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Multiscale network neuroscience in neuro-oncology: How tumors, brain networks, and behavior connect across scales

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Abstract

Network neuroscience refers to the investigation of brain networks across different spatial and temporal scales, and has become a leading framework to understand the biology and functioning of the brain. In neuro-oncology, the study of brain networks has revealed many insights into the structure and function of cells, circuits, and the entire brain, and their association with both functional status (e.g., cognition) and survival. This review connects network findings from different scales of investigation, with the combined aim of informing neuro-oncological healthcare professionals on this exciting new field and also delineating the promising avenues for future translational and clinical research that may allow for application of network methods in neuro-oncological care.

Keywords

connectome | functional connectivity | glioma | graph theory | structural connectivity

Background

A fascinating parallel thread runs through recent neuroscience and oncology research. Neuroscience has shifted from localizing brain function at specific brain regions to a connectivity-based view of how behavior comes about through orchestrated patterns of activity in anatomically distributed networks.[1] Similarly, oncological research has uncovered different types of bidirectional cross-talk between cancer cells and other organs, systems, and cells, and particularly the nervous system.[2] In neuro-oncology, the brain tumor clearly interacts with the networked nature of the brain. Although the clinical application of such network insights is still a future perspective, there are lines of evidence pointing toward its potential to help better diagnose, monitor, and treat neuro-oncological patients. Now is the time to integrate fundamental, translational and applied research to ensure that network insights will benefit clinical practice in the future. This review, therefore, starts off with a crash course into network theory and how it can be applied to the brain at multiple scales, aimed at unlocking knowledge on this approach for clinicians and researchers alike. We then capture the current state-of-the-art research on the multiscale brain network in the presence of a tumor. We finish with future perspectives of this exciting field and delineate what is needed to work toward clinical application of its findings.

The Origins of Network Theory

Leonhard Euler (1707–1783), a polymath delving into mathematics and physics, formulated the inaugural theorem of graph theory. He solved the standing mathematical question of whether a path across 2 islands and the banks of the river Pregel in the city of Königsberg could be found with the same starting and end point without using any of the 7 bridges more than once. Euler represented each island and each river bank as nodes, or "vertices" in graph-theoretical jargon (see Table 1 for a glossary of terms), and connected the nodes that had a bridge between them with a link, or "edge", creating the first graph or network representation of a system. He was then able to prove that such a route was not possible.

In the centuries that followed, graph theory has been used in many fields ranging from chemistry and physics to biology and sociology. All that is needed to apply the wealth of theoretical knowledge and plethora of algorithms

Table 1. Alphabetized glossary of relevant terms and abbreviations as used in this review

Term or abbreviation	Meaning or definition
Adjacency matrix	Matrix representing all nodes and links in a network in a numeric form
AMPA receptor	Receptor for the excitatory neurotransmitter glutamate
Average path length	Average number of minimal steps it takes to get from each node to each other node in the network
Brain cell cultures	The culturing of a population of brain cells in a dish
Betweenness centrality	Total number of shortest paths running through a node, reflecting its importance or hubness
Binary network	Network in which links are either present or not, and thus have value 0 or 1
Clustering coefficient	Number of actual connections between a node's neighbors divided by the possible number of connections between neighbors
Degree centrality	Total number of connections of a node, reflecting its importance or hubness
Directed network	Network in which links have direction and thus go more from one node to the other, instead of in both directions equally
dMRI	Diffusion MRI
Edge	Connection or link between nodes in a network
Ex vivo brain slices	Maintaining a slice of brain tissue intact and alive outside of the body
Functional connectivity	Level of statistical interdependency between time series of brain activity from two different nodes
GABA	Most frequently occurring inhibitory neurotransmitter
Global efficiency	Inverse of path length
Macroscale	At the brain region or whole-brain level
MEA	Multi-electrode array, used to measure cellular activity
MEG	Magnetoencephalography
Mesoscale	At the level of groups and/or circuits of cells
Microscale	At the level of individual cells
Modularity or community detection	Subdividing the network into subgroups of more highly inter-connected nodes
Neurogliomal synapse	Glutamate-dependent synapse connecting neurons to tumor microtube networks
Neuroligin-3 (NLGN3)	Protein relevant for synaptic functioning
NMDA receptor	Receptor for the excitatory neurotransmitter glutamate
Resting-state fMRI (rsfMRI)	Functional MRI acquired during a no-task condition
Small-world network	A type of network that combines high local segregation (ie, high average clustering coefficient) with high global integration (ie, short average path length)
Undirected network	Network in which links are equally bidirectional
Vertex	Node in a network
Weighted network	Network in which links have different weights

from graph theory is a relevant definition of nodes and links. Nodes are typically canonical units of the system at hand, such as people in a social network, proteins in a pathway interaction network, or cities in a country. Links can be defined in different ways, depending on the problem that needs solving. In sociology for instance, one of the first seminal network studies used letters sent through postal mail to draw links between people, with the aim of assessing the veracity of the phrase "it's a small world" through graph theory.[3] In this case, a letter was either sent or not, so each link was either set to 1 or 0. Moreover, the letters went unidirectionally from one person to the other, not the other way around, rendering this a binary, directed network. Conversely, the number of texts or emails sent back and forth between pairs of people could be counted to represent links in a weighted, undirected communication network. Another difference between these two networks could be the structural versus functional link definition: a letter exists as an object in the physical world, but digital communication much more reflects the functional transfer of information without in itself reflecting a physical entity. So, structural links are usually physical entities, whereas functional links may have structural counterparts, but could also reflect a number of potentially indirect physical processes at the same time.

After defining the nature, presence, weight, and directionality of links between all pairs of nodes in a system,

the visual graph representation of the system reveals itself (see Figure 1A for an overview of graphs with different link types). Coupled with each graph is its algebraic representation: the adjacency or connectivity matrix (Figure 1B). The matrix rows and columns represent nodes. Each matrix element represents a link, for instance, $link_{i-j}$ between $node_i$ and $node_j$. The matrix is the basis for all further graph analyses.

One can use graph measures to assess different network properties, also referred to as "network topology," which can largely be summarized into 3 main categories. The first is integration, which captures the extent to which the network is globally traversable. In the small-world experiment, the average number of times the letter needed to be forwarded to get from any starting person to a particular target was calculated, which is known graph theoretically as the average path length (Figure 1C).[4] The average path length of the mail network was found to be 6 confirming not only the idea that it *is* a small world after all, but also coining the concept of "6 degrees of separation." This phrase is still exploited by social network platforms such as LinkedIn. Global efficiency is also a network measure that captures the ease with which a network can be traversed.[5] Conceptually, the integration of a network is seminal for its coherent functioning. Complex systems that operate at some optimal level typically have relatively high integration to facilitate whatever overall process happens in the system, be it getting letters to a specific person or connecting job seekers to potential prospective employers.

Segregation is the second important characteristic of most networks. Segregative graph measures capture the tendency of a network to cluster into smaller subparts, characterized by the high interconnectedness of its nodes. The clustering coefficient, for instance, is calculated by dividing the number of connections between any network neighbors of a node, by the total number of possible connections between those neighbors (Figure 1C).[4] Networks having both high average clustering coefficient and short average path length are coined "small-world" networks, due to their optimal topology toward information transfer. Modularity is based on the same idea of specialization of groups of nodes: modularity or community detection algorithms assess the presence and location of subgroups of nodes that are more connected to each other, than to

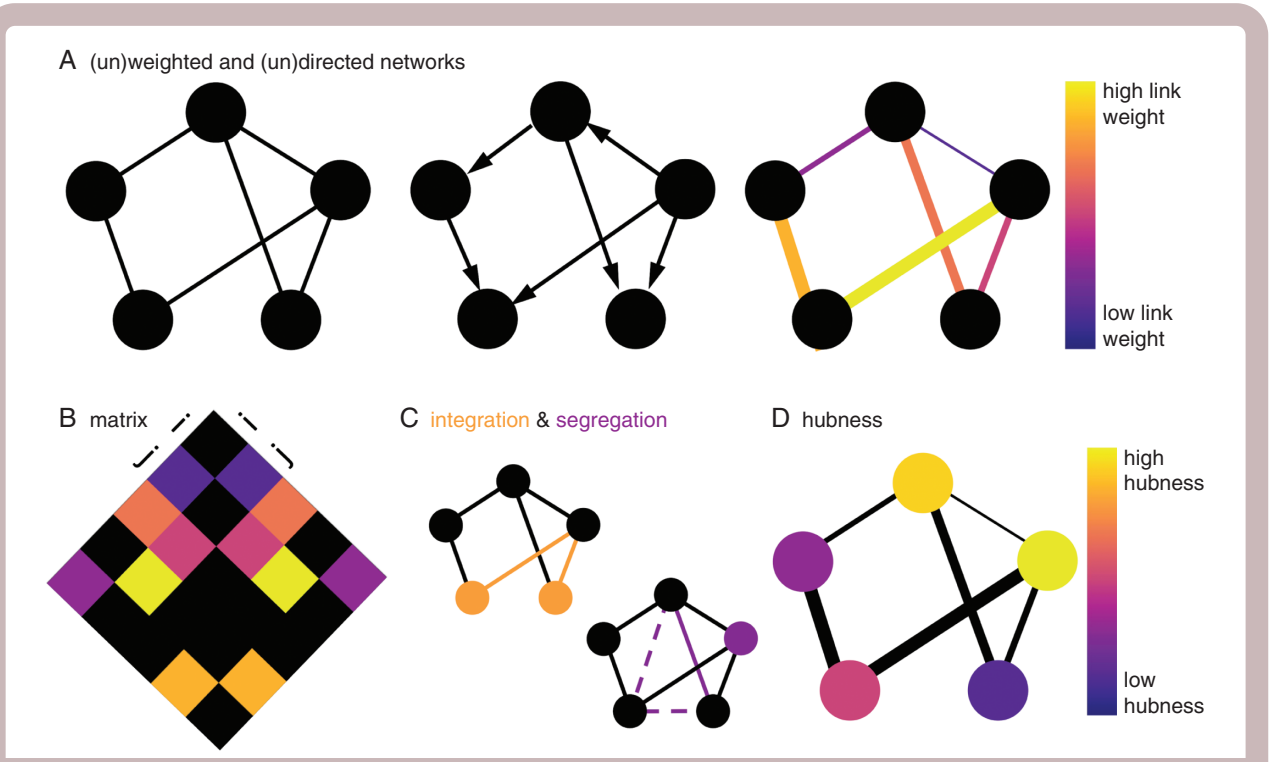

Figure 1. Networks and their most important features. In (A), different types of networks consisting of 5 nodes (eg, $node_i$ and $node_j$) are indicated. The left network has binary (present or not) and undirected (bidirectional) links. The middle network has binary links as well, but these are directed as indicated by the arrow heads. The right network has weighted links, with the colormap indicating that bright yellow links have a high weight, and darker purple links have low weight. The thickness of the lines also represents the weight in this figure. (B) depicts the matrix representation of the weighted network at the top right with the same color scale. Each row and each column represent the nodes in the network, while each element captures the weight of the link between pairs of nodes. The diagonal of the matrix, that is, the connection between a node and itself, is drawn in black to reflect that self-loops are not considered in this network. Moreover, other elements are black if a connection is not present according to the left-most network of panel A. (C) Schematically reflects integration between 2 exemplar orange nodes, as indicated by the dotted orange line with a path length of 2. The clustering coefficient of the purple node is calculated by dividing the total number of connections present between the neighbors (one solid purple line in this case) by the total number of possible connections between a node's neighbors (3 in this case, as indicated by all purple lines, also the dotted nonpresent links), which yields a value of 0.33. In (D), the hubness (i.e., total summed weight of a node's connections which reflects node strength) of each node is indicated through its color code.

nodes in the rest of the network.[6] The presence of clusters, modules, communities, or cliques is evident in almost all complex systems: our social networks are grouped by joint hobbies or interests, while railway systems typically have lots of local or commuter trains connecting neighboring towns and cities, in addition to the express service trains that support global integration.

The final category of often-used graph measures is that of nodal importance or "hubness." A hub is a node that is deemed more influential than others (Figure 1D), for instance through having a high number of total connections reflected by the graph measure of degree centrality, through having a large number of shortest paths between all nodes in the network running through it (i.e., betweenness centrality), or through connecting different modules (i.e., participation coefficient or connector hubness). Such hub nodes orchestrate what happens in the network as a whole. Moreover, hub nodes failing is a much bigger issue for network resilience than when problems arise in other nodes: just imagine the difference in impact of outages of Google versus the Neuro-Oncology Practice journal website on overall internet traffic.

As is clear from the real-life examples provided in this section, network theory offers a quantitative way of assessing the structure and function of many different types of complex systems. One of the most elegant features of the approach is that it is based on a solid theoretical foundation, yet it is still data driven. Moreover, the variety of network measures available makes it possible to assess the global properties of the system. At the same time, network theory can also be used to investigate and potentially manipulate individual nodes according to the more localizationist tradition, while also taking the rest of the network into account.

Network Neuroscience

The brain consists of a network of interconnected and electrically active neurons and glial cells that are organized in specialized, but connected, brain regions. These features make the brain especially suited for network analysis across different spatial scales (see Figure 2). The first brain network analysis was done on the complete neural network of the nematode worm C. Elegans.[4,7] This analysis revealed high clustering combined with a short average path length and the worm's brain was therefore deemed to have a small-world network topology.

Since then, network analyses have been performed on the brain at several scales. The most favored technique to study network features of brain cell cultures is the use of multi-electrode arrays. Here, electrical activity of the network is measured using multiple electrodes that can record the activity of a single cell or of several cells in the electrode's vicinity. Such recordings in neuron and glial cell cultures obtained from prenatal rat cortex revealed that cellular networks evolve over time.[8] Younger cultures

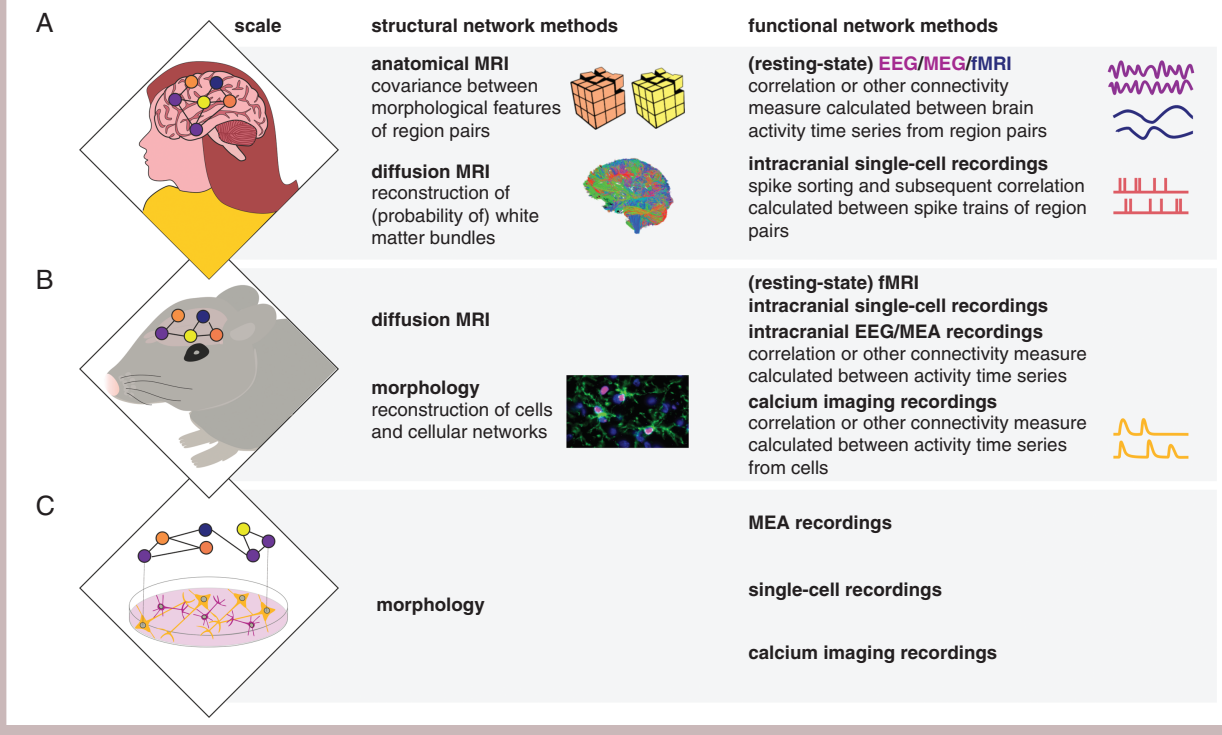

Figure 2. Schematic figure on network analysis of the brain across scales. Brain networks can be assessed in (A) humans at the macroscale using imaging techniques (structural, diffusion, and functional MRI), or neurophysiological recordings (magnetoencephalography or electroencephalography), in (B) rodent models using MRI, EEG, MEA, *in vivo*, or *ex vivo* calcium imaging or electrophysiology recordings, or in (C) brain cell cultures using MEA, calcium imaging recordings or electrophysiology.

exhibited more random network features, while mature cell networks had a small-world topology. These findings have been robustly replicated across various culture conditions. Interestingly, in primary hippocampal cultures, small-world characteristics of the network diminished after inducing epileptic-like neuronal activity with glutamate, highlighting the clinical relevance of network disturbances at the cellular level.[9]

Moving from the micro- to the mesoscale, small-world properties have also been established within *ex vivo* brain slices (i.e., maintaining a slice of brain tissue intact and alive outside of the body). A calcium imaging study of cornu ammonis 3 (CA3) hippocampal slices demonstrated that GABA-ergic neurons play a key role in shaping the activity of local small-world brain networks.[10] *In vivo* recordings of local neural networks have also been performed. For example, MEA recordings in the monkey visual cortex have revealed that the visual cortex network also possesses small-world features.[11]

Since micro- and mesoscopic networks are difficult to study in the (living) human brain, most network neuroscientific work is based on macroscale neuroimaging and neurophysiology. Nodes are typically chosen according to a brain atlas or parcellation, for instance, based on cytoarchitectonic similarity (see Figure 2A).[12] Structural links can be measured through diffusion MRI (dMRI), which allows for reconstruction of the white matter tracts connecting different regions (Figure 2B). Another structural link definition is based on a volumetric or morphological similarity between regions according to structural MR images, based on the evidence that regions with covarying volume or morphology are indeed connected.[13,14] Functional links in human brain networks are typically based on statistical dependencies between regional activity patterns, termed functional connectivity.[15] Brain activity can be measured through functional MRI (fMRI), electroencephalography (EEG), and magnetoencephalography (MEG), after which some sort of correlative analysis of the resulting regional time series is used to obtain a functional network.

Although networks in brain cells, animal brains, and the human brain are mainly studied in isolation, there is remarkable similarity in brain connectivity and network features across scales of measurement. Animal studies have revealed that brain regions characterized by larger neurons, longer axonal lengths, and higher synaptic density at the micro- and mesoscales also typically have a higher number of links and more integrative connections in the macroscale brain network.[14,16,17] In humans, postmortem work has revealed similar multiscale network properties, whereby relevant cellular characteristics go hand in hand with structural network features.[18–20] It, therefore, seems that brain networks spanning the micro-, meso-, and macroscales share similar features, which are also conserved across species.[21]

Ultimately, these multiscale network topological features of the brain give rise to its functioning.[22,23] Across macroscale modalities, early network neuroscientific studies have reported on the relevance of high global integration, ample local segregation, and the presence of hub nodes for normal cognitive functioning.[24–26] Recent studies connecting these large-scale networks to the microscale have shown similar relevance of cellular features for cognition. Dendritic complexity and action potential kinetics of a region in the temporal lobe, for instance, have been positively correlated to intelligence in patients undergoing surgical resection to mitigate severe epilepsy.[27] Another study using both fMRI and MEG acquired in these same patients revealed the well-known association between verbal memory and the extent of functional network centrality of the same temporal region as part of the default mode network (DMN; one of the most frequently investigated subnetworks or modules in functional brain networks[28]).[29] Moreover, microscale integrative properties of the neurons within the investigated DMN region went hand in hand with the cognitively relevant macroscale network centrality.

Networks in Neuro-Oncology

In recent years it has become clear that gliomas do not consist of cells growing in isolation, but rather that within gliomas, tumor cells form an electrically active network that is integrated into the brain network by neuron-tumor synapses. This complex interplay between the tumor and brain networks may render glioma the ultimate network disease, which is further highlighted by the fact that glioma patients present with symptoms that relate not just to the tumor and its location, but also to cognitive impairments that may indicate disruptions in the spatially distributed brain network.

Glioma cells form a functional cellular network via tumor microtubes; cellular protrusions that connect neighboring tumor cells.[30] Gap junctions between tumor cells and microtubes allow calcium waves to propagate and contribute to tumor growth. In glioblastomas, the most malignant type of glioma, approximately half of all tumor cells are involved in such microtube networks, while these numbers are significantly lower in oligodendrogliomas and variable in astrocytomas.[31,32] Interestingly, a recent study investigated the network topology of glioma tumor cell networks *in vitro* and *in vivo* in a mouse xenograft model.[33] A small subset of so-called "hub cells" proved to be highly interconnected and thus important within the tumor network, which also has small-world properties.[33] This is probably why therapies that only eliminate a subset of tumor cells (e.g., tumor resection, chemotherapy, and radiotherapy) cannot effectively destroy the entire tumor network: one might have to effectively target particularly all hub cells to do real damage. This study highlights the important role that network theory can play in the development of effective strategies for the treatment of glioma.

Apart from connections with other tumor cells, glioma cells are also integrated into the broader brain network. Via (peri)synaptic contacts with neurons, glutamatergic signaling from neurons onto glioma tumor cells encourages tumor growth.[34] Glioma cells can also benefit from signaling molecules secreted by surrounding neurons. For instance, neuroligin-3 and brain-derived neurotrophic factor are known to stimulate tumor growth.[35,36] Contacts between tumor cells and neurons do not only occur at the tumor rim but have also been identified in tumor cells

that have migrated away from the tumor, further into the brain. It may therefore not come as a surprise that brain tumors are more frequently found in brain regions with inherently high neuronal activity.[37] On top of being reactive to glutamate secreted by neurons, glioma cells themselves also secrete glutamate. This, in combination with the fact that glioma glutamate secretion leads to high peritumoral glutamate levels rendering the peritumoral tissue hyperexcitable, creates a positive feedback loop that stimulates tumor growth.[38]

Intuitively, pathologically high activity of the peritumoral area affects distributed functional brain networks. There is only one animal study to date in which the effects of a brain tumor on brain networks were investigated.[39] Mice with xenografted glioblastomas showed functional connectivity changes within the ipsilateral hemisphere, both around the tumor and at a distance. Of note, although glioma presents with direct mechanisms between the glioma network and neuronal activity, the phenomenon of hyperexcitability and widespread hyperconnectivity has been established in many other neurological conditions, such as Alzheimer's disease.[40,41] These cross-disease findings underline the need for further preclinical investigations into how cellular networks interact with the large-scale connectivity disturbances that may ultimately cause symptoms.

A large proportion of the macroscale network literature has used MEG to report on frequency-dependent differences in network topology of glioma patients. In the lower frequency bands (delta to alpha), higher local functional connectivity and network segregation have consistently been reported, while global integration of the network is lower than in healthy controls.[42–48] With rsfMRI, studies have uncovered pathologically high connectivity as well, particularly between the hubs of the brain (e.g., regions in the DMN) and the more peripheral regions,[49] as well as global efficiency losses and DMN disintegration, which seem just as present in the contralateral hemisphere as on the ipsilateral side.[50–53] Structural network topology is also different in brain tumor patients as compared to healthy controls, with differences also not being limited to the peritumoral region or even the hemisphere containing the tumor.[54,55] Of note, most macroscale network studies on brain tumors have been performed in glioma patients, but similar results have been reported in patients with meningiomas[56] and brain metastases.[57]

Network topology is relevant for disease course: functional network connectivity has been shown to predict (progression-free) survival, whether it concerns local connectivity[58–60] or more global fMRI network topology.[49] The extent to which the tumor region itself is connected to and integrated into the global brain network has also been found relevant for survival.[60,61] Moreover, patients' network topology harbors correlations to their functional status and cognition. The higher the segregative properties of the functional brain network, the higher patients' seizure frequency,[45,46] and the poorer their cognitive functioning, especially when overall integration is also low.[43,52,57,62–65] A particularly interesting relationship exists between brain-wide functional connectivity of the tumor region itself, and postoperative outcomes in terms of cognition: resection of low connectivity areas within and around the tumor seldomly results in postoperative cognitive decline, while (peri)tumor voxels with high connectivity to the rest of the brain are best left behind to preserve cognition.[66–69]

As hinted at before, there are indications that the spatial preference of tumors to occur in particular brain areas (e.g., frontotemporally) relates to healthy or intrinsic variations in local activity and network connectivity,[37,70,71] potentially due to spatial variations in for instance transcriptomics underlying both regional network topology and vulnerability to neoplasms.[72] Furthermore, glioma patients with tumors in regions that are normally characterized by high local clustering tend to have nonpathological network topology, while those patients with more uncommonly situated gliomas in areas of low clustering do show large differences in global network topology compared to controls.[70] Particularly complex is the fact that although mesoscale connectivity, as measured with MEG, is predominantly high around the tumor in a seemingly distance-dependent manner,[44] macroscale regional network topological measures such as local clustering and centrality deviate from healthy controls in varying directions.[73,74]

In summary, a rich collection of multiscale network interactions has been revealed, which link cellular brain-tumor cross-talk to global network topology to behavior in multiple ways (see Figure 3 for a schematic overview connecting these findings across scales). How intrinsic multiscale spatial variations, tumor location and invasion, and dynamic network topological trajectories synergize and thereby impact the disease course and patients' functional status remains to be seen.[75]

Clinical Perspectives

Potential future applications of network theory to clinical neuro-oncological practice are myriad (see Figure 4 for a schematic overview). At diagnosis, the association between the tumor, brain network topology, and disease course may be particularly relevant for prognostication. As reviewed in the previous section, tumors that are located in regions with intrinsically high local and integrative connectivity, and that themselves show functional integration with the rest of the brain have a less favorable disease course, both in terms of survival and functional and cognitive decline.[58–61,68] Adding markers of activity, local connectivity, and global integration to the diagnostic workup through rsfMRI or MEG/EEG may help health care professionals guide patients in this difficult phase of the disease, and may in the future aid in delineating which patients are most at risk of short survival and/or low quality of life. When predicting progression-free survival (PFS), for instance, high local functional connectivity as measured with MEG has a hazard ratio of ~2, after adjusting for other predictors of PFS.[58] Large cohort studies, preferentially stratified for molecular tumor subtype and other predictors of survival, would be necessary to accurately assess the added clinical value of such markers. Importantly, although several of these promising studies have used MEG, the clinical applicability of any markers based on this neurophysiological modality is likely limited. Only a small number of hospitals is equipped with an expensive and expertise-dependent MEG system. Ideally, these larger cohort studies (also)

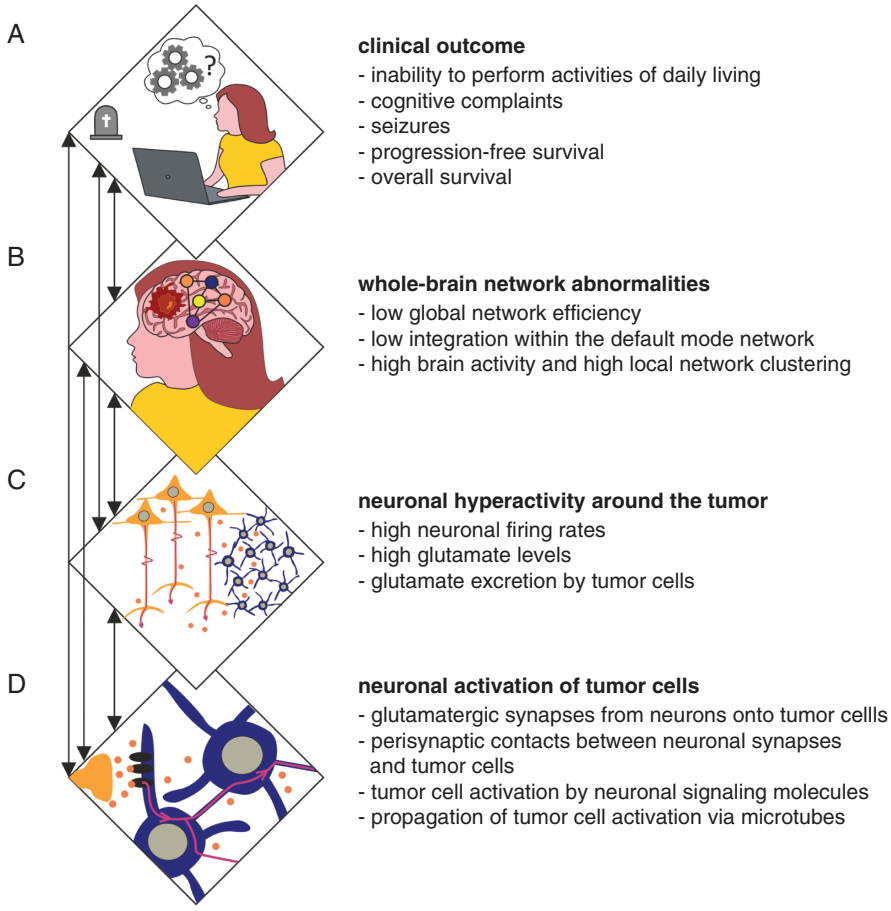

Figure 3. Multiscale network findings in neuro-oncology. (A) depicts clinically relevant outcomes in glioma patients. (B) reflects the types of global brain network abnormalities observed in glioma patients. In (C), a hyperactive neuronal network surrounding the tumor is displayed. The heightened neuronal activity leads to more secretion of glutamate around and within the tumor. Neurons in orange, tumor cells in blue, glutamate as orange circles and cellular activity in pink. In (D), neurons are shown to form synapses onto tumor cells where glutamate secretion activates tumor cells. The activation of one tumor cell gets propagated to neighboring tumor cells via tumor microtubes. The activation of tumor cells leads to glutamate excretion further enhancing tumor activity. Across all panels, arrows are drawn to indicate that findings from different scales may go hand in hand potentially due to causal relationships.

include EEG, as this is a low-cost, widely available technique with potentially comparable promise. Indeed, high local functional connectivity has also been reported in EEG recordings of glioma patients,[44] high local connectivity has been related to poorer cognitive functioning,[76] and visual assessment of higher local EEG hyperexcitability has been related to shorter survival.[77] Luckily, for patients, undergoing MEG or EEG is typically less burdensome than MRI, particularly for those who feel uncomfortable in the small MRI bore or find the loud MR acquisition unpleasant. Ultimately, most useful would be to have fMRI, MEG, and EEG data available in the same large cohort of patients, to facilitate a comparison across modalities.

Potentially the most promising avenue for clinical implementation of network approaches in neuro-oncology, is to use functional connectivity based on resting-state MEG to guide tumor resection. Several scientific publications from the team at University of California San Francisco (UCSF) on this topic show that preoperative MEG is able to reveal which parts of the tumor and its surroundings can be safely resected without causing postoperative deficits, since those regions are typically not functionally connected to other brain regions.[66–69] Replication of these findings by others would be a next step toward potentially wider implementation of this approach in neuro-oncological centers, particularly since most hospitals equipped with MEG have the same system, which could facilitate replication and subsequent clinical implementation. Although the limited availability of MEG remains an issue to be taken into account here, the application of this type of connectivity mapping may not lend itself very well to EEG, due to its limited spatial resolution and need for a reference electrode. Moreover, the neurophysiological characteristics of rsfMRI are very different from MEG/EEG signals, which renders its potential for this application less evident. There are, however, studies also showing a relationship between rsfMRI features describing areas to be resected or preserved as compared to intraoperative mapping,[78,79]

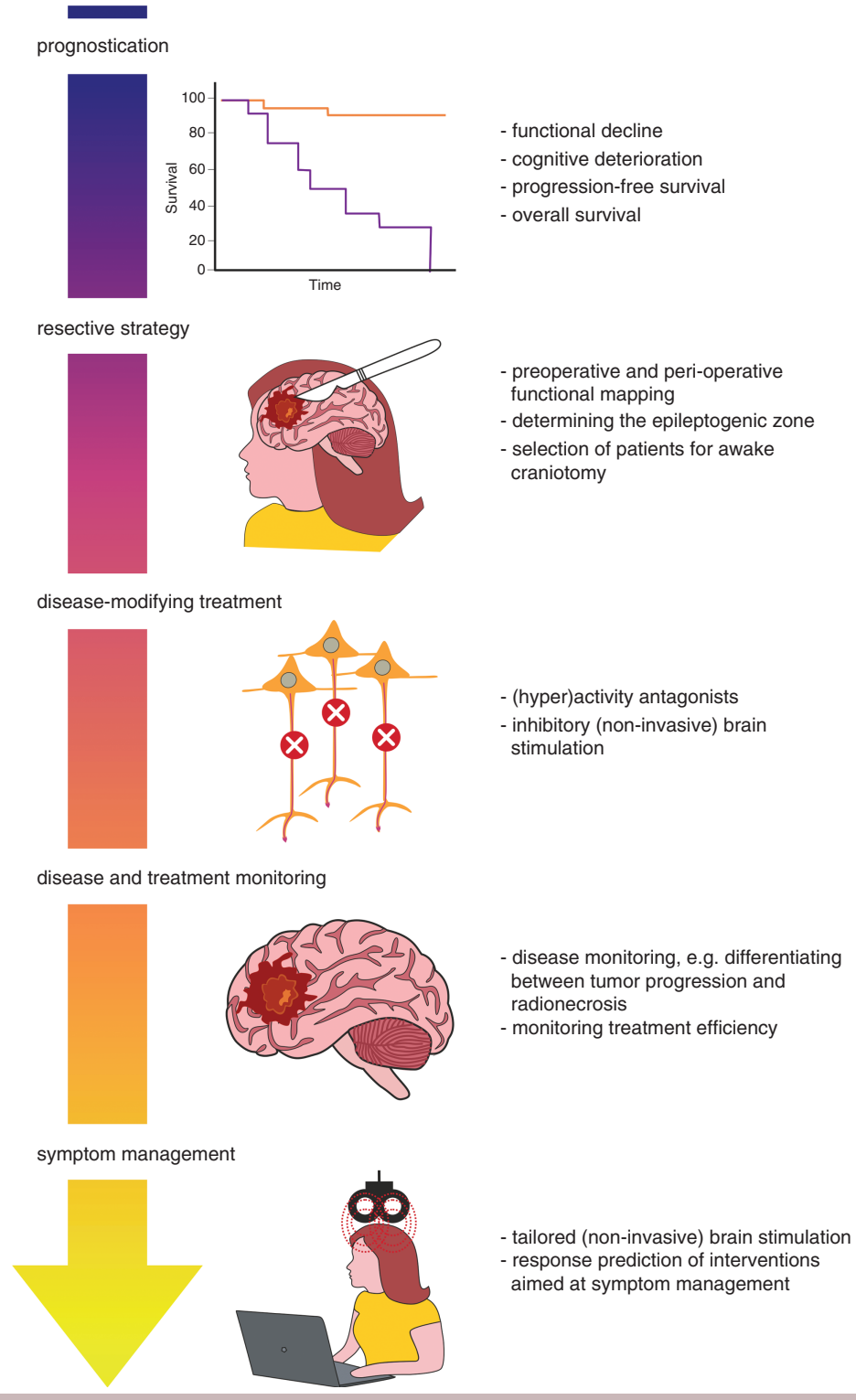

Figure 4. Schematic figure depicting potential future clinical applications of multiscale network neuroscience along the disease course. Brain network analysis studies might aid clinical practice at multiple stages ranging from prognostication, resective strategy, disease-modifying treatment, disease and treatment monitoring to symptom management.

although potentially at a lower spatial resolution.[80] Studies that link the resection of these high connectivity hubs to intraoperative mapping and/or functional outcome could help determine whether rsfMRI yields similarly promising results for clinical application. In this context, it is also important to consider the potentially confounding effects of

using different MRI systems and different analysis pipelines across different hospitals.[81]

Since local functional connectivity and integration between tumor cells and surrounding neurons at the micro- and macroscales relate to survival, it is worth investigating whether connectivity assessments could aid in monitoring tumor growth after initial resection of the tumor. Distinguishing real tumor growth from pseudoprogression with standard MRI is difficult, particularly in patients who undergo radiotherapy and who may therefore develop radionecrosis.[82] One cross-sectional study in glioma patients undergoing primary treatment after tumor resection explored the value of MEG local connectivity in discerning between patients with a growing versus stable tumor according to MRI.[44] Results show that individual differences between patients were large and related to PFS, but not to tumor growth at the same time point, potentially due to the cross-sectional set-up of the study. As such, the predictive value of local connectivity may be limited to PFS at the group-level. For monitoring purposes, longitudinal research, preferably (also) using EEG, is necessary to investigate whether repeated measurements of local connectivity could help differentiate between real tumor growth and pseudoprogression at any timepoint during clinical follow-up.

Since there is ample cross-talk between neuronal and tumor networks, treatments that impact brain activity in some way are of interest.[83,84] Consider for instance perampanel, an anti-seizure medication that inhibits glutamate action through AMPA antagonism. It reduces tumor proliferation and invasion in animal xenograft models, hypothetically through inhibition of brain activity.[85] Another potentially interesting drug is levetiracetam, which has generally been associated with altered brain activity[86,87] longer survival in some but not all studies,[88] and improved cognition across conditions.[87] In the future, non-invasively measured local brain activity and connectivity (EEG or MEG) may become relevant for monitoring the efficacy of such treatments, in order to assess whether the medication actually inhibits tumor-promoting brain processes and to what (spatial) extent.

Finally, there are indications that network neuroscientific methods may be useful for rehabilitation and symptom management. For instance, non-invasive brain stimulation is becoming increasingly interesting in glioma patients in different phases of the disease. Before tumor resection, such stimulation may be used for "prehabilitation."[89,90] After tumor resection, rehabilitative interventions may be more effective when combined with non-invasive stimulation.[91] Moreover, stimulation may be relevant to alleviate cognitive impairments as well.[92] Moreover, although seizures are always considered a potential side effect of brain stimulation, none of the studies performed in glioma patients so far reported seizures. It is important to note that most studies used a single stimulation session for mapping purposes,[93] which could pose less risk for seizures than therapeutic (repeated) application of stimulation. However, a recent postoperative rehabilitation study stimulating multiple times a day for a week also did not report any seizures in a cohort of 31 glioma patients.[91] Network measures may help target the stimulation to the most useful brain region in every individual patient: previous studies have shown associations between network connectivity of the stimulation target and behavioral outcome.[94–96] Future clinical studies are necessary to explore the efficacy of such network-based targeted therapies. In terms of choosing a modality, rsfMRI shows most evidence toward this application: almost all studies into network targets of stimulation across conditions use rsfMRI,[97] while this has also been specifically argued for in glioma patients.[98]

Conclusion

There is ample innovation in the scientific field where network neuroscience and neuro-oncology meet. Gliomas contain networks of interconnected tumor cells, while there is extensive cross-talk between these tumor networks and the supposedly healthy brain around them, be it at the cellular, mesoscale, or macroscale network level. Although clinical implementation of network approaches is still scarce, there is promise in the realms of diagnosis and prognostication, surgical intervention, and both disease and treatment monitoring. Future interdisciplinary studies combining fundamental and/or preclinical approaches with translational and/or clinical outcome measures should be performed to deliver on these promises.

Conflict of interest statement

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