Brain networks under attack:

robustness properties and the impact of lesions

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Abstract

A growing number of studies approach the brain as a complex network, the so-called *connectome*. Adopting this framework, we examine what types or extent of damage the brain can withstand – referred to as network *robustness* – and conversely, which kind of distortions can be expected after brain lesions. To this end, we review computational lesion studies and empirical studies investigating network alterations in brain tumor, stroke and TBI patients. Common to these three types of focal injury is that the topological properties of a node do not determine its likelihood to be affected by a lesion. Furthermore, large-scale network effects of these focal lesions are compared to those of a widely studied multifocal neurodegenerative disorder, Alzheimer's disease, in which central parts of the connectome are preferentially affected. Results indicate that human brain networks are remarkably resilient to different types of lesions, compared to other types of complex networks such as random or scale-free networks. However, lesion effects have been found to depend critically on the topological position of the lesion. In particular, damage to network hub regions – and especially those connecting different sub-networks – was found to cause the largest disturbances in network organization. Regardless of lesion location, evidence from empirical and computational lesion studies shows that lesions cause significant alterations in global network topology. The direction of these changes though remains to be elucidated. Encouragingly, both empirical and modeling studies have indicated that after focal damage, the connectome carries the potential to recover at least to some extent, with normalization of graph metrics being related to improved behavioral and cognitive functioning. To conclude, we highlight possible clinical

implications of these findings, point out several methodological limitations that pertain to the study of brain diseases adopting a network approach, and provide suggestions for future research.

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Abbreviations: DWI = diffusion-weighted imaging; fMRI = functional MRI; HGG = high-grade glioma; LGG = low-grade glioma; MEG = magnetoencephalography; TBI = traumatic brain injury.

Introduction

Throughout the history of cognitive neuroscience, there has been an ongoing debate as to whether cognitive functions are localized within specific regions of the brain or emerge from dynamical interactions between various brain areas (Catani *et al.*, 2012). Recent advances in noninvasive *in vivo* neuroimaging technology now allow the construction of comprehensive whole-brain maps of the structural and functional connections of the human cerebrum at the individual level. The ensemble of macroscopic brain connections can then be described as a complex network – the *connectome* (Hagmann, 2005; Sporns *et al.*, 2005). Using graph theory, a powerful framework to characterize diverse properties of complex networks, it has been consistently demonstrated that the human connectome reflects an optimal balance between segregation and integration (Sporns, 2013). Thereby, both perspectives on the origin of cognitive functions have been unified.

Providing a novel perspective to study the brain's organization and functioning in health and disease, connectome analysis has found rapid applications in clinical neuroscience. Disturbed interactions among brain regions have been found in nearly all neurological, developmental and psychiatric disorders (Griffa *et al.*, 2013; van Straaten and Stam, 2013; Cao *et al.*, 2015; Fornito and Bullmore, 2015). In addition, relationships between network topology and cognitive functioning have been revealed. For example, strong positive associations have been found between global efficiency of structural and functional networks and intellectual performance (van den Heuvel *et al.*, 2009; Li *et al.*, 2009). Hence, network analysis could be used to identify biomarkers of specific brain functions and symptoms, thereby carrying the potential to allow more objective diagnosis, to monitor recovery or progression processes over time, and to predict effective treatment options.

In addition, the availability of structural and functional connectomes has enabled the construction and validation of computational models of large-scale neuronal activity (Ghosh *et al.*, 2008; Deco and Kringelbach, 2014). In particular, dynamical models can be implemented on the structural connectome to simulate brain activity, after which predicted and empirical functional connectivity can be compared to evaluate model performance. Overall, it has been demonstrated that brain activity strongly depends on the underlying structural connectivity (Deco and Corbetta, 2011). By virtually lesioning structural connectomes, computational models thus can be used as unique predictive tools to investigate the impact of diverse structural connectivity alterations on brain dynamics. That is, computational modeling enables to investigate what types or extent of damage the brain can withstand – referred to as network *robustness* – and conversely, which kind of distortions can be expected after brain lesions, including those purposively induced by surgery. Furthermore, biologically inspired dynamical models can provide insights into the local dynamics underlying large-scale network topology in health and disease. Hence, they may provide an entry point for understanding brain disorders at a causal mechanistic level. This might lead to novel, more effective therapeutic interventions, for example through drug discovery, optimized presurgical planning, and new targets for deep brain stimulation (Deco and Kringelbach, 2014).

In this review, we briefly discuss how the brain can be studied from a complex networks perspective. Adopting this perspective, we focus on the properties of brain networks underlying network robustness. In turn, we review computational lesion studies and empirical studies investigating network alterations in brain tumor, stroke and TBI patients. Common to these three types of focal injury is that there is no clear mapping between the anatomical lesion site and its topological characteristics within the brain network. Furthermore, large-

scale network effects of these focal lesions are compared to those of a widely studied multifocal neurodegenerative disorder, Alzheimer's disease, in which central parts of the connectome are preferentially affected. To conclude, we highlight potential clinical implications of these findings, point out several methodological limitations that pertain to the study of brain diseases adopting a network approach and provide suggestions for future research.

Construction and analysis of brain networks

Network construction

From a complex networks perspective, the brain can be represented as a graph (Sporns, 2011a, 2011b). In such a graph, network *nodes* correspond to brain regions, whereas *edges* describe the connectivity between brain regions. Depending on the nature of these connections, at least three different classes of brain networks can be studied (Friston, 1994; Sporns, 2011a, 2011b): in *structural connectivity* networks, edges represent anatomical links between brain regions; in *functional connectivity* networks, edges are defined as statistical dependencies between remote neurophysiological events; and in *effective connectivity* networks, edges capture the causal influences of one region on another. In this review, we focus on the two most frequently investigated types of large-scale brain network: structural and functional. In addition to the type of connectivity being examined, networks can also be differentiated into binary versus weighted networks. In binary networks, a specific threshold is applied to the connections, resulting in links being either present or absent. In weighted networks, on the other hand, links also contain information about connection strength. Advances in neuroimaging techniques, and in particular in MRI, have enabled the noninvasive *in vivo* estimation of such structural and functional connections. The most popular techniques to map the human connectome include DWI tractography to assess

structural connectivity (Sporns, 2011b), and (resting-state) fMRI for the estimation of functional couplings (Biswal *et al.*, 2010). In addition, EEG and MEG are also frequently employed techniques to examine functional connectivity. Once the nodes and edges have been defined and estimated, all information can be summarized in a connectivity matrix. In such matrices, rows and columns represent nodes, while matrix entries denote links. Figure 1 shows the workflow for obtaining a structural and functional connectivity matrix, and corresponding brain network.

Network analysis by means of graph metrics

Based on a connectivity matrix, topological properties of a network can be examined by a rich array of graph metrics provided by the general framework of graph theory. Graph metrics can be largely classified into measures covering aspects of *segregation*, *integration*, and *centrality* (Rubinov and Sporns, 2010) (Fig. 2A). In this section, we briefly discuss the most important graph measures within each of these categories. Table 1 gives an overview of all graph metrics used in this review. For more details and an in-depth discussion of graph metrics, we refer the interested reader to Rubinov and Sporns (2010).

Segregation refers to the ability for specialized processing to occur within densely interconnected groups of brain regions. The *clustering coefficient* of a node is an important measure of segregation, quantifying the number of connections that exist between the direct neighbors of a node as a proportion of the maximum number of possible connections (Watts and Strogatz, 1998). If a node's neighbors are densely interconnected, they form a cluster or clique, and they are likely to share specialized information. The average clustering coefficient across all network nodes is the clustering coefficient C of the network, which is used as a global metric of the network's level of segregation. Another measure of segregation is

modularity, which not only describes the presence of densely interconnected groups of nodes, but also estimates the size and composition of these individual groups. The modular structure can be revealed by subdividing the network into modules by maximizing the number of within-group links and minimizing the number of between-group links (Girvan and Newman, 2002; Guimerà and Amaral, 2005). *Hubs* – highly interconnected nodes (Sporns *et al.*, 2007; see below) – can then be described in terms of their roles in this community structure. That is, *provincial hubs* link primarily to other nodes in the same module, whereas putative *connector hubs* have links that are distributed across multiple different modules (Guimerà and Amaral, 2005; Bassett *et al.*, 2006).

Integration, on the other hand, relates to the capacity of the network to rapidly combine specialized information from distributed brain regions. Measures of integration are commonly based on the concept of communication paths and their path lengths. A path is a unique sequence of nodes and links that represents a potential route of information flow between pairs of brain regions, and path length is given by the number of steps (in a binary graph) or the sum of the edge weights (in a weighted graph). Hence, path length indicates the potential for integration between brain regions, with shorter paths implying stronger potential for integration. On a global level, this translates to the *characteristic path length* of the network, calculated as the average shortest path length between all pairs of nodes in the network. A related measure is *global efficiency* (Latora and Marchiori, 2001), defined as the average inverse shortest path length. In contrast to the characteristic path length, global efficiency can be meaningfully computed on disconnected networks, since paths between disconnected nodes have infinite path lengths and correspondingly zero efficiency.

Centrality measures describe the importance of network nodes and edges to network functioning. The simplest index of centrality is node *degree* – the number of links connected to a given node. Combining the degree of all nodes in the network yields the *degree distribution*, which is an important marker for network development and resilience. Another measure of importance is *betweenness centrality*, defined as the fraction of all shortest paths in the network that pass through a given node (edge). Bridging nodes (edges) that connect disparate parts of the network often have a high betweenness centrality. As such, degree and betweenness centrality are two of several metrics to identify brain regions that play a key role in global information integration between different parts of the network, so-called *hubs* (Sporns *et al.*, 2007).

In order to make more meaningful inference about the topological organization of the connectome, graph metrics have to be normalized, since raw values of network measures are influenced by basic low level network properties such as the number of nodes, connection density, and degree distribution (van Wijk *et al.*, 2010). Specifically, network metrics are typically benchmarked to appropriate null or reference networks that share the same basic properties (i.e., number of nodes, connection density, and degree distribution), but have other properties destroyed through construction. The exact definition of an "appropriate" reference network depends on the network measure that is being benchmarked and the connectivity measure used to derive edge weights (for a more elaborate discussion on this topic, see Fornito *et al.*, 2013 and Zalesky *et al.*, 2012). Nonetheless, the most simple and frequently used reference model is a random network generated with a rewiring algorithm that preserves the degree distribution of the network under study (Maslov and Sneppen, 2002). The two most commonly reported normalized graph measures include the normalized clustering coefficient γ, and the normalized characteristic path length λ.

By combining different values of clustering coefficient and characteristic path length, different network topologies can be described (Fig. 2B). The extremes have either a high clustering coefficient and long characteristic path length (regular *lattice* network), or a low clustering coefficient and a short characteristic path length (random network). The intermediate *small-world* topology (Watts and Strogatz, 1998) is characterized by a clustering coefficient greater than that of an equivalent random network ($\gamma > 1$), yet it has approximately the same characteristic path length as an equivalent random network ($\lambda \approx 1$). The ratio $\sigma = \gamma/\lambda$ is often used and must be greater than 1 to define small-worldness of a network (Humphries *et al.*, 2006; Humphries and Gurney, 2008). Such a network topology is commonly thought to reflect an optimal balance between segregation and integration. A small-world architecture seems to be the key common feature shared by many complex systems (Watts and Strogatz, 1998), and there is mounting evidence that healthy structural and functional brain networks also show this kind of organization across various modalities (Stam, 2010).

Robustness of brain networks

The brain can be highly robust to physical damage. However, relatively small lesions sometimes have broader effects than would be predicted based on their extent and location. In order to clarify this somewhat contradictory picture, several studies (Albert *et al.*, 2000; Kaiser and Hilgetag, 2004; Achard *et al.*, 2006; Kaiser *et al.*, 2007; Alstott *et al.*, 2009; Joyce *et al.*, 2013) have investigated the organizational properties underlying network robustness.

In general, it has been found that robustness of complex networks depends critically upon the organizational structure of the network and the nature of the attack. Regarding the organizing principle of the network, network architectures can be defined according to the graph

properties described above, leading to main classes such as random, small-world, scale-free, hierarchical, and geometrical networks (Albert and Barabási, 2002). Three of those have been compared extensively with regard to their robustness properties, namely random, scale-free and small-world networks. In *random* networks, edges exist between any pair of vertices with probability *p,* causing the majority of nodes to have a similar number of connections. The resulting degree distribution follows a binomial probability distribution. For a large number of nodes, this can be approximated by a Poisson distribution, and hence the term "exponential degree distribution" is also used to define these types of networks (Bollobas, 1985). In contrast, the degree distribution of many real large networks has been shown to follow a power law distribution. Since power laws are free of a characteristic scale, these networks are referred to as *scale-free* networks (Barabási and Albert, 1999; Barabási *et al.*, 1999). This implies that many nodes have few connections, whereas a small number of nodes has many connections. *Small-world* networks (Watts and Strogatz, 1998), then, are a type of scale-free network, defined by the small-worldness parameter σ, as discussed before (Amaral *et al.*, 2000). With regard to the nature of the attack, two types of attack are commonly investigated (Bullmore and Sporns, 2009): random deletion of nodes/edges, and targeted attack of nodes/edges based on their centrality within the network. By deletion of nodes or edges, removal of specific brain regions or connections between regions is respectively simulated. Network robustness is then typically assessed by measuring the ability of the graph not to fragment into subgraphs when elements of the graph are removed.

Applied to the study of robustness features of the mammalian brain, Kaiser *et al.* (2007) found that the intact structural connectivity organization of cat and macaque monkey cortices bears more resemblance to scale-free networks than to random or small-world networks. After lesioning nodes or edges from the structural connectivity matrix (Kaiser and Hilgetag, 2004;

Kaiser *et al.*, 2007), relatively high robustness of the networks was found against random node or edge failure. This came at a high cost, though, since the networks were extremely vulnerable to targeted attack of their most central nodes and edges. These results further corroborate general findings on robustness properties in scale-free networks (Albert *et al.*, 2000).

Human brain networks, in contrast, have been shown to have an exponentially truncated power law degree distribution (Achard *et al.*, 2006; Wang *et al.*, 2009), at least when studied at macro-level (Guye *et al.*, 2010). This type of degree distribution is associated with a lower probability of very high degree nodes, compared to networks with a pure power law degree distribution. Studies examining robustness properties of human networks (Achard *et al.*, 2006; Alstott *et al.*, 2009; Joyce *et al.*, 2013; Crossley *et al.*, 2014) have indicated that the human connectome is approximately as resilient to random failure compared to random and scale-free networks. On the other hand, they were found to display significant vulnerability to targeted attack of central nodes. In comparison to scale-free networks with pure power law degree distributions, however, they were still relatively robust to targeted attack of central nodes.

Lesion effects predicted by computational modeling studies

The fact that human brain networks show remarkable resilience to different kinds of attack compared to other types of complex network configuration of course does not imply that they are immune to any type or extent of lesion. Given the availability of whole-brain structural and functional connectivity maps and large-scale computational models to simulate biophysically plausible neural activity, several studies (Young *et al.*, 2000; Sporns *et al.*, 2007; Honey and Sporns, 2008; Alstott *et al.*, 2009; Stam *et al.*, 2010; Cabral *et al.*, 2012;

Váša *et al.*, 2015) have assessed the effects of structural lesions on the brain's wiring diagram (Table 2). As depicted in figure 3, this can be achieved by virtually lesioning a structural connectivity matrix and subsequently applying an appropriate computational model to this lesioned matrix in order to simulate brain activity. Lesion effects can then be evaluated by comparison of simulated and empirical unlesioned functional connectivity matrices, for example by calculating various graph measures.

One of the first studies investigating the consequences of structural lesions was performed by Sporns *et al.* (2007), using macaque and cat cortical connectivity data. They first sought to identify hub regions within the networks, since lesions in these regions may have unusually large consequences on the remaining network's organization. Results indicated that the intersection of node degree, motif fingerprint, betweenness and closeness centrality allows for the identification of hubs. In addition, they distinguished between provincial and connector hubs (Guimerà and Amaral, 2005; Bassett *et al.*, 2006). Simulating a lesion by deletion of either a provincial or connector hub node was found to have opposite effects on the small-world organization of the remaining structural network. In particular, lesions of connector hubs led to large increases in the small-worldness index, caused by an increased distance between clusters combined with an even larger increase in functional segregation (i.e., increased clustering coefficient). In contrast, removal of provincial hubs resulted in decreases in small-worldness, caused by a decrease in clustering accompanied by a smaller effect (increase or decrease) in characteristic path length.

Moving beyond these purely structural analyses, subsequent studies have implemented various large-scale dynamical models to predict resting-state functional connectivity after virtual lesions (Young *et al.*, 2000; Honey and Sporns, 2008; Alstott *et al.*, 2009; Stam *et al.*,

2010; Cabral *et al.*, 2012; van Dellen *et al.*, 2013; Váša *et al.*, 2015). Overall, it has been found that lesions cause specific patterns of altered simulated functional connectivity among distant, even contralateral, regions of the cortex. However, network position of the lesion – both anatomically and topologically – appeared of critical importance in predicting the magnitude of lesion effects. Topologically, it was found that lesions of hub regions within the network have the largest effects on simulated functional connectivity patterns, though lesion impact sometimes differed according to the specific centrality metric that was used to define hub nodes. In addition, a distinction has to be made between two types of hub nodes based on their position within the community structure of the network, corroborating previous findings on structural connectivity alterations after virtual lesions (Sporns *et al.*, 2007). That is, lesions of connector hubs were found to cause the largest and most widespread disturbances in simulated functional connectivity, particularly within the default-mode network. This was explained by the resulting increased characteristic path length of the remaining network. Alterations after lesioning provincial hubs, on the other hand, were found to be more confined to the hub's own cluster. Regarding the lesion's anatomical position, results indicated that especially lesions along the cortical midline (comprising the medial frontal and medial parietal regions), the temporo-parietal junction and the frontal cortex result in the largest disturbances in simulated functional connectivity. Interestingly, parts of some of these anatomically vulnerable regions, such as the posterior cingulate cortex and precuneus, appear to overlap with both the default-mode network and a core group of structural hubs identified by Hagmann *et al.* (2008).

Further evaluation of lesion effects using graph measures (Stam *et al.*, 2010; Cabral *et al.*, 2012) showed that virtual lesions result in a reorganization of simulated functional network topology. The direction of these changes was however inconsistent between both studies.

Probably, this can be attributed to methodological differences, given that both studies used different structural (data), dynamical and lesion models.

Lastly, one study (Stam *et al.*, 2010) explored effects of acute virtual lesions over time, thereby focusing on recovery and plasticity of brain networks after lesions. Results revealed that over time, the network recovered most of its original structure, though the recovery rate and pattern was different for different network properties. In particular, normalized clustering, normalized characteristic path length and modularity showed an exponential approximation to the original values, whereas the degree correlation showed a transient positive peak some time after the lesions. Based on these findings, the authors hypothesize that recovery from a lesion reflects, to some extent, a replay of events during network evolution.

Focal brain lesion effects: Empirical evidence from brain tumors, stroke and TBI

In this section, we review the empirical literature regarding the effects of brain tumors, stroke, and TBI on the brain's structural and functional organization. Common to these three types of focal injury is that there is no unequivocal relationship between the anatomical lesion site and its topological features within the brain network .

Gratton *et al.* (2012) examined a heterogeneous group consisting of stroke, brain tumor and TBI patients to investigate the effects of these lesions on the functional connectome. Using resting-state fMRI data and a graph theoretical analysis framework, results showed that damage to brain regions important for communication between sub-networks (i.e., *connector hubs*) lead to decreases in modularity. In addition, this network dysfunction extended to the structurally intact hemisphere. In contrast, lesions located in brain regions important for

communication within sub-networks (i.e., *provincial hubs*), did not have this effect. A subsequent study by Warren *et al.* (2014) further corroborated the importance of the network community structure to predict lesion effects. In particular, they used resting-state fMRI data of patients with focal lesions that were classified as situated in either "target" or "control" locations, depending on whether the lesion location exhibits correlated activity with multiple brain systems in the healthy connectome. Specifically, target locations were defined as brain regions with high system density (a measure of the physical proximity of multiple brain systems) and high participation coefficient (a measure of the number of different systems with which a node has strong signal correlations). On the other hand, control locations were identified as regions with high degree centrality, and low system density and participation coefficient. Results indicated that damage to target locations is associated with severe impairments across several cognitive and behavioral domains, whereas lesions to control locations has more limited consequences. Hence, from these studies it can be concluded that the three types of focal brain lesions considered can have a widespread, nonlocal impact on functional brain network organization, especially when lesions are situated in regions important for communication between sub-networks, with significant implications for cognitive functioning and behavior.

In the next sections, we provide a more in-depth discussion of studies examining brain tumors, stroke and TBI, and their influence on the connectome.

Brain tumors

A brain tumor can be described as a mass or growth of abnormal cells in the brain. In adults, the most common types of primary brain tumors are gliomas, developing from glial cells, and meningiomas, developing in the meninges (Fisher *et al.*, 2007). The malignancy of brain

tumors can be described based on the World Health Organization grading system, with grade I tumors being the least malignant and grade III (for meningioma) or IV (for glioma) tumors being the most malignant. Hereby, malignancy relates to the speed with which the disease evolves, the extent to which the tumor infiltrates healthy brain tissue, and chances of recurrence or progression to higher grades of malignancy. As such, tumor grade is an important component in predicting patients' treatment response and prognosis. Of note, grade I and II brain tumors are often referred to as low-grade tumors, whereas grade III and IV are described as high-grade tumors. Regardless of tumor grade, size or location, however, brain tumor patients frequently suffer from impairments in various cognitive domains, which are often difficult to explain based solely on the focal structural damage caused by the tumor (Taphoorn and Klein, 2004). Hence, it is probable that brain tumors interfere with global functional network organization, rather than impacting only the site of the lesion. Therefore, several studies have been conducted aimed at characterizing network topology alterations in brain tumor patients, before and after tumor resection (Table 3).

To explore brain tumor patients' functional network topology, the first studies used resting-state MEG (Bartolomei *et al.*, 2006; Bosma *et al.*, 2009; van Dellen *et al.*, 2012). Initial results revealed significant network alterations in the presence of a brain tumor, with lower segregation and higher integration compared to healthy controls. Subsequent studies distinguished between different tumor types, and showed that LGG patients' functional networks are less well integrated compared to those of healthy controls and HGG patients. Network segregation, on the other hand, was found to be decreased in high frequencies and increased in low frequencies. In contrast, network topology of HGG patients did not differ significantly from healthy controls. Using resting-state fMRI data (Xu *et al.*, 2013; Huang *et al.*, 2014), LGG patients' functional networks showed lower integration. In addition,

functional network hubs were displaced from right insula and right posterior cingulate cortex in controls to right thalamus and right posterior cingulate cortex in patients. Results regarding network segregation, on the other hand, were less consistent.

After tumor resection, H. Wang *et al.* (2010) demonstrated an increase in beta band segregation and integration in a sample of meningioma, LGG, and HGG patients. Using a minimum spanning tree analysis approach (Tewarie *et al.*, 2015), van Dellen *et al.* (2014) aimed to characterize functional network topology changes after epilepsy surgery in a group consisting of mainly LGG patients. Their results indicated an increase in minimum spanning tree leaf fraction and a decrease in minimum spanning tree betweenness centrality and eccentricity after tumor resection in patients who were seizure-free after surgery, compared to patients who still had post-operative seizures. These findings indicate that the global functional network of patients whose surgery was successful was characterized by a more integrated topology. The authors hypothesized that this finding might be related to the surgical removal of local pathological hubs. In contrast, Huang *et al.* (2014) did not find significant network alterations after frontal LGG resection.

Thus far, only one study has examined structural network alterations in a sample of meningioma, LGG, and HGG patients (Yu *et al.*, 2016). Results revealed only minor differences in global structural network properties, compared to healthy controls. In particular, increased normalized clustering was found in patients compared to controls, whereas no significant group differences were detected in other global measures of integration, nor in network segregation. Furthermore, network hub locations differed slightly between patients and healthy controls, though the majority of network hubs (10/15) was shared by both groups.

In conclusion, these studies indicate that the global organization of functional networks is affected by the presence of brain tumors, and especially LGG tumors. In particular, LGG patients' functional networks are characterized by decreased segregation in high frequencies and decreased global integration. Hence, preliminary results from longitudinal analyses could point towards a "normalization" of functional network topology after tumor resection. In addition, associations between graph metrics and cognitive functioning have been found, suggesting these metrics may be of potential clinical value. For example, LGG patients that showed higher MEG-theta normalized clustering tended to show worse executive functioning skills (van Dellen *et al.*, 2012), whereas lower global efficiency was related to lower full, verbal, and performance IQ scores (Xu *et al.*, 2013). Furthermore, significant alterations in network centrality measures have been found, both before and after tumor resection.

HGG patients' functional network topology, on the other hand, did not differ significantly from that of healthy controls as reported by one preliminary study (van Dellen *et al.*, 2012). This result could be explained by considering the temporal pattern of the injury inflicted to the brain. That is, in a study on the difference in reorganization patterns between acute and slow-growing lesions (Desmurget *et al.*, 2007), it was hypothesized that it might take time before network reorganization becomes evident on a global scale. Since HGGs often present as acute, fast-growing tumors, this might explain the lack of topological alterations in this group of patients. Therefore, future research might benefit from distinguishing between different tumor types, according to the specific (temporal) disease mechanism.

Regarding structural network alterations in brain tumor patients, results from the first study indicate that global network topology is mostly preserved. Nonetheless, it has been

demonstrated that lesion-specific histological features are associated with different white matter alterations (Campanella *et al.*, 2014). In particular, displacement of white matter pathways was found in meningioma tumors. In LGG patients, a mixed pattern of tract deviation and disruption was found, whereas HGG tumors were associated with an almost complete disruption of fiber bundles. Hence, future research is warranted to investigate whether structural network alterations also differ according to tumor-specific histopathological features.

Stroke

A stroke occurs when blood flow to an area of the brain is cut off, resulting in cell death. Stroke is one of the main causes of adult disability worldwide, with many patients suffering from motor deficits (Lawrence *et al.*, 2001), aphasia (Berthier, 2005) or spatial neglect (Appelros *et al.*, 2002), depending on the lesion location. Nevertheless, only few studies so far have examined functional and structural network topology in stroke patients (Table 4).

With regard to stroke patients' functional network organization, de Vico Fallani *et al.* (2009) used EEG data recorded during a motor task from one asymptomatic stroke patient and a group of healthy control subjects. Results indicated that, compared to healthy controls, the patient's functional network showed lower local and global efficiency, and lower mean node degree. Next, a longitudinal resting-state fMRI study was conducted in stroke patients with motor deficits, examining functional topology of the motor execution network over time (L. Wang *et al.*, 2010). In the acute phase after stroke, no significant differences were found in normalized clustering, normalized characteristic path length, or betweenness centrality between patients and healthy controls. Over one year of recovery, though, patients showed lower normalized clustering within the motor execution network, suggesting a shift takes

place towards a more random network configuration with less functional segregation. Moreover, this shift was correlated with restoration of function, reflected by improved motor skills, decreased degree of disability in daily activities, and less stroke symptoms. Hence, this change towards a more random network configuration could possibly represent an adaptive recovery process. A similar longitudinal study investigated whole-brain functional network organization in stroke patients suffering from motor impairments, using task-based fMRI data (Cheng *et al.*, 2012). Results indicated that after three months of recovery, patients with right-hemisphere stroke show decreased network integration during an ipsilateral finger tapping task. In contrast, no significant trends were found during a contralateral finger tapping task, or for left-hemisphere stroke patients.

The topology of stroke patients' structural networks was investigated by Crofts *et al.* (2011) and Falcon *et al.* (2015), using DWI data of chronic stroke patients and healthy controls. Using traditional integration and centrality graph metrics (global efficiency, betweenness centrality and degree centrality), no significant differences were detected between healthy controls and chronic stroke structural connectomes. However, Crofts *et al.* (2011) also computed *communicability* (Estrada and Hatano, 2008) as a measure of the ease with which "information" can spread across the network. This measure did reveal significant group differences. In particular, they found that communicability is reduced in patients in regions surrounding the lesion in the affected hemisphere, as well as in homologous locations in the contralesional hemisphere for a subset of these regions. They also identified regions with increased communicability in patients that could represent adaptive, plastic changes post-stroke.

In sum, stroke seems to mainly affect functional network topology, while disturbances in structural organization in the chronic phase after stroke appear limited. However, further (whole-brain) investigation is clearly needed to clarify the inconsistencies found in functional network alterations after stroke. In addition, relationships between stroke symptoms and changes in network topology should be subject of further examination, in order to foster development of novel therapeutic interventions.

Traumatic brain injury

Traumatic brain injury occurs when an external mechanical force traumatically injures the brain, resulting for example from traffic accidents and falls. Even years after the insult, many TBI patients suffer from disability, particularly due to cognitive impairments (Whitnall *et al.*, 2006; Chen and D'Esposito, 2010). Although focal brain injury often occurs as a result of TBI, the location and extent of such lesions are often insufficient to explain the persistent cognitive deficits (Bigler, 2001). Besides focal lesions, however, TBI also results in diffuse/traumatic axonal injury, affecting the integrity of long-distance white matter tracts (Povlishock and Katz, 2005). Given that cognitive functions depend on the coherent activity of widely distributed brain networks (Mesulam, 1998) – that might have become disconnected as a result of diffuse axonal injury – several studies have adopted a network approach to examine the effects of TBI (Table 5).

Firstly, alterations in structural network topology have been found in TBI patients (Caeyenberghs, Leemans, De Decker, *et al.*, 2012; Caeyenberghs *et al.*, 2014; Fagerholm *et al.*, 2015; Hellyer *et al.*, 2015; Yuan *et al.*, 2015). Regarding network segregation, TBI patients' structural networks showed increased segregation in the acute phase post-injury compared to patients with orthopedic injuries, whereas similar or decreased segregation was

found in the chronic phase in comparison with healthy structural connectomes. In both acute and chronic TBI patients, however, structural networks have been consistently found to show decreased integration. Furthermore, a trend towards decreased centrality has been found in acute and chronic TBI patients, both for the network as a whole and for specific network hubs. Moreover, sub-optimal integration and centrality measures were found to be associated with cognitive and behavioral impairments, illustrating their potential clinical value. Specifically, reduced global efficiency was related to poorer executive function (Caeyenberghs *et al.*, 2014), reduced node degree in two hubs was associated with TBI symptom severity (Yuan *et al.*, 2015), reduced mean degree was related to poorer balance performance (Caeyenberghs, Leemans, De Decker, *et al.*, 2012), and reduced overall betweenness and eigenvector centrality correlated with the extent of cognitive impairment, both in patients with and without microbleed evidence of diffuse axonal injury (Fagerholm *et al.*, 2015).

Functional network topology changes after TBI are more variable, possibly due to the great heterogeneity in neuroimaging modalities that were adopted. In the (sub)acute phase (i.e., within six months) after TBI (Nakamura *et al.*, 2009; Castellanos *et al.*, 2011; Tsirka *et al.*, 2011), a modest trend towards increased segregation and integration compared to healthy controls was revealed during resting-state. In addition, the mean strength in MEG delta band functional connectivity networks was increased, and the degree distribution showed slower decay compared to healthy controls, indicating an increase in the number of highly interconnected regions. However, almost all metrics were found to be normalized to levels approximating those observed in healthy subjects after standard treatment (Nakamura *et al.*, 2009; Castellanos *et al.*, 2011).

In chronic TBI patients, Pandit *et al.*, (2013) found increased integration in patients' functional networks compared to healthy controls, though this was only the case in patients who also showed evidence of diffuse axonal injury, as measured by reduced fractional anisotropy and increased mean diffusivity in long-distance white matter tracts. In contrast, in a study by Caeyenberghs, Leemans, Heitger, *et al.* (2012) no significant alterations in functional network integration were found, though their sample consisted almost exclusively of TBI patients with signs of diffuse axonal injury. On the other hand, the authors did report increased local efficiency in patients compared to healthy controls. Both studies, however, indicated changes in functional network centrality measures. In particular, Caeyenberghs, Leemans, Heitger, *et al.* (2012) found increased mean degree and strength in TBI patients' functional networks compared to healthy controls. Additionally, they identified hub nodes in the right dorsolateral prefrontal cortex and left dorsal premotor cortex in patients, in addition to the hub in the right insular lobe found in healthy controls. Pandit *et al.*, (2013), on the other hand, found decreased degree and betweenness centrality in the posterior cingulate cortex, a region forming part of the brain's structural core (Hagmann *et al.*, 2008). As such, it became less of a hub in patients compared to controls.

These studies thus suggest that although TBI temporarily disrupts optimal functional network organization, some network properties may restore over time. This normalization hypothesis is supported by the observed associations between restored graph metrics and improved measures of cognitive functioning. In particular, Castellanos *et al.* (2011) showed an association between normalization of delta band characteristic path length and Performance IQ of the WAIS-III intelligence task, whereas Caeyenberghs, Leemans, Heitger, *et al.* (2012) found a positive correlation between mean degree on the one hand and executive functioning and TBI symptom severity on the other hand. Normalization of functional network centrality

measures, however, appears to be more limited, and may account for the persistent cognitive impairments in TBI patients (Crossley *et al.*, 2014).

Finally, one study has compared structure and function in the same sample of chronic TBI patients and healthy controls (Caeyenberghs *et al.*, 2013). Their results showed increased functional connectivity strength within the switching network, implying a relatively more dense network structure compared to healthy controls. Segregation and integration of patients' functional networks, on the other hand, did not differ significantly from those of healthy controls, supporting the normalization hypothesis of functional network topology. Regarding structural network alterations, also no significant group differences were found. Additionally, no significant association was found between graph metrics of structural and functional connectivity in both the TBI and the healthy controls group. Hence, topological properties of the functional networks could not be solely accounted for by properties of the underlying structural networks. However, combining complementary information from both imaging modalities did improve prediction accuracy of executive control performance.

Computational lesion modeling versus empirical results of focal damage

In this section, we evaluate the correspondence between predictions made by computational lesion studies and results from empirical studies examining focal brain lesions.

Regarding the prediction of lesion effects, converging evidence from both computational modeling and empirical studies point to the critical importance of the topological position of lesions. In particular, lesions in hub regions within the network – and especially those connecting different sub-networks (i.e., *connector* hubs) – were found to have the largest impact on network topology. In order to identify these hub regions, various studies have

indicated that node degree or strength is insufficient. Rather, other centrality measures such as betweenness centrality, closeness centrality, or participation coefficient, or a combination thereof, are more suited to identify hub nodes of the network. Concerning the lesion's anatomical position, one modeling study (Alstott *et al.*, 2009) predicted that especially lesions along the cortical midline, the temporo-parietal junction and the frontal cortex have the largest and most widespread effects on functional connectivity. Interestingly, parts of some of these anatomically vulnerable regions, such as the posterior cingulate cortex and precuneus, overlap with the core group of structural hubs identified by Hagmann *et al.* (2008). Hence, these results appear to further corroborate the importance of the topological lesion position in predicting lesion effects.

Regardless of the specific lesion type and location, alterations in network segregation and integration properties have generally been found, both in computational lesion and empirical studies. However, the direction of these changes remains unclear. Presumably, several inconsistencies in the direction of network alterations across studies can be attributed to heterogeneity in lesion etiology within studies and differences in neuroimaging modality between studies. In addition, it has been shown that preprocessing and network construction techniques can also substantially influence graph theoretical results (e.g., Fornito *et al.*, 2013). Further methodological research, possibly leading to a consensus approach regarding network construction and analysis, is thus required to clarify large-scale network effects of various types and stages of brain damage.

Lesion effects on network hubs and centrality measures in general were investigated less frequently in clinical studies, and have not been addressed in computational lesion studies so far. Yet, preliminary empirical results indicate that focal brain lesions cause displacement of

network hubs and alterations in centrality properties of structural and functional networks. Although additional research focusing on network centrality changes after brain lesions is definitely warranted, these preliminary findings appear to corroborate and extend a recent meta-analysis performed by Crossley *et al.* (2014). In this extensive meta-analysis, a total of 26 neurological and psychiatric disorders were investigated, with results pointing towards a central role of brain hubs in various brain disorders. Specifically, in nine out of 26 disorders, including Alzheimer's disease and schizophrenia, lesions were significantly more likely to be located in hubs of the normal structural connectome. The authors hypothesize at least two major convergent factors could explain the implication of hubs in various brain disorders. First, hubs are more functionally valuable, especially for "higher-order" cognitive functions. As a result, lesioned hubs are more likely to be symptomatic than lesioned non-hubs. Second, hubs are more biologically costly and therefore more vulnerable to a diverse range of pathogenic processes. Examining the involvement of network hubs and the association between hub damage and lesion symptoms thus may be a promising path towards understanding the effects of different types and stages of focal brain damage. For example, future research could investigate whether characteristic stroke symptoms such as aphasia and spatial neglect result from damage to domain specific hubs for language and attention, respectively.

Finally, both modeling and empirical studies have indicated that after focal lesions, the connectome carries the potential to, at least to some extent, recover its original functional organization. Moreover, several empirical studies have demonstrated that such recovery is related to improved behavioral and cognitive functioning. This provides further support for the normalization hypothesis, and highlights the potential clinical usefulness of network analysis.

Focal brain lesions versus Alzheimer's disease

In contrast to focal brain lesions such as TBI, brain tumors and stroke, in which the topological properties of a node do not determine its likelihood to be affected by a lesion, it has been demonstrated that hub regions are preferentially affected in Alzheimer's disease, a multifocal neurodegenerative disorder (Stam *et al.*, 2009; de Haan *et al.*, 2012). In order to examine whether large-scale network results differ according to the way lesions propagate through the network, we compare large-scale network alterations after TBI, brain tumor and stroke to those observed in patients with Alzheimer's disease. Specifically, given the plethora of studies having addressed structural and functional network changes in Alzheimer's disease, several review studies published in this domain are examined (He *et al.*, 2009; Pievani *et al.*, 2011; Greicius and Kimmel, 2012; Reid and Evans, 2013; Tijms *et al.*, 2013; Dai and He, 2014; Dennis and Thompson, 2014).

Regarding network segregation and integration alterations in Alzheimer's disease patients, tentative conclusions drawn by these review studies varied greatly, with some of them even being contradictory. In particular, consensus exists in that Alzheimer's disease results in abnormal structural and functional network segregation and integration. However, the direction of the alterations remains unclear. Furthermore, although it has been shown that hub regions are preferentially affected by Alzheimer's disease (Stam *et al.*, 2009; de Haan *et al.*, 2012), the impact of Alzheimer's disease on network hubs and centrality measures in general have not yet been subject of extensive investigation. Scarce evidence though indicates hub regions' centrality within the network decreases, even up to a point where they lose their "hub" status, possibly due to atrophy of particular areas.

Despite these mixed findings, graph metrics could prove useful in clinical practice, as demonstrated by associations between graph metrics and indices of disease severity and cognitive functioning. For example, Brier *et al.* (2014) have found alterations in clustering and modularity in preclinical Alzheimer's disease patients similar to, but smaller than in symptomatic patients. Furthermore, lower characteristic path length and higher normalized clustering have been found to be associated with more severe cognitive impairments in Alzheimer's disease patients (Stam *et al.*, 2007, 2009).

Based on these findings, it can be concluded that both focal lesions – in which there is no unequivocal association between the location of the lesion and its topological features within the brain network – as well as Alzheimer's disease in which hub regions are preferentially affected, cause global alterations in structural and functional network topology. At first sight, this appears to contradict results from studies examining network robustness properties described before. That is, human brain networks were found to be relatively robust to random failure, while being especially vulnerable to targeted attack of central nodes in the network. However, an important factor that is not taken into account in studies examining network robustness properties is that network damage inflicted at random can propagate further through the network. In particular, disease processes can spread throughout the network, with propagation being determined by the topological organization of the network. As such, it seems intuitive that topologically central regions are particularly vulnerable to various pathological processes. Hence, mere removal of nodes and their links – used to simulate random brain lesions – does not capture the complexity of how disease processes affect the connectome.

In order to unravel exactly how network organization changes in response to different types and stages of brain lesion – a prerequisite for the application of network analysis in clinical practice – further research is clearly warranted. In particular, additional efforts are required to enable comparison across studies. To this end, future research might benefit from categorizing patients according to lesion etiology and/or stage (e.g., LGG vs. HGG; moderate acute vs. moderate chronic TBI), as well as a consensus approach on network construction and analysis. Lastly, relationships between network properties and cognitive or behavioral indices should be subject of further investigation.

Methodological issues in network analysis of lesioned brains and future directions

In interpreting results from the reviewed studies, several methodological issues have to be taken into account that pertain to the study of brain diseases adopting a network approach. Firstly, detailed lesion descriptions are often lacking. For example, only half of the TBI studies discussed in this review reported whether evidence of diffuse axonal injury was present in patients. In addition, focal brain lesions are often accompanied by secondary disease processes such as Wallerian degeneration after TBI and stroke, or the development of edema after different types of brain injury. These limited lesion descriptions hinder the possibility of distinguishing effects – both on the network level and on cognition or behavior – caused by focal versus diffuse, and primary versus secondary brain injury.

Secondly, it has been shown that the presence of white matter injury – as is often the case after TBI – can bias tractography estimation (Hua *et al.,* 2008). In particular, the procedure may fail if the amount of white matter damage to a tract is sufficiently large, as fractional anisotropy then will often be low enough or the uncertainty high enough to impair

performance of tractography algorithms. Therefore, alternative approaches have been developed, that use atlases of white matter tracts derived from control subjects, which are applied to guide subsequent analyses in patients (Singh *et al.*, 2010; Squarcina *et al.*, 2012). However, this technique has only been adopted in two of the most recent DWI studies in TBI patients (Fagerholm *et al.*, 2015; Hellyer *et al.*, 2015).

The next issue involves the parcellation scheme applied to define network nodes. To this end, various techniques exist, among them anatomical, random, or functional parcellation, or without applying a parcellation scheme and analyzing the brain with a node in each voxel. However, even in healthy controls, there is no established standard for node definition. In the presence of brain lesions, when anatomy is often distorted and underlying function can be changed, this issue is further complicated. Nonetheless, a substantial part of the clinical MRI studies discussed in this review have overlaid standard anatomical or functional atlases to lesioned brains, disregarding potentially large deviations from normal anatomy and function. Additional research into parcellation, taking into account these possible deformations, is therefore clearly warranted. One possible approach would be to utilize multimodal imaging information, for example to identify anatomical regions based on the important white matter tracts that connect them.

Finally, we believe the field is now ready to move beyond mere descriptions of disease processes. That is, future studies should focus on generating hypotheses about underlying pathophysiological mechanisms and make clinically useful predictions concerning key prognostic indicators. In particular, correlates between graph metrics and specific behavioral or cognitive indices have been found in several brain lesion studies, but often these are too general to apply as a biomarker in a subject-specific predictive context (Castellanos *et al.*,

2013). As demonstrated by a recent study on epilepsy surgery, graph theory analysis may however be used to predict the efficacy of neurosurgical treatments and to avoid cognitive deficits. In particular, Doucet *et al.* (2015) demonstrated that graph measures of segregation, integration and centrality derived from the presurgical functional connectome of patients with temporal lobe epilepsy predicted between 68% and 99% of postsurgical cognitive performance across different domains. Hence, it should be investigated whether similar predictive associations can be found between graph metrics – based on structural or functional connectivity, or a combination of both – and specific behavioral or cognitive functions in patients with focal brain lesions, in order to aid treatment planning. In parallel, future computational modeling studies could use patient-specific empirical structural connectomes combined with biologically inspired dynamical models in order to shed light on the local dynamics underlying altered large-scale network topology in different types of brain lesions. To this end, The Virtual Brain (www.thevirtualbrain.org) could be applied, a neuroinformatics platform for large-scale network simulations using biologically realistic structural connectivity (Sanz Leon *et al.*, 2013). This simulation environment enables model-based simulation, analysis, and inference of neurophysiological mechanisms across different brain scales that underlie the generation of macroscopic neuroimaging signals including fMRI, EEG and MEG. A great advantage of this platform is that it allows the reproduction and evaluation of personalized configurations of the brain by using individual empirical structural connectivity data. This personalization facilitates an exploration of the consequences of pathological changes in the system, permitting to investigate potential ways to counteract such unfavorable processes. In this regard, one study has examined brain dynamics underlying stroke using The Virtual Brain (Falcon *et al.*, 2015). Their results indicated an increase in long-range coupling in stroke patients compared to healthy controls, suggesting a preponderance of local over long-range brain dynamics. In addition, increased long-range

coupling was related to lower values of global efficiency. As such, this study highlights the global impact of stroke, despite its relatively focal damage.

Conclusion

In conclusion, human brain networks appear remarkably resilient to different types of lesions, compared to other types of complex networks such as random or scale-free networks. Possibly, this could be attributed to the exponentially truncated power law degree distribution found in large-scale human brain networks (Achard *et al.*, 2006; Wang *et al.*, 2009). In particular, such networks consist of fewer "mega-hubs" compared to scale-free networks with pure power law degree distributions, which might render them slightly less vulnerable to targeted attack of central nodes within the network.

Of course, this does not imply that human brain networks are immune to any type or extent of damage. In particular, lesion effects have been found to depend critically on the topological position of the lesion, with damage to network hub regions – and especially those connecting different sub-networks (i.e., *connector* hubs) – causing the largest disturbances in network organization. This finding might lead to novel, more effective therapeutic interventions. For example, determination of patient-specific network hubs in proximity to brain tumors could help guide pre-surgical planning in order to minimize cognitive impairment, and future research can investigate whether disease-affected hub regions could serve as new targets for deep brain stimulation.

Regardless of the specific lesion location, however, alterations in global network topology have been found in empirical studies examining brain tumors, stroke, TBI, and Alzheimer's disease, as well as in computational lesion studies. Therefore, these pathologies can be

considered as “disconnection syndromes” from a complex networks perspective (Guye *et al.*, 2010). In order for these network alterations to become clinically useful, though, much more research is required to unravel exactly how network organization changes in response to different types and stages of brain damage. To this end, future research would benefit from categorizing patients according to lesion etiology and/or stage, as well as a consensus approach on network construction and analysis, to facilitate comparison between different studies. Once these methodological obstacles are resolved, potential clinical applications are numerous. That is, biomarkers of specific brain functions and symptoms could be identified, thereby carrying the potential to allow more objective diagnosis, to monitor recovery or progression processes over time, and to predict effective treatment options.

Complimentary, computational modeling holds great promise to shed light on the local dynamics underlying altered large-scale network topology in different types of brain lesions. Though still in its infancy, computational modeling may provide an entry point for understanding brain disorders at a causal mechanistic level, possibly leading to novel, more effective therapeutic interventions.

In sum, the studies discussed in this review provide the foundation for, and highlight the possibility of, applying connectome analysis in clinical practice. Therefore, we would like to encourage the neuroscientific community to invest in revealing underlying pathophysiological mechanisms and making clinically useful predictions concerning key prognostic indicators, making use of this novel and promising complex networks perspective.

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Figure legends

Figure 1. Workflow for obtaining structural and functional connectivity matrices and corresponding brain network. (a) Structural connectivity strength between any two regions is calculated, for example by using the count or density of reconstructed streamlines connecting any two regions. For visualization purposes, the logarithm of structural connectivity strength is shown in the structural connectivity matrix; (b) Functional connectivity strength is calculated as the pairwise statistical dependency between average time series of any two regions; (c) Representation of regions (nodes) and connections (edges) in the brain.

Figure 2. Important complex network concepts. (A) Visual representation of segregation, integration and centrality concepts within the graph theoretical framework, and corresponding frequently used graph metrics. (B) Representation of three important types of complex network, with the small-world network representing an intermediary state between regular and random networks with regard to integration and segregation properties.

Figure 3. Workflow for computational lesion modeling. (1) Empirical structural connectivity (SC) matrix is calculated by parcellating the brain and calculating structural connectivity strength between any two regions. Subsequently, the empirical structural connectivity matrix is virtually lesioned, for example by removal of a subset of nodes and all their edges. For visualization purposes, here the logarithm of structural connectivity strength is shown; (2) An appropriate dynamical model is applied to the lesioned structural connectivity matrix, resulting in simulated brain activity time series; (3) Simulated brain activity time series are converted into a simulated functional connectivity (FC) matrix; (4) Simulated and empirical unlesioned functional connectivity (FC) matrices can be compared, for example by utilizing graph metrics. Adapted with permission from Falcon *et al.* (2016).