therefore exist, but currently there is no direct evidence of a role for homeostatic plasticity in cycling.

Homeostatic mechanisms that regulate neuronal excitability have already been proposed to function with sleep–wake changes, and these processes could affect seizure likelihood. The Synaptic Homeostasis Hypothesis (SHH) for sleep[35,36] suggests that cortical excitability increases during wakefulness, and homeostatic synaptic downregulation occurs during sleep (reviewed in Cirelli and Tononi[37]). According to SHH, synaptic strength in cortex increases during wakefulness, perhaps in response to associative/Hebbian plasticity driven by experience.[38] During sleep, homeostatic downscaling of synaptic strength would then optimize the capacity for associative plasticity during wakefulness.[38] Homeostatic downregulation of synaptic strength has been reported during sleep in a range of animals, from the fruit fly[39] to fish[40] to mammals, including humans.[41] The circadian cyclicality of many seizures could be generated by this waxing and waning of synaptic strength. During regular sleep–wake cycles, SHH suggests that synaptic excitability, and by extension seizure likelihood, is greatest after periods of wakefulness, just at the onset of sleep. With sleep deprivation, cortical excitability increases even further,[41] potentially explaining the finding that sleep deprivation makes seizures more likely and longer sleep periods reduce seizure likelihood.[42] Importantly, the synaptic downscaling seems to happen primarily during slow-wave sleep,[43] so by the time rapid eye movement (REM) sleep develops after preceding rounds of non-REM sleep, cortical excitability would be reduced. This could explain the difference in seizure likelihood during the two types of sleep, with seizures occurring during non-REM sleep at a rate 50–90 times greater than during REM sleep.[44]

It is important to note, however, that the SHH model is not universally accepted.[45,46] It raises many questions yet to be answered, like why experience-dependent cortical plasticity proceeds during slow-wave sleep[47] and why some patients have seizures upon wakening. Similarly, in applying SHH to explain changes in seizure likelihood, we have oversimplified the sleep state-dependent changes in networks and activity patterns that might be intrinsically seizurogenic[30] or suppress seizures.[48] Nonetheless, the synaptic homeostasis hypothesis establishes a framework for testing the possible roles of homeostatic plasticity in regulating seizures with circadian rhythms.

In the ideal world, the role of homeostatic plasticity in cyclic seizures could be assessed by neurophysiological monitoring for a buildup of synaptic strength before a seizure. The early studies of homeostatic plasticity relied on whole-cell electrophysiology in isolated neurons or acute slices to measure synaptic strength[3,15]; unfortunately, this level of electrophysiology is not available in human subjects. Single- or multiunit measurements of neuronal firing rates might be useful in this context, but

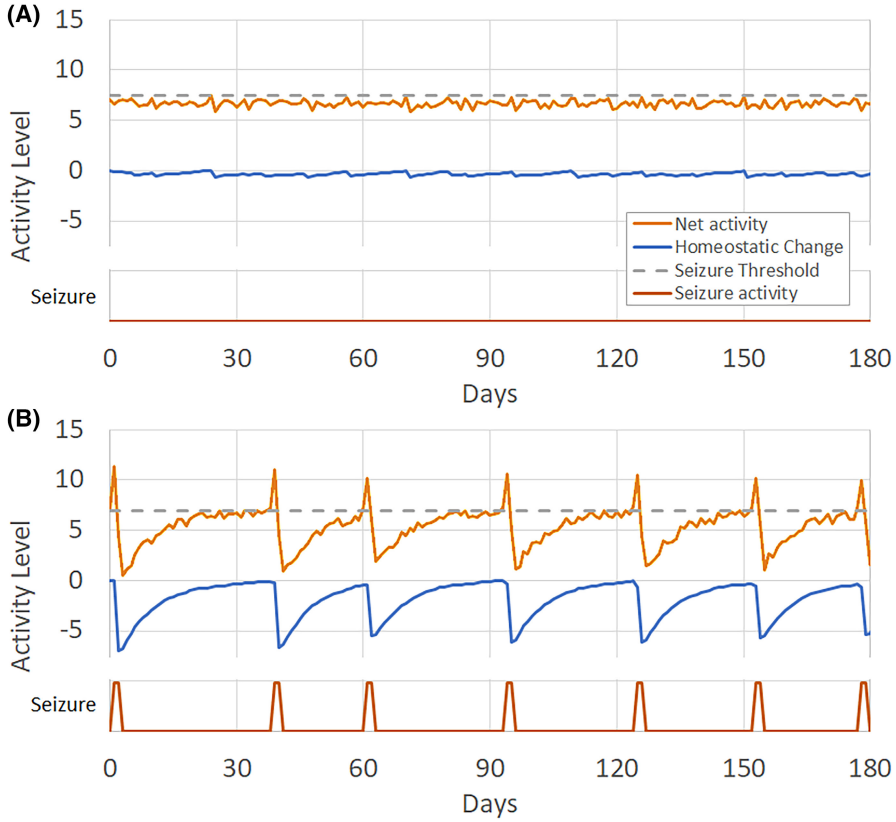

FIGURE 2 Cyclicality determined by homeostatic mechanisms. (A) Brain activity (orange) is kept around an average level through homeostatic mechanisms (blue), despite fluctuations driven by the environment, modeled here as random fluctuations in the activity. As long as the fluctuations are small enough, the net activity level does not cross the seizure threshold (dashed line). (B) If fluctuations are large enough to cross threshold, a seizure is generated (times of seizures are marked with the red line). The seizure activates a fast inhibitory homeostatic mechanism (sharp drop in the blue line) that suppresses the seizure, and once the seizure is over, brain activity is depressed compared to baseline. A slow excitatory homeostatic mechanism then starts to restore the activity to baseline, bringing it again near the seizure threshold. The time course of the slow homeostatic process determines the cyclicality of seizures. With the time course of the homeostatic mechanism modeled here, the seizures occur approximately every 30 days. If the time constant of the homeostatic process were smaller, the seizure cycle would be shorter. The same model as in Figure 1 was used to generate this figure, with the addition of a noise term to tonic excitation; the time constants, seizure threshold, and root mean square noise amplitude were tuned to achieve a monthly seizure frequency.

are only rarely available in Phase 2 intracranial studies, and are even less frequently present in the epileptogenic zone or for long enough durations to capture one or more seizure cycles.[49,50] Interictal EEG patterns might eventually provide a tool to assess the state of synaptic strength in a large region of brain, but at the moment it is not clear how changes in synaptic strength would manifest on an EEG. In some subjects with cyclic seizures, interictal epileptiform activity increases shortly before seizure onset and subsides as the seizure cluster does (see for example figure 2 in Karoly et al.[27]). However, interictal discharges measured on scalp EEG are indicators of relatively large cortical areas that are synchronously active[51] and likely underestimate the abnormal activity between seizures, and it is not clear that they can be used to estimate synaptic strength in a brain region. Theta power during wakefulness correlates with sleep propensity after sleep deprivation[52] and, along with larger amplitude slow waves in early stages of sleep, has been proposed as a marker of global increased synaptic strength.[36] Data for this proposal are limited and, to our knowledge, there has not been an examination of theta power changes near a seizure onset zone in relation to the timing of cyclic seizures. Thus, at the moment, there is not a clinical biomarker that can probe synaptic strength or follow seizure propensity.

5 | HOMEOSTATIC PLASTICITY OF FIRING RATES ALONE CANNOT OPTIMIZE CORTICAL FUNCTION

Homeostatic changes that adjust intrinsic neuronal firing rate alone, like the changes described with chronic alcohol use, will not necessarily lead to optimized brain function. John Beggs and coworkers first noted that changes to intrinsic neuronal properties could keep neuronal activity at

TABLE 1 Example putative mechanisms and time courses of homeostatic plasticity

Time course	Mechanism	Model system	Reference
5–10 min	Presynaptic vesicle pool size and release probability changes	Mouse cerebellum; measured after postsynaptic receptor blockade	34
~1 day	Engaging a disinhibitory microcircuit	Mouse visual cortex; measured after monocular visual deprivation	103
1–2 days	Scaling of quantal amplitudes	Cortical culture with chronic blockade of activity	3
<7 days	Downregulation of $GABA_A$ receptors	Chronic alcohol exposure in cultured rat hippocampal neurons	21
Days–weeks	Change in AMPA receptor subunit ratios (GLUR1/GLUR2)	Sensory cortical areas in the mouse brain; measured in response to dark rearing	104
Days–weeks	TNFα-dependent synaptic scaling	Mouse visual cortex; measured after monocular visual deprivation	102

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; $GABA_A$, γ-aminobutyric acid type A; GLUR, glutamate receptor; TNFα, tumor necrosis factor α.

a set point firing rate in ways that would not necessarily result in improved information processing.[12] This is particularly the case when a reduction of activity is due to loss of inputs. For example, a neuron that becomes isolated from all but one input could increase its responsiveness to that one input such that it fires an action potential every time the input neuron fires an action potential. This would result in two neurons with optimized firing rates, but there would be no new processing or emergent properties. Hsu et al.[12] suggested instead that homeostatic changes in neuronal connectivity are needed in addition to changes in intrinsic firing rates. Homeostatic processes that keep the connectivity pattern around a critical set point optimize information throughput and storage ability.[53–55] Modeling suggests that homeostatic adjustments of both neuronal connectivity and intrinsic neuronal firing rates are needed to prevent degradation of function.[12] Homeostatic changes in both neuronal connectivity and intrinsic firing rate have been studied in models of PTE, discussed in the next section.

6 | HOMEOSTATIC PLASTICITY IMPLICATED IN PTE

Focal abnormalities that reduce excitatory inputs within the cerebral cortex could result in seizures through homeostatic plasticity. The average activity of a neuron can be considered as the product of the rate of input activity and the size of response to a single input. With many inputs, as would be expected with normal connectivity, a neuron's response to each input can be small and still produce a reasonable amount of postsynaptic activity. When long-range excitatory inputs are reduced, however, homeostatic compensation would be needed to reestablish normal average postsynaptic activity. In the short term, this compensation could happen either by increasing responses to individual inputs or by increasing local connectivity. Hsu et al.[12] explored the parameter space of a computational model of a neuronal network that included both types of short-term homeostatic mechanisms as well as Hebbian plasticity. Surprisingly, they found that changes in local connectivity needed to be rapid to maintain stability in the network. Homeostatic changes in firing rates, by contrast, lagged. Because local connectivity is predicted to increase after deafferentation, activity in the partially deafferented patch would be more correlated across neurons and the seizure risk increased. As a corollary, each surviving long-range input would drive a larger population of neurons in the deprived cortex. If just a few inputs drive a large area of interconnected cortex, even small fluctuations of input activity might be amplified and also increase the likelihood of seizures.

Animal studies of PTE provide electrophysiological and modeling support for aspects of the homeostatic

plasticity model for the development of focal epilepsy. Work in the 2000s showed that partial deafferentation of cortical tissue can lead to paroxysmal electrical activity, including seizures, both acutely and weeks after the injury.[56,57] In computational studies, the Sejnowski group showed that a biologically plausible implementation of homeostatic plasticity could drive deafferented tissues to develop such paroxysmal, seizurelike activity.[58–60] Avramescu and Timofeev,[61] in a technically difficult set of follow-up experiments, measured the effectiveness of both excitatory and inhibitory inputs to a partially deafferented piece of cerebral cortex in vivo. Using in vivo paired intra- and extracellular recordings, they found that the deafferented cortical tissue was hyperexcitable, and that residual excitatory, but not inhibitory, inputs were more effective in modulating its activity. The changes in excitability did not happen immediately, with variations in properties seen over weeks. These studies outlined how homeostatic plasticity in the context of reduced inputs could increase the driving ability of the few remaining excitatory inputs and predispose brain tissue to experience seizures.

A large series of anatomical and electrophysiological experiments have explored the cellular and molecular changes that occur with PTE, most thoroughly in the cortical undercut model system of PTE (reviewed in Prince et al.[62]). The net effect of the observed changes is in line with the expectations of homeostatic regulation. Both upregulation of excitatory activity and downregulation of inhibitory activity have been found in tissue deprived of its normal inputs. Changes in the excitatory system include increased effectiveness of synaptic activity (homeostasis of intrinsic firing rate), as evidenced by increased release probability of glutamate at excitatory synapses[63] and an increase in the frequency of excitatory postsynaptic currents.[64] In addition, axonal sprouting was seen on layer V pyramidal neurons within undercut cortex, with the appearance of newly formed functional, and perhaps hyperexcitable, connections with nearby neurons.[65,66] This is consistent with the homeostatic drive to increase excitatory connections to and from surviving neurons when original inputs are damaged (Figure 3). Changes in the inhibitory system are complementary, with comparatively smaller inhibitory neurons and decreased density of contacts onto excitatory pyramidal cells seen after cortical deafferentation (Figure 3).[62,66–68]

One interesting related finding is that epileptogenesis after brain trauma seems to be prevented by local application of the sodium channel blocker TTX.[69,70] In an initial study, Graber and Prince applied TTX or control vehicle over rat cortical areas partially denervated by cortical undercutting, and then examined activity in slices 10–15 days later.[69] Epileptiform activity could be evoked in 58% of slices from control brains and in at least one slice from all 12 control rats tested. By comparison, epileptiform activity was evoked from only 6% of slices from the TTX-treated rats, and no epileptiform activity was seen in slices from nine of the 11 treated rats. In a follow-up study, the same authors reported that cortical activity blockade with TTX during the first 3 days after injury was needed to prevent the development of epileptiform activity.[70] They proposed that there was an activity-dependent process with a short time course that led to epilepsy after cortical injury. In the discussion of their modeling results (introduced at the beginning of this section), Hsu et al.[12] suggested that the fast activity-dependent process that leads to epilepsy is the homeostatic increase in local connectivity predicted

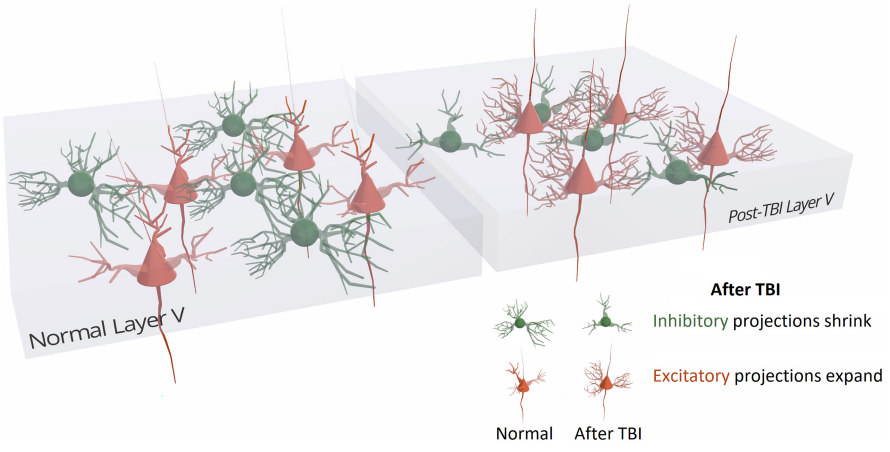

FIGURE 3 Homeostatic plasticity of local circuitry after partial cortical isolation. Under normal conditions, local connections allow efficient processing and transmission of information through neural circuits with a balance of inhibitory and excitatory connections. When inputs are reduced to an area by traumatic brain injury (TBI), the average activity decreases, followed by an arborization of excitatory connections (orange: pyramidal cells in Layer V of neocortex) and a shrinkage of the inhibitory (green) dendritic tree.[62,66–68] These changes increase the local excitation and reduce the local inhibition, compensating for the loss of excitatory inputs from the long-range connections.

to occur in the hours to days after deafferentation. They then suggested that activity blockade by TTX might delay connectivity changes long enough for mechanisms that mediate firing rate homeostasis to play out, eliminating the drive for changes in connectivity and preventing the development of an epileptic circuit.

7 | DO DEVELOPMENTAL CHANGES IN HOMEOSTATIC PLASTICITY ACCOUNT FOR SOME OF THE DIFFERENCES BETWEEN ADULT AND CHILDHOOD EPILEPSIES?

The extent and location of homeostatic plasticity seems to depend on age in mammals. Plasticity of both synaptic connectivity and synaptic scaling has been described in multiple species. The classic physiological experiments of Hubel and Wiesel first demonstrated increased activity-dependent plasticity early in the course of mammalian visual system development; these developmental windows came to be known as critical periods or sensitive periods.[71,72] Anatomical studies suggested that changes in synaptic connectivity likely underlie the activity-dependent changes; thalamocortical axonal arbors could change rapidly in response to sensory deprivation only during developmentally critical periods.[73,74] These activity-dependent changes in thalamocortical arbors can be interpreted as either Hebbian plasticity (in which active connections from nondeprived inputs are strengthened if the postsynaptic neurons are even slightly driven by the nondeprived eye) or homeostatic plasticity (in which the postsynaptic cortical neurons are deprived of activity, so upregulate their inputs from active inputs). Homeostatic synaptic scaling also varies by neocortical layer and age. Early in development synaptic scaling is present in the thalamocortical input Layer 4, but is lost there at the end of the critical period.[75] However, synaptic scaling persists in Layers 2–3 into adulthood, albeit likely with a different mechanism.[76] The net effect of these developmental changes is that homeostatic plasticity is more extensive early in life than during adulthood.

Traumatic brain injuries can cause epilepsy in both children and adults, with some evidence for a higher risk for PTE in patients older than 15 years (when compared to younger patients with similar traumatic brain injury severity).[77] Studies in an animal model also found a dependence on age for the risk of PTE; older cats in which a cortical area was partially deafferented were more likely to develop chronic seizures than were younger cats that underwent the same procedure.[56,78] These authors proposed that homeostatic mechanisms were able to restore cortical excitability to a normal level in young animals but not in old animals.[78] This group then explored a computational model of PTE in which both synaptic scaling and axonal sprouting varied with age.[79] Their simulations suggested that the more capacity for axonal sprouting and synaptic scaling, the less likely seizures would occur. The more extensive homeostatic plasticity seen in young mammals might therefore protect the young brain from developing PTE, potentially explaining the lower PTE risk in children younger than 15 years compared to those older.

More speculatively, it is possible that developmental changes in homeostatic plasticity (along with other brain maturation processes like myelination, interneuron development, hormonal changes, and changes in Hebbian mechanisms at the end of the developmentally critical period) might play a role in limiting certain epilepsies to specific ages. Landau–Kleffner syndrome (LKS), for example, reveals itself near the peak of the developmentally critical period for language development and disrupts comprehension (reviewed in Issa[80]). For some reason, however, seizures in continuous spikes and waves during slow-wave sleep (CSWS) tend to resolve by the early teens. If fluctuations in seizure propensity are driven by homeostatic plasticity at the thalamocortical input site, the developmental loss in homeostatic plasticity could contribute to the cessation of seizures in LKS and other CSWS syndromes.

8 | ASSESSING THE ROLE OF POTENTIAL MECHANISMS OF HOMEOSTATIC PLASTICITY IN EPILEPSY

Possible homeostatic mechanisms after seizures have been proposed based on animal model systems of epilepsy.[14,15] One example comes from the work of Khan et al.,[81] who found that enhancer of zeste homolog 2 (EZH2) was upregulated in mouse hippocampal neurons immediately after a bout of status epilepticus, during the latent period in which seizures are unlikely. EZH2 is a histone methylase important for regulating gene expression. EZH2 expression peaked 2–5 days after the first bout of kainic acid-induced status epilepticus and fell to baseline levels within 20–30 days. They then showed that inhibiting EZH2 function increases the spontaneous seizure burden after status epilepticus, suggesting that EZH2 normally regulates a pathway that is turned on after seizures and that reduces seizure likelihood for a limited period.

EZH2 meets many of the criteria for a homeostatic mechanism; it is induced by large changes in activity, it acts to keep the activity profile at near-normal levels, and it has a limited time course. However, it has only been

shown to function once, after the initial episode of status epilepticus, which is an extreme condition, and in the transition from acute seizures to epilepsy. That EZH2 reduces seizure likelihood in the latent period is significant whether or not it is part of a homeostatic mechanism, but it serves as an example of what is needed to validate a homeostatic mechanism. To prove it is a normal homeostatic mechanism, it would need to be shown that EZH2—or another similar candidate protein—can be regulated in a graded fashion in response to moderate changes in activity, that it helps keep the neuronal circuits in an activity range where information transfer and Hebbian plasticity are near optimal, and that it functions even when tissue is not becoming epileptogenic.

9 | THERAPEUTIC IMPLICATIONS

Although the role of maladaptive homeostatic plasticity in epileptogenicity is speculative, clinical experience is consistent with its proposed role, and clinical studies in humans could provide data to support or refute its putative role. For example, hypometabolism (as identified on interictal positron emission tomography [PET] scans) is a well-described interictal feature of epileptogenic tissue. Historically, it has been suggested that epileptic tissue is damaged, and that damage results in hypometabolism.[82] If instead epileptic tissue is functionally normal but is deprived of activity in the interictal period, it would appear hypometabolic. Focal interictal hypometabolism is therefore consistent with both the "damaged tissue" model and the "deprivation-induced homeostatic plasticity" model of epileptogenicity. If the "deprivation-induced homeostatic plasticity" model is correct, it would predict that the metabolic activity within epileptogenic tissue fluctuates with the periodicity of cyclic seizures. Long after a seizure, as excitatory homeostatic mechanisms ramp up, the tissue would be predicted to take on a more normal level of metabolism. This might be testable by asking whether the localizing ability of interictal fluorodeoxyglucose PET scans is best in the week after a seizure cluster and worst in the week before a seizure cluster.

Immediately after a seizure, by contrast, homeostatic mechanisms are predicted to suppress activity around the seizure onset zone, possibly by increasing local inhibition. Studies in rodents undergoing repeated seizures showed an upregulation of hippocampal benzodiazepine receptor density within 24 h of the seizures,[83] and that the density of receptors normalized by 28 days.[84] Flumazenil PET (FMZ-PET), which identifies surface $GABA_A$ receptors, has been used in humans to look for similar changes in benzodiazepine binding at different times relative to seizure activity. In a small number of patients who had repeated FMZ-PET scans, Bouvard et al.[85] found that only the PET scan a few days after a seizure localized the seizure onset zone. Counterintuitively, the improved localizing ability of FMZ-PET at short postictal periods was associated with less, rather than more, FMZ-PET signal at the ictal onset zone. The authors speculated that the decrease in FMZ binding could be related to increased binding of endogenous ligand to the receptors, but it is also likely that $GABA_A$ receptors are not upregulated after a seizure in all locations or all species.[85]

If increased input activity to epileptogenic tissue is what is needed to reduce the likelihood of seizures, it could be possible to modulate seizure probability by providing exogenous electrical stimulation. Neuromodulatory devices like the vagus nerve stimulator, responsive neural stimulator (RNS), and deep brain stimulator could function, in part, by engaging homeostatic plasticity. Each device likely works on two different time courses. Electrical stimulation during a seizure near the seizure onset zone has been shown to sometimes abort seizurelike activity.[86,87] This seizure-terminating effect could potentially occur by blocking information flow through the seizure network necessary for seizure generation,[88] by local suppression of cortical activity,[89] by disrupting corticothalamocortical loops central to some types of seizures,[90,91] by desynchronizing epileptic networks at the time of seizure spread,[92] or by an as of yet undefined mechanism. Although the disruption of seizures as they start was the first mechanism proposed for the RNS device,[93] it is now clear that it is not the only—and perhaps not even the primary—way that the device reduces seizure frequency.[94] All three devices give many more stimulations in a day than a patient has seizures, and seizure frequency decreases over years.[94,95] The ultimate effect on seizures is likely a combination of acutely aborting seizures when they start and reducing the likelihood of seizures starting. It has long been known that electrical stimulation of brain tissue can induce changes in protein expression and in circuitry (reviewed in Duman and Vaidya[96]). For example, electroconvulsive therapy increases the expression of brain-derived neurotrophic factor and its receptor TrkB,[97,98] fibroblast growth factors,[99] and vascular endothelial growth factor, which in turn can induce hippocampal cell proliferation.[100] The reduced likelihood of seizure onset would be expected if homeostatic mechanisms were engaged by electrical stimulation.[12,13,101]

An alternate approach to reducing seizure frequency could be to inhibit the sensitizing (slow excitatory) phase of homeostatic plasticity. Independent mechanisms have been shown to decrease neuronal sensitivity in response to overactive circuits and to increase neuronal sensitivity in response to activity deprivation (see Table 1 for examples). Because the sensitizing phase of homeostatic

plasticity is expected to increase seizure likelihood, inhibiting this pathway could prevent seizures without changing the activity levels in normal tissue. Although several mechanisms of sensitization have been identified in vitro and in in vivo model systems,[3,21,34,102–104] it is not yet clear which, if any, is applicable to epilepsy or is general enough to be targeted pharmacologically.

10 | CONCLUSIONS

Homeostatic plasticity encompasses a set of mechanisms that modulate neuronal activity based on recent history. Normal functioning of these mechanisms in normal brain tissue optimizes information processing and learning, and by keeping activity levels in a narrow range they likely help prevent seizure activity. But disruption of normal connectivity or rapid changes in activity levels increase the risk of seizure activity, in part because homeostatic mechanisms fail to restrict neuronal activity to a limited range. Homeostatic plasticity does not have to be invoked to explain every type of seizure, nor is it even the primary driver of epileptogenicity in epilepsy types, like PTE, where it has been proposed to play a role. However, incorporating the concept of a regulatory mechanism that depends on recent activity into our understanding of seizure propensity might allow different treatment approaches. Prince et al.[62] emphasized that, even for one type of epilepsy (PTE) there are a multitude of pathological processes potentially at play, "making it unlikely that an intervention focused on any one of them, in isolation, will emerge as a prophylactic 'silver bullet.'" It might be possible, however, to engage many of the inherent homeostatic mechanisms to stabilize neuronal excitability through exogenously delivered activity; devices like the RNS or deep brain stimulator might be acting this way. Finally, exploration of potential emergent properties of models of homeostatic plasticity might further our understanding of the dynamics of seizures in our refractory patients.

AUTHOR CONTRIBUTIONS

All authors contributed to writing this critical review. Naoum P. Issa was project lead. Katherine C. Nunn contributed to literature review and writing. Shasha Wu, Hiba A. Haider, and James X. Tao contributed to writing sections.

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CONFLICT OF INTEREST

The authors have no relevant conflicts of interest.

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