Trends in Neurosciences

CellPress OPEN ACCESS

Opinion

The selfish network: how the brain preserves behavioral function through shifts in neuronal network state

Albrecht Stroh [1,2,*] Susann Schweiger, [1,3,4] Jan-Marino Ramirez, [5] and Oliver Tüscher [1,4,6,*]

Neuronal networks possess the ability to regulate their activity states in response to disruptions. How and when neuronal networks turn from physiological into pathological states, leading to the manifestation of neuropsychiatric disorders, remains largely unknown. Here, we propose that neuronal networks intrinsically maintain network stability even at the cost of neuronal loss. Despite the new stable state being potentially maladaptive, neural networks may not reverse back to states associated with better long-term outcomes. These maladaptive states are often associated with hyperactive neurons, marking the starting point for activity-dependent neurodegeneration. Transitions between network states may occur rapidly, and in discrete steps rather than continuously, particularly in neurodegenerative disorders. The self-stabilizing, metastable, and noncontinuous characteristics of these network states can be mathematically described as attractors. Maladaptive attractors may represent a distinct pathophysiological entity that could serve as a target for new therapies and for fostering resilience.

Highlights

Early shifts in network activity constitute an important first step in the transition from a healthy towards a disease state.

These network states are often characterized by neuronal hyperactivity – putatively the start of activity-induced neurodegeneration – and are associated with subtle, yet discernable, behavioral dysregulations.

Local network changes can also occur in regions and brain circuits that are not associated with the clinical symptoms of later-stage disease.

It can be argued that from the viewpoint of the neural network, early changes in network activity are not necessarily governed by the aim of preserving long-term functionality, but rather by the attempt to achieve a state that is temporarily stable (a notion we refer to as the selfish network).

Early neural network state transitions follow attractor-like dynamics and may represent a distinct entity that could be leveraged for new therapies and for fostering resilience.

The concept of a selfish network

Many neurological diseases can be diagnosed long before the onset of apparent phenotypic changes [1–4]. This is paralleled by advances in neuroimaging [5–7] and neurophysiology [8–10], enabling the identification of subtle changes in the spatiotemporal dynamics of neural network function in animal models and humans [11–16]. These technological advances revealed that many neurological diseases manifest at the network level long before they become detectable by their disease-defining phenotypic changes [17–21]. This leads to the important question of when do the well-known fundamental homeostatic mechanisms of neural network regulation become maladaptive. Here, we propose that early shifts in network activity constitute an important first step in the transition from a healthy towards a disease state. Importantly, from the viewpoint of the neural network, early changes in network activity are not necessarily governed by the aim to preserve long-term functionality, but primarily by the attempt to achieve a state that is temporarily stable. The proposed term of a **selfish network** (see Glossary) reflects this perspective, which stands in sharp contrast to a teleological view: that is, that the network aims to assume a state that is optimized for maximal long-term protection of the organism in order to achieve behavioral functionality. The selfish network concept shares similarities with the selfish gene concept [22], which also provided inspiration for the term. In both entities, the fate of the individual carrier (of the network, or of the gene) is not seen as the primary driving force. Selfish genes do not prioritize the long-term survival of the given species, and **selfish networks** do not prioritize the long-term survival of its neurons. Rather, selfish networks aim for short-term stability, selfish genes for short-term transmission to the next generation, and, in that, both behave short-sightedly.

[1]Leibniz Institute for Resilience Research, Mainz, Germany
[2]Institute of Pathophysiology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany
[3]Institute of Human Genetics, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany
[4]Institute of Molecular Biology (IMB), Mainz, Germany
[5]Center for Integrative Brain Research at the Seattle Children's Research Institute, University of Washington, Seattle, USA

[6]Department of Psychiatry and Psychotherapy, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany

*Correspondence:
albrecht.stroh@lir-mainz.de (A. Stroh) and oliver.tuescher@lir-mainz.de (O. Tüscher).

There is mounting evidence for an early emergence of neuronal **hyperactivity** associated with subtle, yet discernable, behavioral dysregulations [23–25]. Local network changes can also occur in regions and brain circuits that are not associated with the clinical symptoms of later-stage disease [26]. We hypothesize that an initial and local maladaptive state driven by the principle of the selfish network can quickly impact and be impacted by other selfish networks that may face similar challenges. This principle makes the boundaries of maladaptive networks spatio-temporally dynamic. Altered network activities can occur outside of the initial molecular pathophysiological insult [27], in a functionally bound brain. As these interactions cascade, the organism is forced to homeostatically maintain functionality. However, once certain tipping points are reached, behavioral functions rapidly decline and severe (sub)clinical phenotypes emerge. We propose that these early **network states** are, in principle, receptive for therapeutic interventions, and occur at all neuronal network spatial scales as they are tightly interconnected [28–30]. To describe the dynamic trajectories of neural network function, **dynamical systems theory** offers opportunities to formulize these sets of stable network states as **attractors**. In the following, we discuss the growing body of evidence supporting this concept and we will describe specific examples to illustrate the impact of the selfish network on disease development and progression.

Increased interindividual phenotypic variability is a consequence of interindividually varying responses of the network to early challenges

Early changes in the activity of networks may mark an important first stage in the transition to chronic neuropsychiatric diseases. As discussed in more detail in later sections, disease states or disease-associated genetic mutations often result in increased inter-individual variability in network characteristics. This heightened variability seems to be a general hallmark of neuronal networks that cope with internal perturbations (Figure 1 green line and insert). In principle, each network can have multiple solutions for coping with local network challenges. **Allostatic** network compensations are characterized by distinct, interindividually differing states, both on the level of the neuronal network (Figure 1 green line and insert; with network compensation phase staring at T1), and on its phenotypic representation (Figure 1 blue line and insert).

The neuronal network controlling breathing offers a good example to illustrate this phenomenon. The network known as the preBötzinger complex (preBötC) [31] serves the specific behavioral function of generating an evenly, clock-like neural rhythm that underlies breathing. This neuronal network is anatomically and physiologically well defined. Located in the ventrolateral medulla, the preBötC continues to generate regular respiratory activity even when experimentally isolated [31–33]. Yet, the respiratory network is vulnerable to metabolic or genetic challenges that can lead to breathing disturbances associated with various disorders. A major driver of respiratory activity is the endogenously released peptide substance P. Genetically knocking out the enzyme (PPT-A) that is required for the production of this excitatory neuropeptide leads to an increased intraindividual variability of respiratory activity [34]. The neuromodulatory state of the respiratory network is also altered in Rett syndrome [35–37]. In an animal model of this neurological disorder, dramatic changes in the regularity and frequency of the respiratory rhythm are manifested at the level of the respiratory network weeks before the appearance of any breathing abnormalities at the organismic level [35].

However, for most other behaviors and neuronal functions it is difficult to temporarily relate changes at the network level with those at the organismic level. This complexity is illustrated in Rett syndrome, in domains other than the respiratory system. In this disorder, the degree of slowing of the background EEG in the delta and theta power and the characteristics of evoked potentials can reliably be related to the disease progression and symptoms severity [38–40]. These EEG changes are likely caused by changes at the network level [41–43] and the first effects

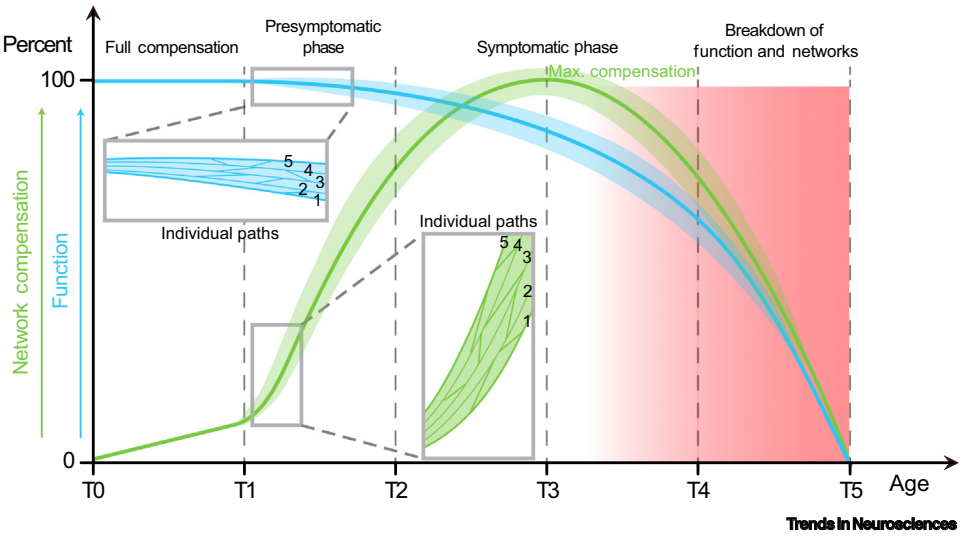


Figure 1. Early increases in interindividual variability of phenotypes in the presymptomatic phase of neurodegenerative disorders may be due to the individual trajectories of network compensation. The schematic illustrates an archetypical progression through disease stages, and the underlying trajectories of network function as well as network compensatory mechanisms. Between T0 and T1 the network is able to fully compensate for the effects of the increasing disease burden; that is, remains within homeostatic boundaries. Between T1 and T3 the disease burden exceeds the homeostatic compensatory ability of the network, leading to early subtle behavioral signs while the network finds temporally dynamic, metastable state solutions differing between individuals. At later stages, particularly at T3, the advanced neuronal cell loss, especially of critical nodes, leading to network sparsification, reduces the degrees of freedom of the network to compensate. This leads to an accelerating decline in function and network compensation, resulting in a common final path of rapid functional deterioration with little interindividual variability.

may be seen as early as when network connectivity is first established by immature neurons [44]. Direct comparisons between network-level changes and changes at the level of the EEG are complicated by a pronounced interindividual variability, but also by temporally dynamic intraindividual variability [45], which is not only seen in Rett Syndrome but also other neuropsychiatric disorders including schizophrenia [46]. In epilepsy, the complex interrelation of local and global shift of excitability can also be perceived as an increase of variability [47–49].

Increased intraindividual, longitudinal variability of neural network structures as well as of cognitive functioning in presymptomatic and early disease states has also been described for Alzheimer's disease (AD) [50–52]. Similarly, in Huntington's disease (HD), increased variability of neural and behavioral/cognitive functioning in the presymptomatic and prodromal phase has been extensively documented [53]. Of note, a certain amount of neural and behavioral variability in itself is physiologic and has been argued to be a prerequisite for neural and behavioral adaption [54,55]. Heightened variability of neural and behavioral functioning, however, may constitute an important marker and hallmark of early network changes long before phenotypic changes become measurable at the organismic level (see Outstanding questions).

Thus, we propose that the appearance of deficits in molecular/cellular and neuronal network functions long before the onset of any observable clinical phenotype seems to be a general principle of disease progression. We hypothesize that the appearance of cellular/molecular deficits in different parts of the nervous system will initiate known homeostatic processes that evolved over millions of years to preserve the neuronal set points [56] – and network functioning – that vary from subject to subject [57–59].

Glossary

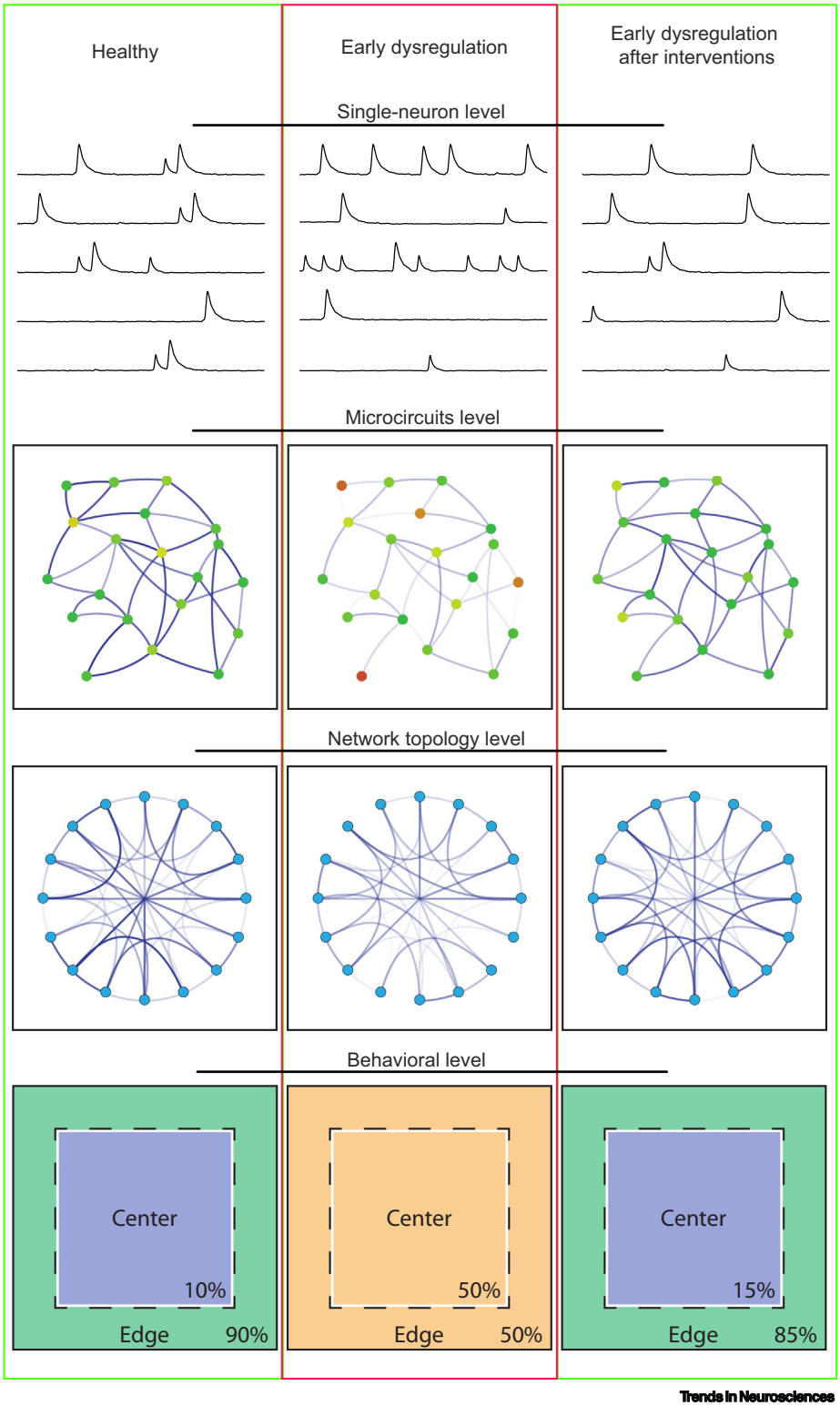
Allostasis: the process by which physiological equilibrium is maintained by a system in response to internal or external perturbation by shifting homeostatic set points.
Attractors: elements in the parameter space with self-stabilizing properties in all dimensions of the parameter space. Within given boundaries, deflections of the trajectory in the attractor will lead to the trajectory returning to the center of the attractor.
Dynamical systems theory: mathematical framework constituting of coupled differential equations describing the interdependency of variables or parameters. The numerical solution of these equations will result in a trajectory moving through the parameter space, which can constitute, for example, self-stabilizing attractors, saddles, oscillations, or nonstable chaos.
Hyperactivity: in the context of neuronal circuits, hyperactivity refers to increase of activity beyond the homeostatic boundaries of either neurons or networks.
Network states: discrete set points of network function.
Network topology: the arrangement of the elements (neurons, axons, dendrites, synapses, etc.) of a communication network, such as a neural network. Physical topology describes the placement of the various components of a network (e.g., location within the brain and connectivity), while logical topology illustrates how data flows within a network.
Neurodegeneration: refers to pathological processes that leads to a loss of function and, ultimately, the loss of nerve cells and disintegration of the nervous system.
Resilience: physical resilience may be defined as the ability to withstand or recover from functional decline following acute and/or chronic distress. Neural network resilience is defined as the maintenance or quick recovery of adaptive, healthy network states during and after exposure to significant challenges, resulting from a dynamic process of adaptation to the given challenge.
Selfish networks: a guiding principle of network behavior according to which networks aim for gaining stable states of network function, irrespective of the long-term survival of the elements of the network, that is, neurons.

Most of these compensatory mechanisms may initially be successful in preserving functionality. But the persisting cellular/molecular deficits will continue to drive networks away from their evolutionary preserved set points. Yet, the many integrative properties of the brain, which include numerous afferent and efferent network interactions and molecular mechanisms [60], will be able to preserve functional abilities for an extended time and remain undetected at the organismic level. We hypothesize that severe signs of a disease become only obvious, at a certain tipping point when the available compensatory mechanisms are unable to further preserve intact functionality resulting in a new metastable set point (Figure 1, phase T3 to T4).

Early network changes associated with hyperactive neurons may constitute a hallmark of presymptomatic disease progression

Network dysregulation at disease stages can occur long before the typical clinical diagnosis or commencement of therapeutic intervention: in presymptomatic phases of **neurodegenerative** disorders such as Parkinson's disease [61] , HD [62], and AD [25,63], and, in the state of remission in episodic, secondary neurodegenerative disorders such as multiple sclerosis (MS) [64]. To probe whether network dysregulations can occur in areas not primarily impacted by the primary pathophysiological challenge, as hypothesized here, a primary sensory cortex, such as the visual cortex, might represent a suitable region to assess local functional architecture. While the primary visual cortex might be mainly associated with the processing of visual afferents, it is a highly integrated region. It receives information from other sensory cortices [65], as well as on the locomotion and emotional state of the organism [66,67], in line with the notion of a bound brain [27]. It seems therefore plausible that internal perturbations originating in distant regions are reflected in multiple local network changes throughout the brain, including the primary visually cortex. For assessing local functional architecture with the aim of detecting neuronal state changes, optical recordings such as two-photon calcium imaging in the visual cortex with single-neuron resolution might be well suited [68,69]. In the primary visual cortex of a mouse model of HD, in an early presymptomatic phase, very far from disease onset, with the disease onset marked by the occurrence of clinically significant motor symptoms, a local network shift toward hyperactivity could be identified [62]. The new network state was characterized by an increase of synchronicity, pointing to an active process in early disease, in line with the proposed concept of early network state changes (Figure 2). In a mouse model of AD, also in the primary visual cortex, long before amyloid plaque formation [25], a distinct new neuronal set point could be observed. This set point was characterized by an altered temporal distribution of spontaneous activity, yet devoid of hyperactivity. Assessing **network topology**, a significant degradation of parameters related to the robustness and capability of the network to compensate node loss could be demonstrated (Figure 2 middle panel, Networks).

In the experimental autoimmune encephalomyelitis (EAE) mouse model of MS, a shift towards hyperactivity in the frontal and visual cortices occurred not at the peak of autoimmune pathology, but during remission, a phase in which the animals did not show any significant motor symptoms [64]. The shift in network function was shown to be induced by the local excitatory neurons via the secretion of tumor necrosis factor (TNF)α, which mediated synaptic plasticity. These networks were not yet targeted by the disease-defining pathology; that is, these networks were devoid of demyelination and T-cell infiltration. These findings suggest an active shift in network architecture, rather than a passive consequence of preceding, remote disease process. This raises an important question: are these early network changes an epiphenomenon which is restricted to the level of networks, and remains within that level, or does it affect other levels such as behavior? While assessing a causal relation of a network state to a distinct behavioral representation remains a challenge, in the three forementioned disease models, subtle but discernable behavioral phenotypes could be observed [25,62,64] (Figure 2 lower panel, Behavior). Whether similar



(See figure legend at the bottom of the next page.)

behavioral correlates of early changes in network function are observed across other conditions remains to be examined (see Outstanding questions).

Interventions may reverse network state dynamics and prevent hyperactivity-induced neurodegeneration

Another important issue is whether the network state switches are reversible, particularly in early stages of disease that are still devoid of large-scale **neurodegeneration**. In the forementioned animal-model studies of neurodegeneration, it was also shown that short-term pharmacological interventions can reduce the compensatory load on the network, and rebalance the network (Figure 2) [62,64,70–72]. This newly regained performance plateau can be stable for time periods that significantly outlast the pharmacokinetics of the applied drug. It is conceivable that rebalancing neuronal network function may not only stabilize and prolong the plateau phase and slow disease progression, but also feedback to modify the cellular pathophysiology [73–76] (Figure 3).

Compensatory mechanisms of the selfish network might result, in turn, in cellular vulnerability. Indeed, maladaptive hyperactivity, even in brain regions not directly affected by the molecular pathology, has been shown to be associated, for instance, with higher levels of apoptosis [64,77]. Thus, maladaptive states involving hyperactive cells may facilitate and accelerate neurodegeneration (Figure 3). In the context of MS, early hyperactivity in remission may constitute the starting point for subsequent neurodegeneration and transition to the chronic progressive phase of the disease, exemplifying the notion of the selfish network, aiming to maintain stability even at expense of harmful long-term outcomes for neuronal survival. Accordingly, it is conceivable that interventions aimed at rebalancing early network changes to avoid hyperactivity may prevent hyperactivity-mediated neurodegeneration.

Network state dynamics across disease models and species can be formalized by attractor states

How can the propensity of early network changes be leveraged for therapeutic interventions, and is it possible to identify optimal time points for interventions? The time point of an abrupt change in network performance can be perceived as a tipping point or – in the light of intervention – a window of opportunity. The notion of a disease tipping point is supported by anecdotal observations in people with AD. Patients and their caretakers often report sudden changes in multiple performance features such as memory performance or orientation, occurring on rather short time scales within days [78,79]. Classically, these observations were regarded as physiological noise within an overall linear decline of a specific performance feature. While the notion of tipping points

Figure 2. Early neuronal state shifts across levels. Rows in the figure illustrate changes at the level of single neurons (upper row), networks (middle rows), and behavior (bottom row). Left column represents the healthy stage, middle column represents an early dysregulation, and right column the situation following administration of network-rebalancing interventions. At the single-neuron level, early maladaptive network state shifts can result in hyperactivity, which can be detected in animal models using methods such as patch-clamp electrophysiological recordings as an increase in excitatory postsynaptic currents, or two-photon calcium imaging as an increase of action-potential related calcium transients [69,103]. At the microcircuits level, and at the network topology level, an altered degree of synchronized network activity is seen in early dysregulation, resulting in a change in network topology. This can be assessed either in animal models, for instance using optical imaging methods such as two-photon calcium imaging, in which the network nodes are single cells, or in humans, for instance, using fMRI at the brain-wide level, in which the network nodes are brain regions. At the behavioral level, an early dysregulation is often characterized by subtle changes for instance in anxiety-related behavior, depicted in a schematic through place preference in the open-field paradigm. The percentage values represent the respective time an animal spends in the center versus the edge of the open field. More time spent in the center is indicative of an anxiolytic phenotype. Notably, therapeutic interventions aimed at the level of the network may rebalance all three levels, from single neurons to behavior.

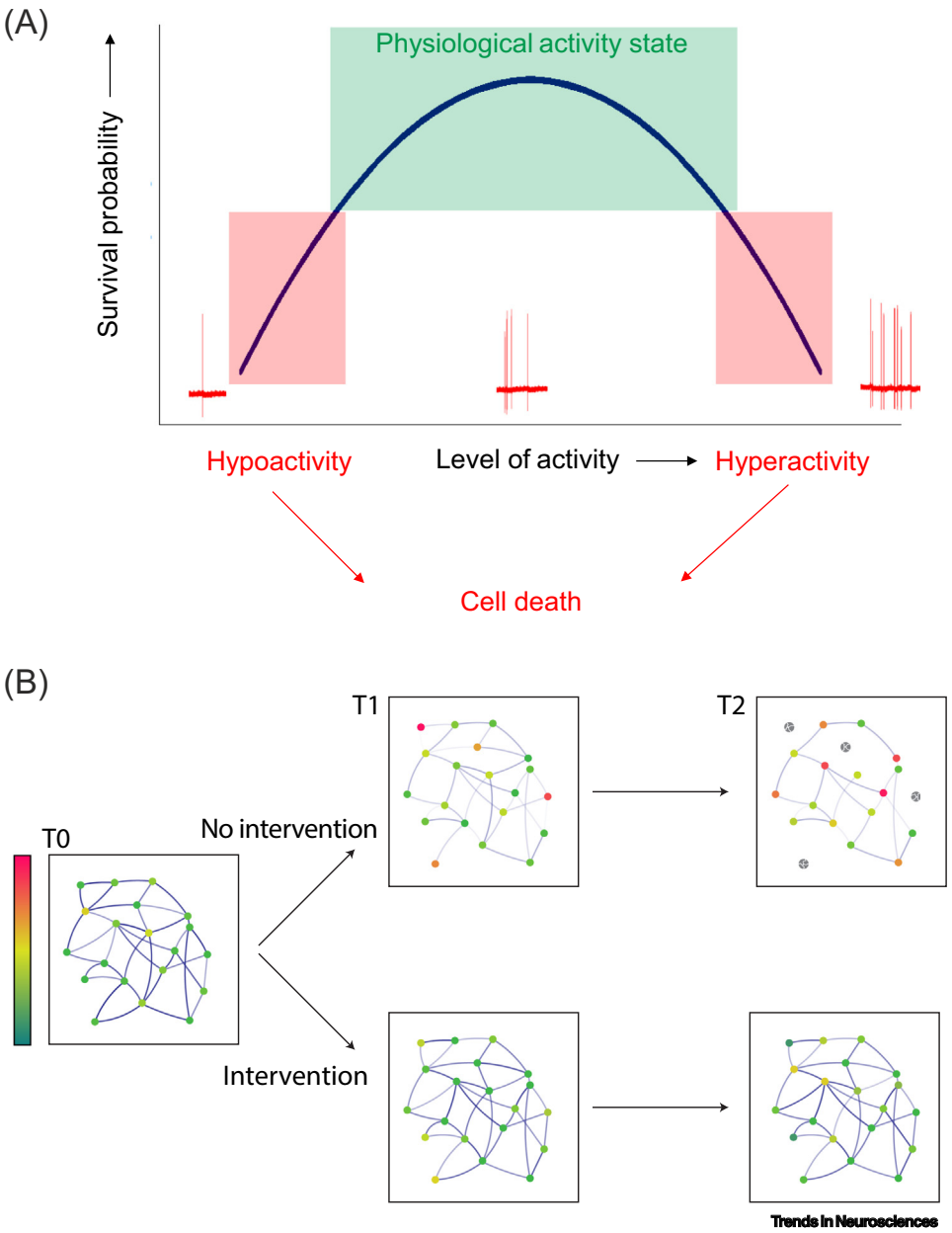


Figure 3. Long-term shift of neuronal activity state to hyperactivity as a starting point for neurodegeneration, amenable for interventions (A) Both hypoactivity and hyperactivity shifts an individual neuron from its physiological activity state. To maintain network homeostasis, the respective neuron is prone to undergo activity-dependent apoptosis leading to secondary neurodegeneration [64]. (B) Transitioning from timepoints T0 to T1 (see Figure 1 for timeline) will be accompanied by the emergence of hyperactive cells, which will undergo activity dependent apoptosis at timepoint T2. Early network rebalancing and hyperactivity-reducing intervention might prevent or delay activity-dependent neurodegeneration.

in disease progression remains to be further substantiated, and tested across diseases, we suggest that such discrete functional changes may be archetypical for the underlying trajectory that starts with aberrant network pathophysiology and ends in the functional phenotype of the disease (Figure 4).

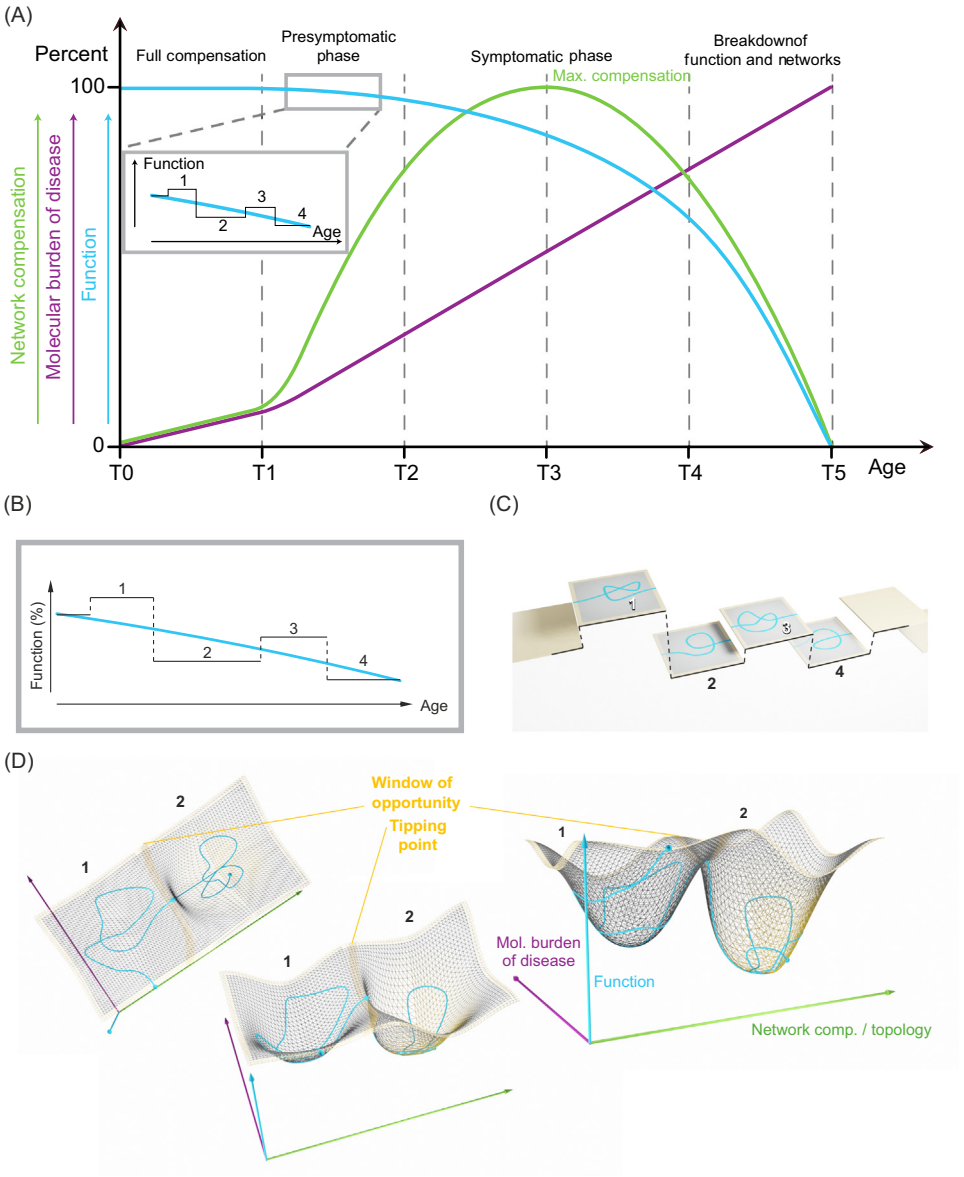


Figure 4. Temporal dissociation between the dynamics of disease burden and functional decline suggests network compensation as critical missing link. (A) On a single-subject level, particularly in the early presymptomatic phase (T1 to T2), subtle function decline (blue line) is characterized as sudden shifts, followed by metastable plateaus (insert), while network compensation (green line) increases and upholds network function until there is no further increase in compensation possible (T3) and network function starts to decline rapidly (T4). Molecular burden accumulates and leads to primary neurodegeneration (purple line). (B) Dynamical systems theoretic formulation of early discrete shifts in function as a succession of plateaus of network states. (C) The systems trajectory (in light blue) moves through the metastable network states. (D) The time of the switch between attractor states represents a window of opportunity (or tipping point) in which subtle changes of the systems trajectory can lead to either regaining of the previous attractor state or succession to another attractor state. Effective network-modulating, one-time therapies will require the identification of these tipping points and the precise timing of therapeutic intervention.

From the viewpoint of network functionality, plateau-like phases alternate with periods of vulnerability that constitute putative tipping points of network performance. Tipping points and plateau-like phases of neuronal network activities are the characteristics of the early stages of disease progression (Figure 4, T1 to T2 and insert).

The stability and the trajectory of network states as well as the transitions between states can be described by the theoretical framework of dynamical systems theory [80]. This mathematical concept was first introduced to biology in the field of population dynamics, studying predator–prey systems [81]. Dynamical systems theory modeling of predator–prey dynamics formalizes this process through coupled differential equations, in which the change of prey population is dependent on the number of predators, which in turn is dependent on the number of prey. Solving these equations numerally results in an oscillatory trajectory for predator and prey, yet, changing the parameters can result in complex systems behavior. Multidimensional systems; that is, coupled differential equations with multiple parameters with corresponding multidimensional parameter spaces can result in trajectory dynamics with stable and self-stabilizing solutions (attractors), as well as unstable solutions (repellers) and semistable solutions (saddles) [82]. Yet, how can the mathematical framework of dynamical systems theory be applied to neuronal network states? A network is commonly topologically described as constituting of nodes and edges [83]. As a first step, we need to transition from this topological view of networks to a network-state-centered approach. Even in the simplified view where each neuron has a binary functional state of either 0 or 1, given that each neuron may have up to ~10 000 synaptic partners, the number of potential states even of a local network of a few thousand cells is immense. Yet, the number of observed network states that are metastable over time is limited, and drastically smaller compared to the number of possible states, and hence can be viewed as a limited set of discrete states [84]. This allows for a dimensionality reduction, transitioning from neuronal space to parameter space, describing most of the variance of the behavior of the system in time. In a simplified view, these parameters governing the network states could constitute the molecular burden of disease, the network compensation, and the functional (behavioral) outcome (Figure 4A). In a second step, we can now model the interaction between these parameters as coupled differential equations. Lastly, the solution of these coupled differential equations results in a parameter landscape, which can contain attractors. Time is now encoded as the trajectory of the system, moving through the parameter landscape (Figure 4C–E) [85]. Within certain boundaries, deflections of the systems trajectory will lead to a return of the dynamic system to the given state. This fits well with the observed systems performance with plateau phases of network function interleaved by rather sudden quantal shifts. When changes are substantial enough, when maladaptive load sums up or when strong risk factors hit the system in a vulnerable state, the network crosses the boundaries and transitions into a different attractor state associated with a change in functionality (Figure 4) [86,87]. In this model, a short-term intervention, applied exactly at the time of transition, can push back the network into its original state [88–90]. In the forementioned study on network dysregulations in an MS model, a one-time injection of TNFα antibody in remission stage restored the functional network state of the local neuronal microcircuit in the visual cortex to a state nondiscriminable from the preinduction state, indicative for the local network re-entering or being pushed back to the preinduction attractor [64]. Interventions aimed at achieving an adaptive attractor which is beneficial for long-term outcomes can be designed in two ways: (i) by changing the trajectory of the network; that is, pushing the system to another attractor with a fixed attractor landscape (as depicted in Figure 4D); or (ii) changing the attractor landscape itself, by modifying the dependency and relation between the parameters. The latter would result in a different dynamical system described by different coupled differential equations.

Ramifications of the attractor state concepts for later disease stages

An important question is how a network finds its way into a new stable attractor state when molecular or cellular factors have forced it out of the original, healthy stage? We propose that a network can adopt stable states only within a given parametric space [91]. This parametric space is defined by borders built by the network itself. The borders are defined by various factors including anatomical network connectivity, age, and developmental stage, but also by risk factors that influence the network [79]. Such risk factors include for instance genetic susceptibilities, immunological challenges, and previous illnesses. These boundaries could also be determined by the accumulated maladaptive load, and by the molecular trajectory of the disease. Perhaps the most critical and dynamic boundary is determined by the remaining, still functional units of the network. In later stages of neurodegenerative disorders, the sparsification of the network caused by the loss of neurons leads to an ever-decreasing parameter space for adaptive attractors. We consider this time point as the breakdown of compensatory mechanisms in which the solutions of the neuronal networks to retain functionality become increasingly limited. The network attains a state that can no longer support normal functioning at the organismic level (Figure 4, between T4 and T5).

Towards network resilience

Understanding mechanisms of network compensation and characteristics of tipping points could help redefine pathogenic mechanisms of neurodegenerative and neuropsychiatric diseases and might pave the way for innovative paths for therapy. In the proposed framework, the progression of a neurological disease can be defined as the breakdown of compensatory mechanisms as neuronal networks transition from one transitory state to the next; each of which represents a temporary solution that may vary among subjects and brain regions [58]. This raises the question of whether the disease onset is characterized by the activation of previously dormant compensatory processes, or alternatively whether these compensatory processes are the same homeostatic mechanisms that continuously maintain normal physiological neuronal network functions. It is well established that the brain is persistently active. This ongoing activity is critical to continuously fine tune and scale synaptic interactions that are continuously changing due to neuronal plasticity [92,93], as well as learning and memory [94–97]. Neuronal network activity and neural network states by themselves are likely agnostic to the causes of change in intrinsic and synaptic mechanisms, and a given network activity is not necessarily different for a physiological process like learning and memory, a metabolic change caused, for example, by ischemia or a pathological change caused by a genetic mutation.

Neural networks on levels of network topology; that is, from synapses and microcircuits to macrocircuits and whole brain networks, may have evolved to find individual solutions when facing adversity [98]. In that, the neuronal network in themselves can be seen to be resilient [99–102]. However, **resilience of the neural** network is limited. If the network assumes maladaptive states; that is, involving hyperactive neurons, it is driven further from its physiological state, surpassing the limits of network resilience.

Concluding remarks and future perspectives

We suggest that the trajectory of network function, governed by the principle of a selfish network, is temporally and spatially decoupled from the underlying molecular and cellular pathophysiology. These maladaptive network states represent a distinct pathophysiological entity, which can be assessed for instance using recordings of local spontaneous activity as a measure of network integrity, and the dynamics of the network behavior can be formalized as attractor states. This may have implications for neurodegeneration-preventing interventions. In designing such interventions, particularly early intervention, two distinct potential pathomechanisms need to be

Outstanding questions

What is the relative contribution of the maladaptive network state versus disease-specific pathophysiological challenges to neurodegeneration?

Which neuronal cell types govern the maladaptive state transitions?

Are stress-related, episodic mental disorders like depression or anxiety disorders in essence disorders of maladaptive neural network states, amenable to short-term pharmacological or physiological interventions?

What are the neurophysiological mechanisms by which local maladaptive network states spread in space and time?

Which methodological advances need to be achieved for personalized network-informed interventions?

Can the attractor-like dynamics of early network changes be exploited for advancing therapy?

Which neuromodulation techniques are most efficient in shifting the network to an attractor more favorable for long-term neuronal survival?

considered: (i) neuronal cell loss can be induced by primary disease-specific cytotoxic pathophysiological events; and (ii) as put forward in this Opinion, neuronal cell loss can result from a second pathomechanism involving hyperactivity-mediated apoptosis as the consequence of a maladaptive network state. Therefore, it is hoped that this perspective may open up new avenues for network-state informed, individualized, and regionalized intervention schemes.

Acknowledgments

We would like to thank Merve Ilhan-Bayrakcı, Saleh Altahini, Roberta Backhaus, and Michael Plenikowski for their help on preparing the manuscript and figures. We thank the Leibniz Association (SAW Learning Resilience, LFV-2021-2-LIR), the Boehringer-Ingelheim Foundation, the State of Rhineland-Palantine (ReALity Innovation Fund P8 & P9), the European Union (H2020-SC1-2017-CNECT-2: Grant No. 777084 DynaMORE), the National Institutes of Health (PO1 HL14454 (Project 2), R01 HL144801, R01 HL151389, R01 HL126523), the Japan Science and Technology Agency (Moonshot R&D Goal 9 JPMJMS2292-1-05), and the German Research Foundation (TRR 128, SFB1193, SFB1080) for their support.

Declaration of interests

The authors declare no conflicts of interest.

References

1. Dominguez-Fernandez, C. *et al.* (2023) Review of technological challenges in personalised medicine and early diagnosis of neurodegenerative disorders. *Int. J. Mol. Sci.* 24, 3321
2. Doroszkiewicz, J. *et al.* (2022) Molecular biomarkers and their implications for the early diagnosis of selected neurodegenerative diseases. *Int. J. Mol. Sci.* 23, 4610
3. Mukherjee, S. *et al.* (2020) Molecular estimation of neurodegeneration pseudotime in older brains. *Nat. Commun.* 11, 5781
4. Sung, Y.J. *et al.* (2023) Proteomics of brain, CSF, and plasma identifies molecular signatures for distinguishing sporadic and genetic Alzheimer's disease. *Sci. Transl. Med.* 15, eabq5923
5. Bollimunta, A. *et al.* (2021) Head-mounted microendoscopic calcium imaging in dorsal premotor cortex of behaving rhesus macaque. *Cell Rep.* 35, 109239
6. Yacoub, E. *et al.* (2020) Ultra-high field (10.5 T) resting state fMRI in the macaque. *Neuroimage* 223, 117349
7. Chao, T.H. *et al.* (2023) Neuronal dynamics of the default mode network and anterior insular cortex: Intrinsic properties and modulation by salient stimuli. *Sci. Adv.* 9, eade5732
8. Dana, H. *et al.* (2019) High-performance calcium sensors for imaging activity in neuronal populations and microcompartments. *Nat. Methods* 16, 649–657
9. Durand, S. *et al.* (2023) Acute head-fixed recordings in awake mice with multiple Neuropixels probes. *Nat. Protoc.* 18, 424–457
10. Dukic, S. *et al.* (2022) Resting-state EEG reveals four subphenotypes of amyotrophic lateral sclerosis. *Brain* 145, 621–631
11. Ramirez-Torano, F. *et al.* (2021) Functional connectivity hypersynchronization in relatives of Alzheimer's disease patients: an early E/I balance dysfunction? *Cereb. Cortex* 31, 1201–1210
12. Kuruppath, P. *et al.* (2023) Hyperexcitability in the olfactory bulb and impaired fine odor discrimination in the Fmr1 KO mouse model of fragile X syndrome. *J. Neurosci.* 43, 8243–8258
13. Tao, Y. *et al.* (2022) Inter-hemispheric synchronicity and symmetry: The functional connectivity consequences of stroke and neurodegenerative disease. *Neuroimage Clin.* 36, 103263
14. Bachmann, C. *et al.* (2020) Firing rate homeostasis counteracts changes in stability of recurrent neural networks caused by synapse loss in Alzheimer's disease. *PLoS Comput. Biol.* 16, e1007790
15. Dahmen, D. *et al.* (2022) Global organization of neuronal activity only requires unstructured local connectivity. *Elife* 11, e68422
16. Zerlaut, Y. *et al.* (2022) Network states classification based on local field potential recordings in the awake mouse neocortex. *eNeuro* 9, ENEURO.0073-22.2022
17. Zarhin, D. *et al.* (2022) Disrupted neural correlates of anesthesia and sleep reveal early circuit dysfunctions in Alzheimer models. *Cell Rep.* 38, 110268
18. Safai, A. *et al.* (2021) Multimodal brain connectomics-based prediction of Parkinson's disease using graph attention networks. *Front. Neurosci.* 15, 741489
19. Helson, P. *et al.* (2023) Cortex-wide topography of 1/f-exponent in Parkinson's disease. *NPJ Parkinsons Dis.* 9, 109
20. Ying, J. *et al.* (2022) Disruption of the grid cell network in a mouse model of early Alzheimer's disease. *Nat. Commun.* 13, 886
21. McTeague, L.M. *et al.* (2020) Identification of common neural circuit disruptions in emotional processing across psychiatric disorders. *Am. J. Psychiatry* 177, 411–421
22. Dawkins, R. (1989) *The Selfish Gene*, Oxford University Press
23. Zott, B. *et al.* (2018) What happens with the circuit in Alzheimer's disease in mice and humans? *Annu. Rev. Neurosci.* 41, 277–297
24. Zhang, W. *et al.* (2016) Hyperactive somatostatin interneurons contribute to excitotoxicity in neurodegenerative disorders. *Nat. Neurosci.* 19, 557–559
25. Rosales Jubal, E. *et al.* (2021) Acitretin reverses early functional network degradation in a mouse model of familial Alzheimer's disease. *Sci. Rep.* 11, 6649
26. Rosenberg, P.B. *et al.* (2015) Neuropsychiatric symptoms in Alzheimer's disease: what might be associated brain circuits? *Mol. Asp. Med.* 43-44, 25–37
27. Singer, W. (2013) Cortical dynamics revisited. *Trends Cogn. Sci.* 17, 616–626
28. Charquero-Ballester, M. *et al.* (2022) Effective psychological therapy for PTSD changes the dynamics of specific large-scale brain networks. *Hum. Brain Mapp.* 43, 3207–3220
29. Dorst, K.E. *et al.* (2024) Hippocampal engrams generate variable behavioral responses and brain-wide network states. *J. Neurosci.* 44, e0340232023
30. Shappell, H.M. *et al.* (2021) Children with attention-deficit/hyperactivity disorder spend more time in hyperconnected network states and less time in segregated network states as revealed by dynamic connectivity analysis. *Neuroimage* 229, 117753
31. Smith, J.C. *et al.* (1991) Pre-Botzinger complex: a brainstem region that may generate respiratory rhythm in mammals. *Science* 254, 726–729
32. Ramirez, J.M. and Baertsch, N.A. (2018) The dynamic basis of respiratory rhythm generation: one breath at a time. *Annu. Rev. Neurosci.* 41, 475–499
33. Baertsch, N.A. *et al.* (2019) A spatially dynamic network underlies the generation of inspiratory behaviors. *Proc. Natl. Acad. Sci. U. S. A.* 116, 7493–7502
34. Telgkamp, P. *et al.* (2002) Long-term deprivation of substance P in PPT-A mutant mice alters the anoxic response of the isolated respiratory network. *J. Neurophysiol.* 88, 206–213

35. Viemari, J.C. *et al.* (2005) Mecp2 deficiency disrupts norepinephrine and respiratory systems in mice. *J. Neurosci.* 25, 11521–11530
36. Deguchi, K. *et al.* (2000) Substance P immunoreactivity in Rett syndrome. *Pediatr. Neurol.* 22, 259–266
37. Weese-Mayer, D.E. *et al.* (2006) Autonomic nervous system dysregulation: breathing and heart rate perturbation during wakefulness in young girls with Rett syndrome. *Pediatr. Res.* 60, 443–449
38. Roche, K.J. *et al.* (2019) Electroencephalographic spectral power as a marker of cortical function and disease severity in girls with Rett syndrome. *J. Neurodev. Disord.* 11, 15
39. Sysoeva, O. *et al.* (2023) Abnormal spectral and scale-free properties of resting-state EEG in girls with Rett syndrome. *Sci. Rep.* 13, 12932
40. Saby, J.N. *et al.* (2021) Multisite study of evoked potentials in Rett syndrome. *Ann. Neurol.* 89, 790–802
41. Calfa, G. *et al.* (2015) Excitation/inhibition imbalance and impaired synaptic inhibition in hippocampal area CA3 of Mecp2 knockout mice. *Hippocampus* 25, 159–168
42. McLeod, F. *et al.* (2013) Reduced seizure threshold and altered network oscillatory properties in a mouse model of Rett syndrome. *Neuroscience* 231, 195–205
43. Calfa, G. *et al.* (2011) Network hyperexcitability in hippocampal slices from Mecp2 mutant mice revealed by voltage-sensitive dye imaging. *J. Neurophysiol.* 105, 1768–1784
44. Sun, Y. *et al.* (2019) Loss of MeCP2 in immature neurons leads to impaired network integration. *Hum. Mol. Genet.* 28, 245–257
45. Banerjee, A. *et al.* (2016) Jointly reduced inhibition and excitation underlies circuit-wide changes in cortical processing in Rett syndrome. *Proc. Natl. Acad. Sci. U. S. A.* 113, E7287–E7296
46. Voytek, B. and Knight, R.T. (2015) Dynamic network communication as a unifying neural basis for cognition, development, aging, and disease. *Biol. Psychiatry* 77, 1089–1097
47. Li, R. *et al.* (2021) Shared and distinct global signal topography disturbances in subcortical and cortical networks in human epilepsy. *Hum. Brain Mapp.* 42, 412–426
48. Lignani, G. *et al.* (2020) Homeostatic plasticity in epilepsy. *Front. Cell. Neurosci.* 14, 197
49. McKavanagh, A. *et al.* (2022) Altered structural brain networks in refractory and nonrefractory idiopathic generalized epilepsy. *Brain Connect* 12, 549–560
50. Burton, C.L. *et al.* (2006) Intraindividual variability as a marker of neurological dysfunction: a comparison of Alzheimer's disease and Parkinson's disease. *J. Clin. Exp. Neuropsychol.* 28, 67–83
51. Gleason, C.E. *et al.* (2018) Cognitive variability predicts incident Alzheimer's disease and mild cognitive impairment comparable to a cerebrospinal fluid biomarker. *J. Alzheimers Dis.* 61, 79–89
52. Jackson, J.D. *et al.* (2012) White matter integrity and reaction time intraindividual variability in healthy aging and early-stage Alzheimer disease. *Neuropsychologia* 50, 357–366
53. Paulsen, J.S. *et al.* (2017) Cognitive and behavioral changes in Huntington disease before diagnosis. *Handb. Clin. Neurol.* 144, 69–91
54. Waschke, L. *et al.* (2021) Behavior needs neural variability. *Neuron* 109, 751–766
55. Festa, D. *et al.* (2021) Neuronal variability reflects probabilistic inference tuned to natural image statistics. *Nat. Commun.* 12, 3635
56. Styr, B. *et al.* (2019) Mitochondrial regulation of the hippocampal firing rate set point and seizure susceptibility. *Neuron* 102, 1009–1024 e1008
57. Wu, C.H. *et al.* (2022) A bidirectional switch in the Shank3 phosphorylation state biases synapses toward up- or downscaling. *Elife* 11, e74277
58. Wu, Y.K. *et al.* (2020) Homeostatic mechanisms regulate distinct aspects of cortical circuit dynamics. *Proc. Natl. Acad. Sci. U. S. A.* 117, 24514–24525
59. Torrado Pacheco, A. *et al.* (2021) Sleep promotes downward firing rate homeostasis. *Neuron* 109, 530–544 e536
60. Valakh, V. *et al.* (2023) A transcriptional constraint mechanism limits the homeostatic response to activity deprivation in mammalian neocortex. *Elife* 12, e74899
61. Wiest, C. *et al.* (2023) The aperiodic exponent of subthalamic field potentials reflects excitation/inhibition balance in Parkinsonism. *Elife* 12, e82467
62. Arnoux, I. *et al.* (2018) Metformin reverses early cortical network dysfunction and behavior changes in Huntington's disease. *Elife* 7, e38744
63. Martinez-Canada, P. *et al.* (2023) Combining aperiodic 1/f slopes and brain simulation: an EEG/MEG proxy marker of excitation/inhibition imbalance in Alzheimer's disease. *Alzheimers Dement. (Amst)* 15, e12477
64. Ellwardt, E. *et al.* (2018) Maladaptive cortical hyperactivity upon recovery from experimental autoimmune encephalomyelitis. *Nat. Neurosci.* 21, 1392–1403
65. Bimbard, C. *et al.* (2023) Behavioral origin of sound-evoked activity in mouse visual cortex. *Nat. Neurosci.* https://doi.org/10.1038/s41593-022-01227-x
66. Fu, Y. *et al.* (2014) A cortical circuit for gain control by behavioral state. *Cell* 156, 1139–1152
67. Niell, C.M. and Stryker, M.P. (2010) Modulation of visual responses by behavioral state in mouse visual cortex. *Neuron* 65, 472–479
68. Grienberger, C. and Konnerth, A. (2012) Imaging calcium in neurons. *Neuron* 73, 862–885
69. Fu, T. *et al.* (2021) Exploring two-photon optogenetics beyond 1100 nm for specific and effective all-optical physiology. *iScience* 24, 102184
70. Adaikkan, C. and Tsai, L.H. (2020) Gamma entrainment: impact on neurocircuits, glia, and therapeutic opportunities. *Trends Neurosci.* 43, 24–41
71. Chu, C. *et al.* (2023) Subthalamic stimulation modulates motor network in Parkinson's disease: recover, relieve and remodel. *Brain* 146, 2780–2791
72. Chang, C.W. *et al.* (2021) Tau reduction affects excitatory and inhibitory neurons differently, reduces excitation/inhibition ratios, and counteracts network hypersynchrony. *Cell Rep.* 37, 109855
73. Iaccarino, H.F. *et al.* (2016) Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature* 540, 230–235
74. Da, X. *et al.* (2024) Noninvasive gamma sensory stimulation may reduce white matter and myelin loss in Alzheimer's disease. *J. Alzheimers Dis.* 97, 359–372
75. Bollinger, J.L. *et al.* (2024) Repeated activation of pyramidal neurons in the prefrontal cortex alters microglial phenotype in male mice. *J. Pharmacol. Exp. Ther.* 388, 715–723
76. Shoob, S. *et al.* (2023) Deep brain stimulation of thalamic nucleus reuniens promotes neuronal and cognitive resilience in an Alzheimer's disease mouse model. *Nat. Commun.* 14, 7002
77. Abiega, O. *et al.* (2016) Neuronal hyperactivity disturbs ATP microgradients, impairs microglial motility, and reduces phagocytic receptor expression triggering apoptosis/microglial phagocytosis uncoupling. *PLoS Biol.* 14, e1002466
78. Cloutier, S. *et al.* (2015) Patterns of cognitive decline prior to dementia in persons with mild cognitive impairment. *J. Alzheimers Dis.* 47, 901–913
79. Crockett, R.A. *et al.* (2019) Head over heels but I forget why: disruptive functional connectivity in older adult fallers with mild cognitive impairment. *Behav. Brain Res.* 376, 112104
80. Breakspear, M. (2017) Dynamic models of large-scale brain activity. *Nat. Neurosci.* 20, 340–352
81. Berryman, A.A. (1992) The orgins and evolution of predator-prey theory. *Ecology* 73, 1530–1535
82. Deco, G. and Jirsa, V.K. (2012) Ongoing cortical activity at rest: criticality, multistability, and ghost attractors. *J. Neurosci.* 32, 3366–3375
83. Bazinet, V. *et al.* (2023) Towards a biologically annotated brain connectome. *Nat. Rev. Neurosci.* 24, 747–760
84. Finkelstein, A. *et al.* (2021) Attractor dynamics gate cortical information flow during decision-making. *Nat. Neurosci.* 24, 843–850
85. Freyer, F. *et al.* (2012) A canonical model of multistability and scale-invariance in biological systems. *PLoS Comput. Biol.* 8, e1002634
86. Kaiser, R.H. *et al.* (2022) Dynamic resting-state network biomarkers of antidepressant treatment response. *Biol. Psychiatry* 92, 533–542
87. Stiso, J. *et al.* (2019) White matter network architecture guides direct electrical stimulation through optimal state transitions. *Cell Rep.* 28, 2554–2566

88. Rich, S. *et al.* (2020) Neurostimulation stabilizes spiking neural networks by disrupting seizure-like oscillatory transitions. *Sci. Rep.* 10, 15408
89. West, T.O. *et al.* (2022) Stimulating at the right time to recover network states in a model of the cortico-basal ganglia-thalamic circuit. *PLoS Comput. Biol.* 18, e1009887
90. Antonoudiou, P. *et al.* (2022) Allopregnanolone mediates affective switching through modulation of oscillatory states in the basolateral amygdala. *Biol. Psychiatry* 91, 283–293
91. Ma, Z. *et al.* (2020) Stability of motor cortex network states during learning-associated neural reorganizations. *J. Neurophysiol.* 124, 1327–1342
92. Sun, Y.Y. *et al.* (2022) TRIM32 deficiency impairs the generation of pyramidal neurons in developing cerebral cortex. *Cells* 11, 449
93. Field, R.E. *et al.* (2020) Heterosynaptic plasticity determines the set point for cortical excitatory-inhibitory balance. *Neuron* 106, 842–854 e844
94. Trasande, C.A. and Ramirez, J.M. (2007) Activity deprivation leads to seizures in hippocampal slice cultures: is epilepsy the consequence of homeostatic plasticity? *J. Clin. Neurophysiol.* 24, 154–164
95. Wen, W. and Turrigiano, G.G. (2021) Developmental regulation of homeostatic plasticity in mouse primary visual cortex. *J. Neurosci.* 41, 9891–9905
96. Wu, C.H. *et al.* (2021) Homeostatic synaptic scaling establishes the specificity of an associative memory. *Curr. Biol.* 31, 2274–2285 e2275
97. Marder, E. and Prinz, A.A. (2002) Modeling stability in neuron and network function: the role of activity in homeostasis. *Bioessays* 24, 1145–1154
98. Chiken, S. *et al.* (2021) Altered dynamic information flow through the cortico-basal ganglia pathways mediates Parkinson's disease symptoms. *Cereb. Cortex* 31, 5363–5380
99. Das, M. *et al.* (2021) Interdependence of neural network dysfunction and microglial alterations in Alzheimer's disease-related models. *iScience* 24, 103245
100. Li, K.T. *et al.* (2023) Memory rescue and learning in synaptic impaired neuronal circuits. *iScience* 26, 106931
101. Jamann, N. *et al.* (2021) Sensory input drives rapid homeostatic scaling of the axon initial segment in mouse barrel cortex. *Nat. Commun.* 12, 23
102. Ruggiero, A. *et al.* (2021) Mitochondria: new players in homeostatic regulation of firing rate set points. *Trends Neurosci.* 44, 605–618
103. Guimaraes Backhaus, R. *et al.* (2021) Pipeline for 2-photon all-optical physiology in mouse: From viral titration and optical window implantation to binarization of calcium transients. *STAR Protoc.* 2, 101010