# Chapter 11

# Neurological Diseases from a Systems Medicine Point of View

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## Abstract

The difficulty to understand, diagnose, and treat neurological disorders stems from the great complexity of the central nervous system on different levels of physiological granularity. The individual components, their interactions, and dynamics involved in brain development and function can be represented as molecular, cellular, or functional networks, where diseases are perturbations of networks. These networks can become a useful research tool in investigating neurological disorders if they are properly tailored to reflect corresponding mechanisms. Here, we review approaches to construct networks specific for neurological disorders describing disease-related pathology on different scales: the molecular, cellular, and brain level. We also briefly discuss cross-scale network analysis as a necessary integrator of these scales.

**Key words** Systems medicine, Multiscale brain networks, Network reconstruction, Molecular networks, Cellular networks, Connectome, Cross-scale analysis, Neurodegenerative diseases, Epilepsies

## 1 Introduction

The human brain is an organ of an extraordinary complexity, where high-level processes emerge from simultaneous and continuous interaction of mechanisms on molecular, cellular, and anatomical scales. We need to properly analyze this complexity to be able to address the question of how brain disorders should be diagnosed and treated. A systems approach is a proper paradigm to address the challenges of brain pathophysiology.

The dynamics and close coupling between different scales of brain physiology are already clearly seen in the development of the nervous system. Importantly, the molecular and cellular processes observed in acute and chronic diseases often reflect and reuse mechanisms of embryogenesis. Many of the canonical pathways such as sonic hedgehog, Wnt, FGF, BMP, and their underlying

*If you look at the anatomy, the structure, the function, there's nothing in the universe that's more beautiful, that's more complex, than the human brain*. Keith Black

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transcriptional regulatory networks are highly conserved during evolution. The homologs or paralogs of certain genes are expressed at different times and in different pre- and postnatal cell lineages [1]. For instance, genes required in the formation of the embryonic vascular system are re-expressed during wound healing in adults. Of course the context of these evolutionary conserved modules within the circuitry of the adult organism differs greatly, which might lead to a different outcome after activation of their expression in an embryonic versus an adult environment [2, 3]. Nevertheless developmental biology can very well inform and support the generation of hypotheses about the disease pathogenesis, especially considering that the developmental processes integrate control on molecular, cellular, and anatomical levels, and the perturbation of this control may reflect the pathogenesis on the later stages [4, 5].

### 1.1 The Molecular, Cellular, and Anatomical Regulation of the Development of the Nervous System

One of the earliest events during embryogenesis is the determination of the principal body axis. Following the development of the primitive streak and the formation of the notochord, different cell layers, mesoderm, ectoderm, and endoderm are formed. The ectoderm located immediately dorsally to the notochord is induced to form neuroectoderm, the precursor of the nervous system. The neuroectoderm, initially a flat sheet, then folds into the neural tube, which in itself differentiates further into a number of neuronal different cell types dependent on their anterior-posterior, dorsal-ventral, and lateral position [6]. The development of the specific neuronal cell types within the spinal cord and the brain including the formation of the peripheral motor and sensory system can be traced back to the induction and programming during these specific early developmental phases [7].

The most anterior part of the neuroectoderm and the neural tube develop into the brain as a result of highly complex folding, proliferation, and migration events [8]. In this period the segmental nature of the brain becomes masked by region-specific migration and outgrowth of specific brain regions, for instance the cortex. Newly developing neurons contain cell-autonomous positional identity information and in addition receive spatial intracellular and extracellular cues guiding their migration and homing within the developing embryo in an anterior-posterior as well as a dorsal-ventral direction. These events are overlaid by the expression and activity of intricate cell survival, apoptotic, proliferation, and differentiation signals, leading to the final formation of the different neuronal and glial cell types and their wiring into the final connectome of the brain [9]. Already during embryogenesis electrical activity of neurons starts and is an important factor in the development of the nervous system [10].

Similarly to neural tube formation, specific molecular and cellular processes govern the segmentation into specific

components of nervous system. One of them is the formation of the midbrain-hindbrain boundary, reflecting the pronounced segmentation of the developing brain [11]. One of the key pathways driving this process is the Wnt pathway. A series of hierarchically organized transcription factors (e.g., EN1, PAX2, PAX8) and secreted morphogens (WNT1, SHH, FGF8) set up an asymmetry at a precise anterior-posterior boundary [12]. It is at this interface where an "organizing center" forms, leading to the differentiation and outgrowth of various neuronal precursors, for instance of the dopaminergic neurons. Tracing specific neuronal subtypes and assigning them specific gene expression signatures have greatly facilitated our understanding of the underlying wiring principles of the nervous system.

Brain development is a process integrating different layers of biological complexity, from genetic programs and molecular mechanisms, through cellular interactions and migration, to the development of functional anatomical regions. It is expected that perturbation of these networks may result in pathogenic states of the brain. Indeed, recent findings suggest that molecular, cellular, and anatomical dysfunction during brain development are for example resulting in epilepsies [13]. Interestingly components of the Wnt pathway are affected in diseases associated with the specific brain regions or neurons later on [14, 15]. These findings fuel intensive efforts under way to develop systems-based computational models for many of the molecular events of nervous system development.

The integration of mechanisms on different layers takes place across the whole life-span of the brain, through its homeostasis to degeneration. Similarly, it is needed to integrate spatial and temporal scales of representation of brain disease to be able to grasp the full picture of neuropathogenesis.

### 1.2 A Systems Approach is Required for Neurological Disorders

The processes of brain development, homeostasis and function, and neurodegeneration are complex. Elaborated architecture and functionality on molecular, tissue, and anatomical levels are constantly changing due to intrinsic brain functions and interactions with the environment. Disorders of such a complex system affect different aspects of its function, ranging from molecular structure, through dysfunction of neuronal subpopulations, to alteration of anatomical or functional brain connectivity. To be able to properly address the challenge of neurological disorders, we need to understand key processes implicated in brain function. For this purpose, existing knowledge is being combined with experimental readouts to construct networks describing pathological processes on molecular, cellular, and anatomical levels in the brain. Constantly improving analytical methods are applied to dissect structure and dynamics of these networks in an attempt to understand the pathology behind.

However, this systems approach is not sufficient to fully answer challenges of neurological disorders. The networks of dynamic topology, responsible for emergence of coherent function of the brain, should be considered along with their relation to other scales of brain organization. For instance, frequency and amplitude of neuronal firing that maps onto interactions of neurons and other cells should be considered in the context of the function of anatomical location containing the neurons, as well as molecular processes responsible for the firing.

In the following sections we review the three physiological scales to consider when approaching neurological disorders: molecular, cellular, and the whole brain. We discuss recent approaches to characterize components of networks on these scales, and to construct and refine networks specific to each scale. Finally, we emphasize the need for cross-scale network analysis to gain further understanding of the complexity of neurological disorders.

## 2 Molecular Interaction Networks

### 2.1 Components

Characterization of disease-related mechanisms on the level of molecular neurobiology is both necessary and extremely challenging. Our knowledge of the physiology of neuronal and glial cells is still limited, mostly because the brain tissue is both heterogeneous and difficult to access. In effect, molecular networks usually represent only a reduced view of the molecular biology of nervous cells. Figure 1 illustrates this reduced network view next to a cell it represents.

This reduced, but not reductionist, view is the essence of disease-oriented molecular networks. The network has to model the processes implicated in the pathogenesis; thus it has to focus only on relevant components and interactions. However, taking into account the multitude of processes implicated in neurological disorders, identifying which elements of the molecular networks are relevant is not a trivial task [16].

Typical components and corresponding interaction types of molecular networks are listed in Table 1, with an indication of potential interactions between different components. It should be emphasized that the network representation describes dynamical processes and the abovementioned interaction types have various temporal and spatial resolutions. For instance, the axonal transport of substrates of synaptic activity is quite different from the calcium transport across the neuronal membrane.

### 2.2 Disease-Specific Molecular Networks

The focus of disease-specific molecular networks depends on the nature of the pathogenesis. This scope ranges from well-defined mechanisms through a set of implicated pathways to a number of

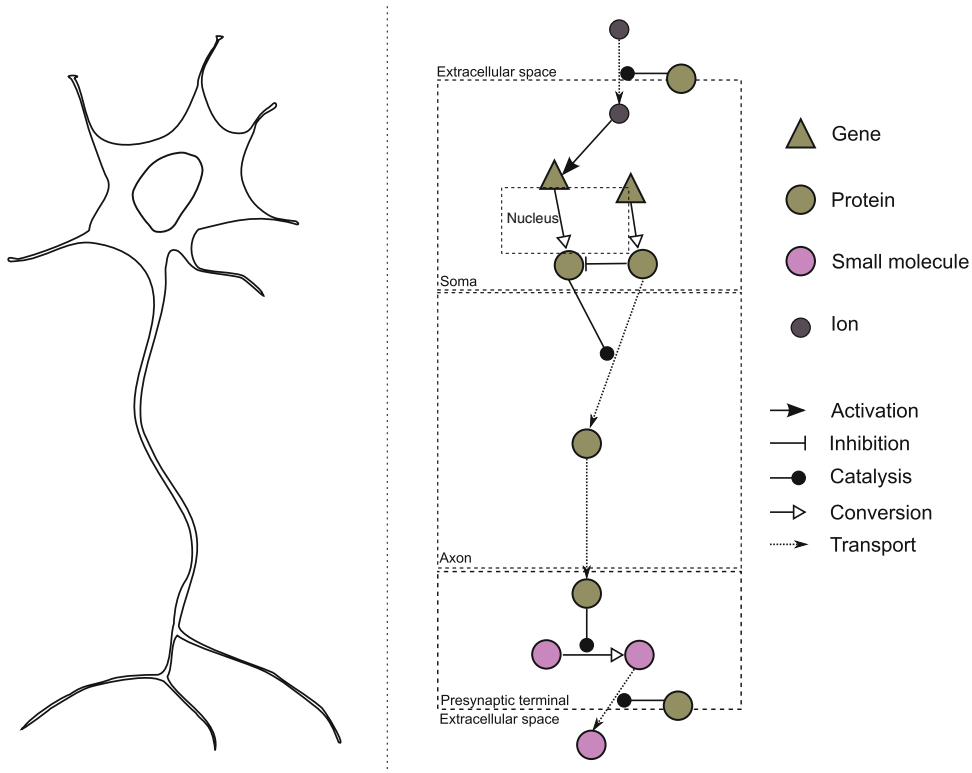


**Fig. 1** A network representing molecular processes in a neuronal cell, illustrating the reduced network view of complex cell physiology. Activation and inhibition interactions describe regulatory events within a neuronal cell. Catalysis interaction denotes a catalyst role of an element. Conversion refers to change of state of molecules, be it biochemical reaction, or protein complex assembly. Transport describes translocation of molecules within the neuronal cell, or across its boundaries

**Table 1**
**Elementsand interaction types typically used for constructing molecular networks.** *See* **Fig. 1 for description of interaction types**

| | Interaction types | | | |
|---|---|---|---|---|
| **Element types** | **Regulatory** | **Catalytic** | **Conversion** | **Transport** |
| Gene/mRNA | • | | • | |
| MicroRNA | • | | | |
| Protein | • | • | • | • |
| Small molecule | • | • | • | |
| Pathway | • | • | • | • |

involved molecules. The focus of the molecular network is in effect closely related to questions that systems-level analyses should answer. The more focused the network model, the more precise

questions may be asked, up to the level of high-quality, computable metabolic models [17].

In the case of prion-like diseases, the causative mechanism is a misfolding prion protein, inducing neurodegeneration and spreading across the nervous system [18]. Regardless of our insight into the structural properties of prions [19], the knowledge about the pathology of this single molecular mechanism is insufficient to propose a cure.

Huntington's disease (HD) is a genetic disorder caused by excessive glutamine repeats in the gene encoding the huntingtin protein [20]. Such mutated huntingtin induces formation of pathogenic inclusions in neuronal cells and is supposed to burden their protein degradation systems. Although the genetic factor is convincingly identified, the exact mechanism of molecular neuropathology remains elusive.

Chronic neurodegenerative disorders, like Alzheimer's disease (AD) or Parkinson's disease (PD), are influenced by a combination of genetic and environmental factors [21, 22]. A number of familial genes and disease-inducing toxins indicate a range of molecular pathways affected in the course of these diseases. Nevertheless, causative factors remain unclear.

Epilepsies are neurological disorders where genetic components are known, or become a risk factor. Here, dysfunction of molecular mechanisms leads to the emergence of pathology on higher levels of organization of the central nervous system [23, 24]. The utility of molecular networks in studying this class of disorder seems to be limited, as existing approaches are reductionistic, not able to apprehend the complexity of the pathology [25].

## 2.3 Construction of Molecular Networks

Construction of networks reflecting molecular level of neuropathology usually follows a number of well-defined steps. In general, these are (a) identification of candidate molecules, (b) connection of the molecules by querying databases or manually curating the interactions, and (c) refinement and evaluation of the network.

### 2.3.1 Identification of Candidate Molecules

Identification of candidate molecules to construct a molecular network is often supported by high-throughput screens in experimental disease models. In many cases associative networks are established using the underlying data, i.e., networks, where interactions do not represent any mechanistic link between connected elements. In the end, these associative networks support candidate prioritization for assembling disease-related, mechanistic models [26–28].

For prion diseases, mouse models [29], cellular models [30], and yeast genetic screens [31] supported construction of molecular networks. Similarly for HD-related pathology, yeast screens helped to prioritize candidates for network construction [32]. Whenever available, human *postmortem* tissue is used for omics

profiling allowing, for instance, to pinpoint genes involved in PD [33–35] and AD [36, 37] pathogenesis. Interestingly, candidates for molecular interaction networks in case of certain epilepsies base on reconstruction from brain tissue biopsies collected during surgical procedures [38].

### 2.3.2 Connection of the Molecules

Establishing interactions between candidate molecules can involve querying databases of molecular mechanisms [39], or manual curation [40]. Profiling of the transcriptome combined with literature-based network reconstruction has been proposed for instance for prion diseases [29, 41] or AD [42] as a method to indicate pathways affected during the disease progression. Network reconstruction based on genomic data, i.e., focused on genetic risk factors of neurological diseases, was proposed for prion [43], epilepsies [44], and PD [45].

The construction of molecular networks may require manual curation either to de novo assemble the interactions between candidate molecules or to review an automatically constructed network. Development of a large-scale, disease-focused network is a challenging task. In the fields of AD [46] and PD [47], heterogeneous molecular interaction maps were established. A more focused approach resulted in the curation of existing metabolic pathways into a brain-specific network [40]. Finally, in the field of PD, even more focused network-based models were constructed, representing in detail processes related to cellular stress of neuronal metabolism and to protein misfolding [48, 49].

### 2.3.3 Refinement and Evaluation

Networks constructed on the basis of analytically identified candidate molecules and interactions are prone to bias. Evaluation and refinement of constructed networks should be performed to ensure their proper focus. The quality of established disease-related networks may be evaluated using relevant experimental datasets mapped on the network structure. Fujita et al. proposed to visualize brain tissue transcriptomics data on their manually curated PD-relevant network [47], what allows to assess its relevance. In case of epilepsies such an evaluation helps to tailor networks for different disease subtypes, for instance focusing on specific neuronal receptors [50] or filtering using gene expression profiles from brain tissue of pharmacoresistant cases [51]. In addition to human brain samples, datasets from disease-related experimental models can be similarly applied [52, 53]. Especially experimental setups focused on detailed analysis of specific pathways are useful in such a network evaluation. For instance, recent work on the mechanisms of the Wnt signaling pathway [54] produced time series of gene expression following Wnt stimulation. Network analysis of these series confirmed known mechanisms governing canonical and noncanonical activation of the Wnt-pathway, and shed light on molecular mechanisms relevant for AD. Although the constructed

network was associative, such gene expression time series data can also be mapped on curated, mechanistic models of the disease to validate their accuracy in reflecting crucial mechanisms.

Besides using tissue-specific experimental datasets, additional sources of information can be applied to refine the shape of developed molecular networks. Recently, microRNAs gained attention as potential modulators of neurological disorders [55–57]. These regulators of mRNA are especially relevant when constructing brain-focused, gene regulatory networks. Similarly, DNA methylation, or protein acetylation, emerges as a potent regulator of a large number of genes in neurological disorders [58–60], which can affect entire functional modules of molecular networks.

### 2.4 Summary: Molecular Networks

Molecular networks of brain disorders are very heterogeneous, such as the data sources used for their construction. Molecular mechanisms of the brain are studied using experimental models, postmortem tissue, and, in particular cases, brain biopsies. When constructing these networks, a trade-off has to be made between network breadth and depth. Large-scale networks provide an overview of disease processes, allowing limited analytical approaches [47]. Moreover, they enable studies on molecular cross-disease comparison, aiming to elucidate overlapping mechanisms between diseases like AD or PD, and diabetes or autoimmune diseases [61–63]. In turn small, focused networks can describe disease-related processes with high quality and using established mathematical frameworks. Simulation of dynamics in such networks allows predictions on causality and temporal resolution of represented processes [48, 64].

Importantly, molecular networks should not be considered as stand-alone structures. The cellular machinery of brain cells works in the context of its embedding tissue, which in turn forms functional areas of the brain. Thus, although prion pathology has a molecular basis, the disease has to be considered also from the perspective of higher order networks. Recent findings on prion interactions with GABA receptors and their influence on excitotoxicity allow forming a link with cellular networks [65]. This link is further reinforced by the findings on the modulatory role of prion protein in the dopaminergic system [66]. It might be necessary to bridge molecular and brain layers to explain symptomatic biomarkers of prion disease [67].

Our knowledge on the molecular basis of HD is insufficient to explain its pathogenesis. This fact suggests broadening the scope of systems analysis beyond the molecular interaction networks. Studies correlating genetics of early HD with neuroimaging studies form a bridge between molecular and brain-level networks [68].

Importantly, higher levels of network representation should be considered when analyzing molecular mechanisms. In PD, degeneration of a particular neuronal populations is observed,

suggesting that cellular interactions [69, 70] play an important role in the pathology. Moreover, growing body of evidence points towards pathological spreading of synuclein aggregates across brain areas [71, 72] as the key mechanism of PD. Higher levels of network organization may provide further understanding in PD pathology. Recent studies in AD and PD follow this concept by analyzing omics of different brain areas affected in PD and AD [37, 73], or genetic factors affecting functioning of brain-level networks [74, 75].

The molecular pathogenesis of epilepsies contributes significantly to the pathology of networks of higher order [76]. Therefore, the need for systems biology is pressing, as their emergent properties span not only over many elements of molecular networks, but also over different network layers.

## 3 Cellular Interaction Networks

### 3.1 Components

The human brain consists of approximately $10^9$ neurons, each of which has on average 100,000 synaptic connections to other neuronal cells [77, 78]. This plethora of neuronal interactions reveals a well-defined network structure, established already during the developmental stage. This network has varying spatiotemporal characteristics as some cells are more locally connected whereas others project to distant regions within the brain and the body, with some connections being longer than a meter [79, 80]. Moreover, the interaction modes between neuronal cells are diverse, being either excitatory or inhibitory in dependence on neurotransmitters and corresponding receptors of their synapses.

While the main brain structure remains stable over lifetime, the brain demonstrates a huge local plasticity compared to all other organs, enabling learning and memory. This plasticity is achieved by an input-dependent rewiring of the neuronal network topology in specific brain regions like the hippocampus and the cortex. The main mechanisms for this rewiring are long-term potentiation and long-term depression that alter synaptic connection between neurons in an activity-dependent manner according to Hebb's learning rule [81, 82].

Importantly, the human brain consists of more than 50 % of glial cells that play an important role in the activity of brain cellular networks. Among these cells astrocytes are the majority, complemented by oligodendrocytes and microglia [83]. Astrocytes translate neuronal activity and the related energy demands to blood flow regulation and corresponding uptake of glucose and oxygen to facilitate neuronal metabolism [84, 85]. Oligodendrocytes insulate axons of the neurons by myelin sheets that allows for fast signal transduction and protects the fragile structure from the exterior [86]. Microglia represent the macrophages of the brain.

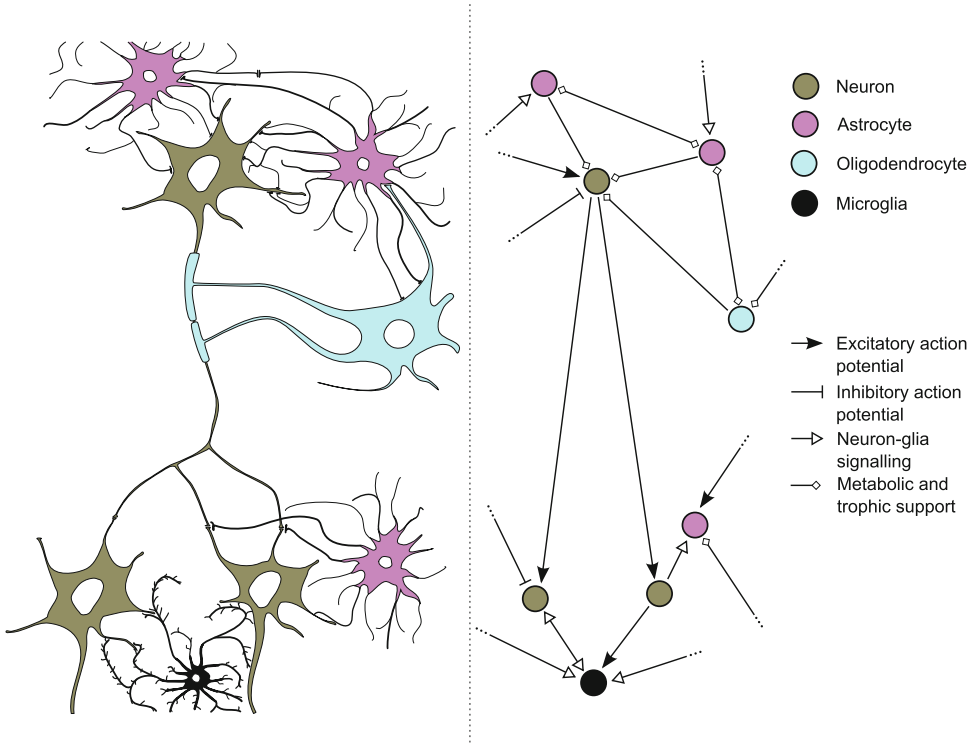


**Fig. 2** The diverse cell types within the brain generate a complex interaction network with different classes of interaction edges that also exhibit distinguished dynamic properties. Excitable connections (excitatory or inhibitory) denote action potentials of the neurons. Metabolic and trophic support interactions represent exchange of substrates required for cellular network homeostasis. Topology-altering interactions denote cellular mechanisms leading to changes in the local network structure

They sense pathogens and damaged cells, migrate to the specific areas, and clean them by phagocytosis [87]. Figure 2 gives a schematic overview of these interactions including a corresponding network representation.

The brain exhibits a wide and heterogeneous spectrum of cellular interactions that covers many spatial and temporal scales. The fastest intercellular signaling occurs between neurons on a millisecond time scale [88]. Thereby electric impulses of axon potentials are transmitted at synapses to connected cells. This fast communication and typical feedback loops enable fast perception, appropriate responses, and refinements of actions [89]. Importantly, the signaling within the neuronal network is also influencing the surrounding glia, which in turn can modulate the neuronal communication.

Astrocytes seal up the synaptic cleft to facilitate chemical information transmission and are responsible for clearing the neurotransmitters from the cleft and recycling them back to the presynaptic terminal [90]. Importantly, astrocytes express receptors for diverse neurotransmitters. For instance, the glutamate release at

glutamatergic synapses activates not only the postsynaptic neuron but also the surrounding astrocytes. Activated astrocytes increase their cytosolic $Ca^{2+}$ on the time scale of seconds, which triggers downstream signaling processes including potential release of ATP and glutamate [91]. This release induces the regulation of the blood flow but also a local amplification process [92]. Subsequently, the signal can propagate within the astrocytic network by intercellular $Ca^{2+}$ waves activating tens of cells and spreading hundreds of micrometer [93], where it may induce or modulate neuronal activity including synapse genesis by long-term potentiation and long-term depression [94].

Oligodendrocytes support neuronal functionality by myelination that occurs on the time scale of minutes to hours [87]. Moreover, recent findings point to their role in metabolic supporting and regulation of neuronal function [95, 96]. Similarly, microglia have a long-term influence on neuronal dynamics. Besides removing pathogens and cell debris, including damaged neurons from the brain, microglia are responsible for synapse pruning [97]. The resulting changes in the neuronal network topology occur on the time scale of hours and are essential for brain function. Interestingly, a similar role was recently reported for astrocytes [98]. Table 2 gives an overview on the different cell types and their role in brain dynamics.

Overall, the huge neuronal connectivity of neurons leads to dense network structures that translate the nonlinear dynamics of the single entities into a mesoscopically more ordered behavior. The resulting fine-tuned activity patterns often exhibit locally synchronized firing of neurons that correspond to specific representations of information such as visual memory [99] or movement controls [100]. The underlying neuronal microcircuits are embedded in and modulated by a number of regulatory cellular interactions that allow for their plasticity and adaptation by changing the network topology [89]. To integrate the different involved levels and scales, we need to rely on systems approaches.

**Table 2**
**Elements and interaction types of cellular networks. The temporal resolution of each interaction is explicitly indicated**

| | Interaction types | | |
|---|---|---|---|
| **Element types** | **Excitable** | **Metabolic** | **Topology altering** |
| Neuron | Milliseconds | Seconds | Hours |
| Astrocyte | Seconds | Seconds/minutes | Hours |
| Oligodendrocyte | | Minutes/hours | |
| Microglia | Minutes | | Hours |

### 3.2 Disease-Specific Network Topology

The challenge to identify disease-specific network topologies and dynamics is to distinguish between primary and secondary effects. Within this context, the general question arises as to how single-cell properties reflecting individual entities are translated to the cellular network behavior that may cause the pathology.

A direct link between molecular modification and impaired network dynamics is observed in epilepsy. In this case, a single mutation of a channel protein can lead to increased excitability on a single-cell level, inducing more frequent spiking [101, 102]. Nodes with such modified properties within the cellular network can induce drastic changes in the mesoscopic dynamics. Higher excitability of single cells can cause globally synchronized activity of many neurons, inducing seizures. At the same time, the affected cellular network is often capable to compensate for synchronized firing. In effect, both time and brain area of seizure occurrence are difficult to predict [103]. Interestingly, for cases where antiepileptic medication does not exhibit seizure-suppressing effects, a possible therapy is to remove parts of the temporal lobe or to disconnect specific projections that allow for seizure spreading [104].

In case of HD, the pathogenic genetic factor is well correlated with the cellular phenotype. Resulting neurodegeneration predominantly takes place in the striatum; however the mechanistic relation between the single-cell characteristic and the pathogenesis on the cellular network level is still not understood. Recent reports suggest an increased neuronal activity that induces larger energy demands and facilitates aging in the corresponding brain areas, leading to earlier cell death [105].

Similarly, current evidence on PD points to an unbalanced energy budget of dopaminergic neurons in the substantia nigra and their corresponding intercellular interactions [106, 107]. Selective vulnerability of these neurons comes from their extra energy demand due to dopamine synthesis and homeostasis of long projections. Disturbances in the energy balance prime these neurons for an early cell death [108]. Moreover, the proportion of glia, and their resulting metabolic support, within affected regions of dopamine synthesis is lower compared to other brain areas [109]. Another factor of dopaminergic degeneration may be the intracellular spreading of misfolded α-synuclein protein [110, 111]. In consequence to the tissue-level stress excessive degeneration of dopaminergic neurons in the substantia nigra depletes the pool of striatal dopamine, affecting the basal ganglia feedback loop coordinating signals from the peripheral nervous system and the sensomotoric cortex [112]. Consequently, thalamic neurons fire synchronously, inducing the stereotypic tremor. The activity of these neurons can be targeted by deep brain stimulation (DBS) that de-synchronizes the neuronal activity and suppresses the tremor [113].

The molecular basis of deregulation of cellular networks can be observed in prion diseases. The misfolding chain reaction leads to

intra- or extracellular aggregates and eventually to neuronal death [114]. The associated changes of the neuronal network structure and corresponding dynamics subsequently evoke neurological symptoms such as dementia. Compared with the described direct dynamical impairments in epilepsy or PD that are observable by highly synchronized neuronal activity, the consequences of the modified network topology in most prion diseases are less understood [115]. A promising approach for a unifying perspective on neurodegeneration is brain energy metabolism linking many phenotypic traits and symptoms across several diseases [116, 117].

## 3.3 Construction of Cellular Networks

Cellular networks are difficult to construct due to the huge structural and dynamical complexity of represented interactions, in particular the specialized neuronal morphology and the extraordinary synaptic connectivity of the neuronal network. The architecture of glial cells, although less elaborate than of neurons, also features processes and multicellular interactions. Determination of a cellular network topology from such a heterogeneous and interconnected mosaic of cells is a nontrivial task for neurohistology.

### 3.3.1 Identification of Cellular Interactions

A first approach to this problem, proposed by Golgi, was the low-efficiency plasma membrane staining with silver chromate. The resulting single-neuron stains revealed the ramified morphology of neurons and the layer-like organization of the cortex [118]. However, this approach is not suited for identification of cellular networks, as only a subset of cells is labeled in a region of interest.

Currently, electron microscopy is applied to track the neuronal interconnections, down to their fine substructures [119, 120]. The resulting large data sets have to be subsequently analyzed, mainly manually, because the variety of synaptic topologies limits automated segmentation approaches. More recent developments of synapse-specific dyes [121] enable more high-throughput investigations and functional regulation studies [122, 123]. A general limitation of all these approaches is that they can identify individual synapses but are unable to allocate these to specific neuron-neuron connections. In the context of network reconstruction, this means that only the edges of the neuronal network are identified without the necessary node associations.

### 3.3.2 Connecting the Elements

This intrinsic difficulty of studying cellular networks in human brain tissue brought a significant focus to animal model studies. In 2007, Lichtman and coworkers established a landmark invention addressing the neuronal connectivity challenge with their transgenic Brainbow mouse model. The approach is based on the random expression of fluorescent proteins of different colors [124] producing cell-specific color mixtures that enable to discern single neurons and identify their connections. In effect, it became possible to describe whole neuronal microcircuits [125]. Although the

Brainbow method allows for identification of neuronal connections, it provides no information on network dynamics.

In the cellular networks of the brain, dynamics is of crucial importance with respect to synaptic signaling and plasticity. Moreover, interactions between glia and neuron-glia cross talk cannot be inferred from histological information as they take place in the extracellular space without direct cell-to-cell connections [126]. Currently, the dynamics of the cellular networks [127–129] are studied using in vitro approaches [130], which provide a good footing to understand disease-specific modulation of network dynamics in vivo [131]. Recent developments combining genetics and optics enable well-controllable optogenetic experimental model systems for neuronal microcircuits [132, 133]. Application of two-photon microscopy on a brain with genetically modified reporters allows imaging of brain areas and optical control of neuronal activity [134]. Imaging and control of neuronal microcircuits are especially plausible to study disorders featuring acute neuronal misfiring, like epilepsy. For other neurological diseases, with a chronic impairment of neuronal network dynamics and associated topology, cellular network reconstruction requires more input information concerning in particular the modulatoryeffect of neuron-glia interactions [135, 136]. However, establishing these interactions in the cellular networks will require approaches allowing simultaneous molecular and activity profiling.

#### *3.3.3 Refinement and Evaluation*

The original Brainbow method is restricted to optically accessible regions. As two-photon microscopy allows for penetration of tissues to the range of a few mm [137], this approach is still beyond typical mammalian brain size. To overcome these limitations, new methods have been developed, allowing to remove the lipids of the tissue by electrophoresis, leading to transparent organs [138, 139]. Clearing a brain and applying specific fluorescent antibody staining enable imaging of a whole brain on single-cell resolution without any sectioning. The resulting brain maps do not only include all neuronal connections [9] but can also provide spatial information on glia localization. When imaging such a treated brain of a patient with autism, Deisseroth and colleagues found abnormal neuronal projections that exhibit closed loops within individual cells [138]. This finding demonstrates how a modified structure may influence brain dynamics and behavior.

Despite the substantial progress, the clearing methods are still restricted to the analysis of a fixed tissue and are unable to monitor the intricate interplay of neuronal network dynamics and structural development. This challenge may be addressed in near future in zebrafish experiments [140]. The transparency of the fish and the availability of genetically encoded $Ca^{2+}$ dyes combined with appropriate image analysis tools [141] will allow for system-wide data acquisition that has to be inferred with computational modeling

[129] for a mechanistic understanding of brain dynamics. Another strategy is to optimize noninvasive diffusion MRI and fMRI techniques (*see* Subheading 4) to single-cell resolution that could reveal microcircuit dynamics in patients and provide bottom-up understanding in neurological pathogenesis. The ambitious Human Brain Project [142] may become an integrative initiative for these approaches.

The evaluation of constructed cellular networks is possible in vivo with available methods. The optogenetics approach allowed Tønnesen and colleagues to achieve light-induced hyperpolarization of neurons in an animal model of epilepsy. Hyperpolarization of certain neuronal populations was found to suppress neuronal bursting, demonstrating new targets for epilepsy treatments [143]. In human brain, the technique of magnetoencephalography (MEG) allows to measure oscillatory activity of neuronal populations in given brain areas [144]. Although MEG lacks single-cell resolution, it allows to track disease-specific frequency patterns, which in turn may validate analytical outcomes of cellular network analyses.

### 3.4 Summary: Cellular Networks

The cellular network level bridges between molecular pathogenesis and the resulting neurological phenotype of the brain. The diversity of the intercellular interactions and their rich spatiotemporal spectrum (*see* Table 2) render this level exceptionally complex to model. At the same time, cellular network analysis may indicate promising candidates for therapeutic interventions, as pathogenic cell properties may be altered by drugs targeting key molecular pathways, or corrected by tissue-level interventions like DBS.

The major challenge for a mechanistic understanding of these intercellular interactions is the high connectivity of the neuronal network and dynamics covering many spatiotemporal scales. This complexity permits experimental methods to focus only on a subset of phenomena and integrative systems approaches are needed to understand underlying signaling mechanisms and support development of novel therapeutic strategies.

## 4 Brain-Level Networks

### 4.1 Components

Network representation is very appropriate to describe brain-level activity. Connectivity of different anatomical and functional brain areas suggests efficient network structure, optimized to provide high-level cognitive functions at a relatively low cost [145]. Disruption of this network is associated with pathological states of the brain. On the other hand, changes in the brain wiring may happen also due to compensatory mechanisms [146]. Similarly to network representations on other levels, we face certain simplification of extremely complex structure of the brain to a set of elements and interactions. Figure 3 illustrates this situation.

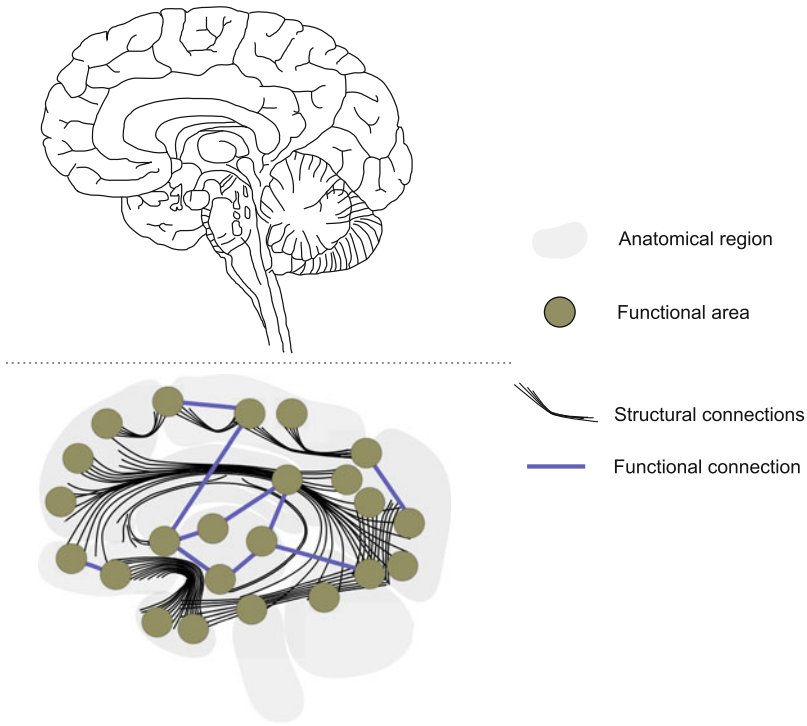


**Fig. 3** Brain-level networks represent connections between anatomical and functional brain areas, representing structural connections of directly interacting groups of neuronal cells, or functional associations between areas co-activated during a given type of brain activity

The number of components of such a network is quite limited, mostly due to the narrow scope of current neuroimaging approaches. In general, it is possible to measure functional areas of the brain by assessing oxygen consumption (fMRI-BOLD), or measure distribution of radiolabeled tracers (PET and SPECT). In turn, structural measurements are achieved assessing diffusion rates in asymmetric neuronal cells (DTI-MRI, or dMRI). Finally, our knowledge on brain topology provides us with certain mapped brain areas and their associated neurotransmitter signaling. It needs to be emphasized that the construction of brain-level networks depends heavily on proper labeling of brain areas. The task of brain parcellation is challenging, and can heavily influence the properties of obtained networks [147]. Table 3 summarizes components and interactions of brain networks.

### *4.2 Disease-Specific Brain Networks*

The goal of a disease-oriented network approach on the brain level is primarily to synthesize experimental readouts from neuroimaging studies into a coherent picture of changes in brain function and structure caused by specific pathogenesis [148]. Because brain networks are inferred directly from neuroimaging readouts, or from established brain topology, they are usually more homogeneous

**Table 3**
**Elements and interactions typically used for constructing brain-level networks**

| | Interaction types | | |
|---|---|---|---|
| **Element types** | **Structural connectivity** | **Functional association** | **Mapped connectivity** |
| Functional area of metabolic activity | • | • | • |
| Functional area of neuronal activity | | • | • |
| Anatomical area | • | | • |

than molecular or cellular networks. Moreover, the neuroimaging framework is similar for all neurological diseases, and network construction efforts aim to identify brain areas associated with specific pathogeneses. Thus, in contrary to molecular networks, mechanisms specific for different diseases will not affect the focus of the network being constructed.

### *4.3 Construction of Brain-Level Networks*

#### *4.3.1 Identification and Connecting of Candidate Areas*

One of the most widely used methods to construct disease-relevant brain networks is functional MRI (magnetic resonance imaging), recording BOLD (blood-oxygen-level dependent) contrast signal in the brain during rest or while performing various tasks. Analysis of an fMRI signal allows to identify activated candidate areas, but is a nontrivial task, often requiring advanced data exploratory techniques [149]. Identified activated areas become elements in a brain-level network, while interactions are established on the basis of correlation of their co-activation [150, 151]. The approaches based on fMRI are numerous in the field of neurological research. In the context of this review it is important to highlight research, where a systems approach is followed to obtain a global picture of the disease. An important example is the work of Baggio et al. [152], who analyzed resting-state fMRI data from PD, mild cognitive impairment, and healthy subjects to reconstruct a global brain network associated with cognitive deficits in PD. Another interesting example of an fMRI study is the construction of a brain network for epilepsy by Toussaint and colleagues [153], aiming to highlight disruption in the functional network of the brain following epileptic discharges. Network approaches to epilepsies are reviewed in [154].

Another approach to identify and connect brain networks is neuroimaging of radiolabeled tracers. This approach highlights specific metabolic processes in the brain, involving the chosen radiotracer. The processes can be general, like glucose metabolism, or disease specific, like circulation of synaptic vesicles. The so-called metabolic networks of the brain are acquired in a similar manner to fMRI-derived networks, namely by analyzing temporal

correlations of radiotracer expression between different brain areas [155]. Such metabolic networks were recently constructed for PD [156] and AD [157].

Structural brain networks represent physical connections between brain regions by white matter fiber tracts. These connections are calculated on the basis of so-called diffusion MRI (dMRI)measures by tractography approaches. Disease-associated alterations, either pathogenic or compensatory, may be reflected in the topology of these structural connections [158]. Interestingly, these structural networks were recently shown to reflect brain response to treatment of PD [159] and epilepsy [160].

Finally, besides neuroimaging-based brain networks, prior knowledge on brain anatomy and function is used to construct networks of disease-specific dysregulation of established brain circuits. One of such circuits is the default mode network, the brain circuit active when the brain performs no particular cognitive task. This network, for instance, was found distorted in AD [153, 161, 162] and in PD [152]. One of the very-well-explored disease-related circuits is the model of basal ganglia dysfunction in PD [163, 164]. The architecture of corticobasal ganglia–cortical loops [165] is in fact a reconstructed network, with interactions being projections of different neuronal subtypes to basal ganglia and cortical regions [166]. Here, the disturbance of these mapped circuits may be assessed using the technique of recording neuronal activity in local brain areas, called electroencephalography (EEG). EEG allows to obtain a good temporal resolution when measuring brain activity during epileptic seizures [167], or permits longitudinal tracking of the disruption of disease-relevant brain circuits, as shown for PD [168].

#### 4.3.2 Evaluation and Refinement

Brain-level networks, whether neuroimaging based, or derived from prior knowledge, need to be evaluated concerning their relevance and refined. One possible approach to reach this goal is correlation with available clinical data. In their study Morales and colleagues [169] performed a cognitive assessment of PD patients along with recording of the fMRI data and constructed non-overlapping subgroups of patients with different cognitive impairments. This allowed them to improve the interpretation of neuroimaging data. Similarly to clinical assessment, drug therapy-related information can improve the quality of obtained networks. In a recent study, Cole and coworkers demonstrated that connectivity among a number of well-defined brain circuits is influenced by dopamine therapy [170]. Finally, longitudinal neuroimaging can greatly help to refine and improve the quality of brain networks. This approach was considered by Seibyl et al. [171] to help stratifying subgroups of subjects and better approach the evolution of the disease.

Certain neurological disorders carry a significant genetic burden. This information can also be used to better tailor the

constructed networks. In their work, Rao and colleagues performed fMRI on HD patients taking into account the number of glutamine repeats in the huntingtin sequence. This stratification, together with a list of HD-associated brain circuits, allowed them to identify networks specific to the forecasted severity of the disease [172]. Genetic stratification was coupled with fMRI measurements of cognitive tasks in PD [173]. In this work Nombella and coworkers demonstrated that three PD-associated alleles influence cognitive systems in PD, although no direct network construction attempt was made.

### 4.4 Summary

Disease-specific brain-level networks are quite homogeneous concerning their composition. Their common denominators are brain anatomy and function. Their construction usually heavily depends on supplementing neuroimaging data, where the most important factors are the choice of subjects and the neuroimaging approach. While dMRI supports construction of networks with fixed topology, fMRI and metabolic imaging can produce dynamic networks. Importantly, networks obtained with the latter approaches are correlation based and represent patterns of temporal associations. Thus, their interpretation needs to be performed with care and prior information on mapped relevant brain circuits has to be taken into account.

Importantly, brain networks are the highest order representation of pathogenic processes in neurological diseases. This aggregated view allows for convincingly linking the network disturbance to clinical endophenotypes. At the same time it is difficult to assess the emergence of the disturbance from the pathology on cellular and molecular levels. Here, improvements in metabolic imaging [156] and genetic stratification of neuroimaging subjects [173] should allow to correlate molecular and brain-level networks.

## 5 Synthesis

The brain is an extremely complex structure and this complexity can be observed on the level of the whole organ, cellular, and molecular organization. This nested network architecture, illustrated in Fig. 4, increases the difficulty in studying pathogenesis of neurological disorders. Nevertheless, systems approaches applied on each of these levels independently start to bring better understanding of the nature of these disorders.

### 5.1 Cross-Scale Network Analysis

Regardless of the level of brain organization, construction of networks for the purpose of systems analysis involves a similar trade-off between the scope and the depth. Broad-scope networks, constructed on the basis of omics screens (molecular) [41], micro-electrode arrays (cellular) [130], or MRI data (brain level)

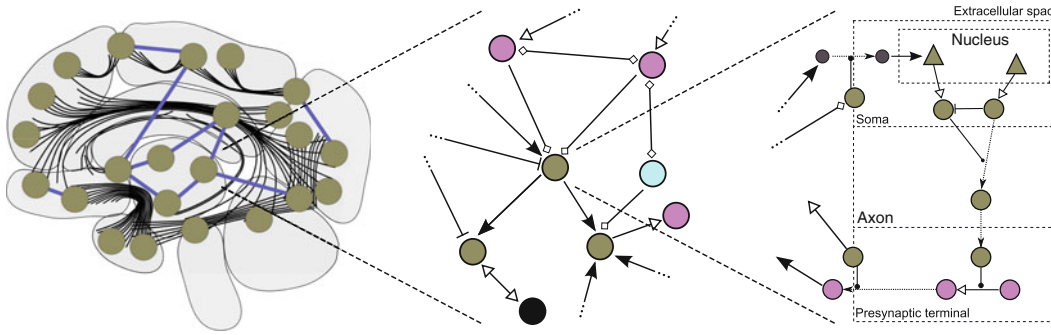


**Fig. 4** Networks representing brain disorder may be deeply nested, with each of the levels contributing to the phenotype

[174, 175], have usually a broad scope, but limited depth. In effect, network- and systems-level analysis provides general large-scale insights into disruption of disease-associated brain function [33], microcircuits [138], and pathways [176]. On the other side, carefully constructed, focused networks offer detailed analyses and conclusions concerning the dynamics of the analyzed system. These focused networks require manual curation on the basis of known molecular interactions (molecular) [49], known or monitored activity of cell populations (cellular) [177], or well-mapped brain circuits (whole brain) [178]. Currently, the size-scope tradeoff is inevitable. However, as the efforts towards high-quality network curation gain community-scale attention [47, 179], and new high-content screening approaches are proposed for network construction [180], we may expect that disease-specific networks will grow in size without sacrificing their quality.

Concerning the nested network architecture, it is important not only to analyze in detail the behavior of a system on a given level of complexity—molecular, cellular, or whole brain—but also to cross the scales with the systems analysis. Experimental approaches allowing to achieve this cross-scale analysis are topic of intensive research. For instance, novel imaging techniques [181, 182] allow us to gain deep insights into the molecular basis of cellular dysfunction, as well as bridge between cellular and brain scales [139].

What remains a challenge is a proper analytical approach to draw meaningful conclusions on the level of nested networks that will ultimately lead to better understanding of the disease. Currently, a number of computational approaches have been proposed that bridge the cellular and brain-level networks, focusing on modeling neuronal activity from specific brain areas to gain insight into whole-brain network dynamics. The granularity of these approaches varies from simulation of spiking behavior of single neuron [183] or neuronal population [184] models based on Hodgkin–Huxley equations to analysis of neurotransmitter release by specific brain circuits using reinforced learning models [185].

A framework bringing together molecular and higher scales still remains to be proposed; however efforts in this direction can be seen in brain network reconstructions concerning molecular profiles of subjects [172, 173].

## 6 Perspectives

Our current understanding of developmental processes, including brain development, encompasses the emergence of organ-level structure and function from elaborate cellular and molecular interactions. We appreciate the importance of temporal and spatial dynamics of these processes, and associate their perturbations with pathogenic states. Similarly, when approaching diseases of an adult brain and analyzing associated pathological processes, we should consider molecular, cellular, and organ-level dysfunction simultaneously. Emerging evidence on close coupling between developmental processes and the condition of specific neuronal subpopulations affected by neurodegeneration [186, 187] reinforces this perspective.

Systems biomedicine in neurology is expected to gain insight into the complex nature of human brain and its disorders, facilitating accurate diagnosis, suggesting efficient treatment, and, finally, allowing for preventing the pathogenesis. An important step to achieve these goals is to consider the brain as architecture of nested networks: molecular, cellular, and brain level. These networks become substrates of various mathematical and computational approaches, with an assumption that a given disorder is a dysfunction on a network level. Assembly of such a multi-layer network will require integration of data, but also of expertise. Community-driven approaches, like the Allen brain atlas [188] or the Parkinson's disease map [47], extending well past the molecular layer, are needed to address this challenge.

Diseases with prominent molecular components, like prion diseases or HD, will primarily benefit from detailed analysis of molecular networks. For these disorders to be pharmacologically treated, it is necessary to accurately identify mechanisms to target. Similarly, in the field of chronic neurodegenerative diseases like PD or AD only symptomatic treatment is available. Consistent failure of drug design [189] and of gene-therapeutic approaches [190] reveals a pressing need for an insightful methodology to identify causal factors of these diseases, which should be likely sought on the molecular level. Importantly, concurrent or integrated analysis of cellular or brain level networks may allow to interpret how both molecular pathogenesis and drug treatment influence higher order brain networks [191].

Disorders like epilepsies will primarily benefit from insights from cellular and brain network analysis. Here, the pathogenic

state emerges in much shorter time frame than in chronic diseases. Distorted patterns of neuronal firing need to be stratified for different epilepsy subtypes and analyzed for their response to treatment [192]. Recent advances in multi-scale [193, 194] and multimodal neuroimaging [195] come forward to meet the needs of an integrative network analysis approach. The assessment of treatment outcomes by cellular and brain network analysis is especially important concerning increasing application of DBS in the field of PD [196], but also epilepsies [197]. Currently, DBS electrodes deliver pacemaking stimulation in single site, and in an open loop. However, the possibility to read out the firing frequency of the neurons at the stimulation site allows designing feedback systems, or considering multi-site stimulation [198]. In both cases, systems analysis of cellular and brain networks is indispensable to properly design the therapeutic approaches.

Finally, advanced therapeutic and preventive approaches can benefit from network analysis integrating molecular, cellular, and brain layers of complexity. One of them is regenerative medicine using stem cells [199, 200]. The main challenge in stem cell grafting is the question where to place them. This, in turn, requires insights integrating information on molecular function of the cell, its role within the targeted tissue, and the impact of the grafted area on the whole-brain network structure and function.

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