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News & Views

# Rethinking the neurosurgical approach to brain disorders from the network neuroscience perspective

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In 1947, an original report describing the use of stereotactic-driven lesioning of the human brain triggered the onset of the functional neurosurgery era; during the 1950s, this lesioning approach began to be applied to the treatment of patients suffering from refractory epilepsy and movement disorders (Text S1 online). Concurrently, therapeutic alterations in brain activity were mainly achieved through focal interventions in anatomical brain structures thought to cause pathological clinical states. However, these focal surgical interventions were primarily based on a limited understanding of how pathological changes in those brain structures could explain the patient's symptoms, since these symptoms usually resulted from a combination of effects generated by multiple brain regions. Furthermore, this focal surgical strategy could not precisely predict the effectiveness of the treatment on an individual basis, i.e., from patient to patient.

With the development of modern deep brain stimulation (DBS) in 1987, the focus of functional neurosurgery shifted to rely increasingly more on the neuromodulation of distributed neural networks to achieve its therapeutic goals; and a preliminary description of neural networks appeared approximately in 2004 (Text S1 online). In recent years, the advent of network neuroscience has also shifted this focus to studying how therapies could affect entire neural networks, rather than a single brain area, to achieve the best possible clinical outcomes [1]. Despite substantial progress in recent years, the understanding of the principles and mechanisms underlying brain disorders remains incomplete. Network neuroscience provides unique opportunities to explore network interactions and to reveal the biological mechanisms associated with several common brain disorders. Together, these innovations are prompting us to rethink how we define neurological disorders, e.g., Alzheimer's disease (AD), Parkinson's disease (PD), and epilepsy (EP), by considering these brain diseases from a neural network perspective. This raises a very important question: how do we carry out functional neurosurgery to optimize the treatment of these patients?

*The gap between individual neurons and brain functions.* In their pioneering work, Golgi and Cajal, who shared the Nobel Prize in Physiology or Medicine in 1906, first identified and highlighted the fundamental role played by a neuronal network. Cajal's work was also essential for the proposition of the "neuron doctrine", which posits that neurons are individual cells that communicate primarily through synaptic contacts. Based on histological observations, Cajal also proposed "the law of functional (dynamic) polarity", which identified the neuron's dendritic tree as the neuron's main component for receiving input, whereas its axon was mainly concerned with transmitting the neuron's output to other cells via its synapses. The neuron doctrine and law of functional polarity were validated by electron microscopy in the 1950s and electrophysiological recordings in the 1960s. Later, in the 1960s and 1970s, the excitatory and inhibitory functions of neurotransmitters such as glutamate or gamma-aminobutyric acid, which are transported between synaptic contacts of excitatory or inhibitory neurons, were well illustrated. Despite these advances, the microscopic structure of an individual neuron in isolation, as well as its single-cell physiological dynamics, could not explain the neurophysiological basis for cognitive functions or the pathophysiological mechanism underlying neurological disorders (Text S2 online).

*Evolution of the understanding of neural networks.* With the development of modern imaging and electrophysiological techniques, this gap between individual neurons and brain functions might be filled. In 1991, a new method was introduced for the large-scale imaging of brain activity, functional magnetic resonance imaging (fMRI), which was quickly followed in 1994 by diffusion tensor imaging (Text S3 online). The combination of these two techniques provided researchers and clinicians with powerful noninvasive methods for mapping brain function activity and structural connectivity in neurological disease patients. Consequently, a more thorough investigation of the functional interactions and connectivity between brain regions was possible. In 2005, Sporns et al. [2] introduced the concept of the "connectome" to describe the global spectrum of connections that interconnect the different elements [1] that define the human brain. In this

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definition, the concept of "neural element" can be applied to a broad range of anatomical brain entities, from a single neuron to a cortical column, all the way to a cortical region or even all cortical areas of the cerebral cortex. Accordingly, the definition of connectivity can be applied, at each level, to the interconnections established between each of these elements (e.g., a single neuron, a cortical column) [2]. Furthermore, the interactions among neural elements and their connections can be investigated with the combination of a large spectrum of mathematical techniques, such as graph theory, dynamical systems theory, and statistical physics (proposed as network neuroscience by Sporns et al. [1] in 2017). In the case of human brain elements and their connectivity, several groups have adopted the classical approach of graph theory, which is based on the analysis of nodes and edges, as a way to characterize the particular connectivity structure and dynamic behavior of large networks formed by connected elements that define a given graph. Interestingly, in the early 1990s, Nicolelis et al. [3,4] introduced a pioneering approach using graph theory to analyze the connectivity of neural networks involved in cardiovascular function control.

In this context, basic and clinical neuroscience can now take advantage of classic types of graph theory analysis. For example, a connection between two neurons can be described as an "edge", which can assume either a binary or a weighted scalar value, and "degree" refers to the number of links (or edges) a node has. Furthermore, neural networks can be represented using hierarchies and subnetworks; in this approach, larger subnetworks are called modules [1]. Typically, nodes within a given module may have more connections between each other than with nodes that lay outside that module. Centrality indicates the importance of a given node compared with other nodes [1]. For example, nodes with a higher "degree" also have a higher "centrality"; it follows, therefore, that nodes with high centrality are also defined as "hubs," and highly interconnected hubs constitute a "rich club". Brain hubs in a "rich club" are functionally valuable, as they are responsible for integrating and modulating various human behaviors [1].

While graph theory has become a leading approach for exploring spatial neural structures in connectome studies and network neuroscience, it mainly describes static or slow temporal resolution intracranial network at the spatial scale. Network studies should encompass the analysis of different networks encountered across many spatial and temporal scales. At least two critical aspects exist regarding the temporal scale or network dynamics; one is the pattern of activity on a fixed structural network, and the other is how different brain hubs are reconfigured [1]. However, the former addresses only superficial empirical avenues, while the latter still lacks reliable models. Thus, the exploration of the network dynamics is still challenging. Recent advances in studying network dynamics include numerical simulation and the virtual brain, which combines the simulation of large-scale brain networks with small-scale spiking networks and provides a potential approach to investigating the network. However, its efficiency in studying network disorders still needs further validation (Text S3 online).

In addition to the temporal scale, the interactions of excitatory and inhibitory neurons at the population level, or the excitatory/inhibitory ratio (E/I ratio), have received increasing attention in recent decades. The two opposing forces affect the physiological and pathological balances not only in the temporal but also in the spatial domain. Thus, the combination of spatial and temporal scales, as well as the E/I ratio, will continue to be investigated in the future (Text S3 online).

*Rethinking brain disorders from a neural network perspective*. Another fundamental property that characterizes hubs is their biological expensiveness, arising due to their requirements for higher levels of metabolic activity to exert their influence. This major metabolic cost occurs because hubs exhibit a higher number of projections (wiring length). As the hubs display both high levels of functional complexity and biological cost, they tend to be more vulnerable to harmful processes, such as neuroinflammation and oxidative stress. As such, these hubs are more often affected by pathological brain lesions [4]. For example, according to a meta-analysis of more than 20,000 patients, at least nine disorders, including schizophrenia, AD, and EP, are more likely to affect brain hubs [4] (Text S3 online).

In addition to the amyloid and tau hypothesis, AD is also defined as a disconnection disorder [5]. According to diffusion tension MRI studies, pathological overload in a given hub can be transferred to other brain hubs that exhibit similarly rich connectivity. As a result of this hub-to-hub transfer process, a wide range of system failures can take place in hubs of rich clubs, leading to the later emergence of clinical symptoms in neurologic patients. This process of hub-to-hub spread may account for the preclinical stage of AD, which may last for up to 15 years before a diagnosis of dementia is finally made. Thus, perturbations of rich-club organization have been identified as an early-stage biomarker for diagnosing AD [5].

In EP, in a series of intracranial electroencephalogram (EEG) recordings, the generation of spikes was found to be more closely associated with rich clubs, since these usually had a lower threshold for the occurrence of pathological coupling between brain hubs [6]. Furthermore, the pathological hub adjacent to the epileptogenic focus was found to be essential for long-range spatial seizure propagation. Additionally, the patients had a better outcome once the surgical field covered the area with high centrality. Therefore, rich-club properties could potentially serve as a biomarker for estimating freedom from seizure postoperatively [6].

Similar to AD and EP, in PD patients, although disruptions of the structure were found to start from peripheral nodes, extension to the rich-club regions occurred at an early stage of the disease. Thus, rich-club connectivity was also proposed as a biomarker for the early diagnosis of PD [7] in addition to cerebrospinal fluid biomarkers and grading scales.

The vulnerabilities of rich-club hubs across different diseases suggest that there is a balance between a network's functional complexity and its biological costs (including metabolism and wiring length). As a result, an index of "fragility" was introduced as a quantitative parameter for evaluating risk in neural networks [8,9]. The fragility index could be considered the threshold beyond which a simulated disease attack on the neural network corrupts it. For the structural network composed of white matter connections, hub fragility is defined as the probability that each hub maintains high-level connectivity with the rest of the network after introducing an incremental randomized perturbation (or simulated attack). This fragility model could indicate neurodevelopmental or pathological deficits that carry a level of predictive power for brain disorders such as schizophrenia [8]. For the functional networks derived from intracranial EEG recordings, fragility is defined as the minimum simulated energy that must be applied to the hub to destabilize the network. The fragility measurement applied to the intracranial EEG was shown to have the best area under the curve (AUC) score among the popular features recognized to be epileptogenic markers, correctly predicting the seizure outcome in 76% of the patients. This was much higher than the 48% correct outcome prediction achieved by clinicians [9].

EP is recognized as an enduring predisposition to recurrent seizures accompanied by epileptic discharge, which results from pathological levels of neuronal synchronization. AD and PD are traditionally identified as degenerative neurological disorders, defined by the pathological production/deposition of beta-amyloid/tau protein and alpha-synuclein, respectively; however, from a network perspective, they share the common vulnerability and fragility of the hubs in rich clubs [5–7,10]. As these hubs are the

core of functional integration, disrupting them could further lead to connectivity abnormalities that create the conditions for the formation of pathological brain states. Therefore, it is reasonable to redefine interventions following the concept and approach of network neuroscience and rich-club organization rules to seek more effective and efficient treatments for the patient.

*How network neuroscience sheds new light on functional neurosurgery*. The aim of functional neurosurgery, from a neural network perspective, should be the restabilization of the network physiological activity. Therefore, to maximize the global treatment effects while minimizing the side effects, we first need to simultaneously determine the spatial and time domains of electrical stimulation based on network mapping. In addition, we must consider the excitatory and inhibitory effects, as neurons with different neurotransmitters exist in the brain. At the same time, we need to know the pathophysiological features of the electrical rhythms to be eliminated.

To map networks, in 2012, Henderson [11] proposed the concept of optimizing the location for DBS using the connectome information from diffusion MRI (dMRI) or fMRI in an approach called "connectomic surgery". In 2020, Pollak commented, "They are anatomically like a funnel. So, the deeper you are, the greater network you can impact" [12]. In the context of connectomic surgery, "information funnels" are represented by substantial hubs in the rich club. One should emphasize, however, that while the concept of connectomic surgery proposes the strategy of determining the target with dMRI or fMRI, despite its recent application to psychiatric disorders [11,12], connectomic surgery neglects to describe the temporal or electrophysiological features for modulating the network dynamics and E/I ratio of neurotransmitters, which also has to be a key component of any network intervention. Additionally, although the network's dynamics are recognized as being essential, the corresponding proper neurosurgical approach to address this issue has yet to be developed (Text S3 online).

In a parallel development, the "information flow in the funnel" was mentioned by Henderson et al. [11] as part of the rationale underlying connectomic surgery. Here, the information flow might be the common pathophysiological target to be eliminated. Ways to achieve this, however, have not been addressed in the literature. After a review of this literature, we noticed that pathological synchronization might play a common role in the pathophysiology of different brain diseases.

Classically, EP has been identified as a disease associated with pathological large-scale neuronal synchronization. Recently, phase-locked patterns of pathological neuronal synchronization, measured in local field potentials, were discovered to gradually appear with the evolution of the dopamine depletion process in an animal PD model [13]. In AD patients, EEG hyperexcitability, as a neural synchronization, was also proposed as a potential biomarker of the disease, in addition to amyloid and tau accumulation [14].

In this new context, blocking pathological neuronal synchronization could return the appropriate neural network to its physiological state. For example, the application of DBS to the subthalamic nucleus (STN) hub blocked subcortical-cortical synchronization and decreased the frequency of epileptic seizures [15]. In addition to DBS, one of the most recent and critical advances in the treatment of PD is spinal cord stimulation (SCS). Classically, the SCS approach has been applied in chronic pain syndromes, but in recent decades, the approach has been shown to block pathological low-frequency synchronization of corticostriatal oscillations. This approach has been proven effective in PD patients suffering from the freezing of gait (FoG) by promoting a comprehensive desynchronization of corticostriatal oscillations. These results highlight the importance of pathological corticostriatal synchronization in mediating the severe deterioration in PD [13]. SCS was also proven to be effective in treating animal EP models [16].

Taken together, these studies have shown that the perspective of combining network neuroscience, which integrates the spatial scope of connectomic neurosurgery, in addition to a consideration of the dynamics of specific targeted neural networks, should offer significant improvements to the clinical outcome of functional neurosurgery. In this context, the neurosurgical approach employed should aim to disrupt pathological neuronal synchronization within the hubs, bringing them to their normal physiological levels. These two aspects are essential in creating a new neurosurgical approach in the near future.

*Network neurosurgery: repairing the spatial and temporal properties of neural networks to improve the therapeutic outcome.* In addition to the spatial domain in previous literature, generally, the neural stimulation approach involves injecting an exogenous electrical signal to modulate the time-varying activity of the neural networks. Thus, modulation of the network is still a temporal domain procedure, and consideration of the dynamics of the network is essential [1]. Again, excitation of a given gray matter region might further result in excitatory or inhibitory effects of other connected gray matter regions, depending on the neurotransmitters involved. Therefore, the E/I ratio, reflecting the effect of the excitatory and inhibitory neurotransmitters, of the targeted neural network should also be considered. Together, electrophysiological methods mainly evaluate these procedures. These findings reinforce the notion that the broad scope of neurosurgical planning based on network neuroscience should include the spatial and temporal properties, as well as the neurotransmitter properties of the targeted neural networks. Therefore, we propose to call this new approach "network neurosurgery" (Fig. 1).

With the notion of "network neurosurgery", the goal of treatment should be to revert the network back to normal, e.g., blockage of the pathological synchronization, rather than intervention to the pathological brain lesion. It would first require quantification of the network to determine the distribution of the target rhythms and hubs with modern network neuroscience approaches such as structural images, diffusion images, fMRI, EEG, intracranial EEG, or magnetoencephalography (MEG) (Text S4 online).

Furthermore, based on the network properties and detected pathophysiological neural activity, it may be possible to push the network toward a more physiological and stable mode of operation with "network control theory" while considering the excitatory and inhibitory properties of the hubs, either by stimulation or thermocoagulation of specific hubs. Interventions could include radiofrequency thermocoagulation (RFTC), laser interstitial thermocoagulation (LITT), DBS, SCS, responsive neurostimulation (RNS), etc. (Text S4 online).

This denotes the importance of integrating multiple disciplines. In addition to neurosurgeons, who can propose requirements and treatment strategies and verify the effectiveness of the operation, neuroscientists are needed to quantify the distribution and dynamics of pathological network activities. In addition, engineers are required to develop and optimize algorithms or devices, e.g., numerical simulation (virtual brain calculation), intellectual stereotactic robot systems, brain-machine interfaces, and closed-loop stimulation equipment. Therefore, network neurosurgery must be carried out in a qualified neurological center (Text S3 online).

Technically, in addition to the lesioning approaches (RFTC and LITT), network neurosurgery would use exogenous electrical stimulation to affect endogenous brain rhythms to improve patient symptoms. Specifically, the dynamic global distribution of the network connectivity can be calculated, and the network dynamics can be evaluated to determine the pattern of electrical stimulation delivered at each time point. Further intervention might involve

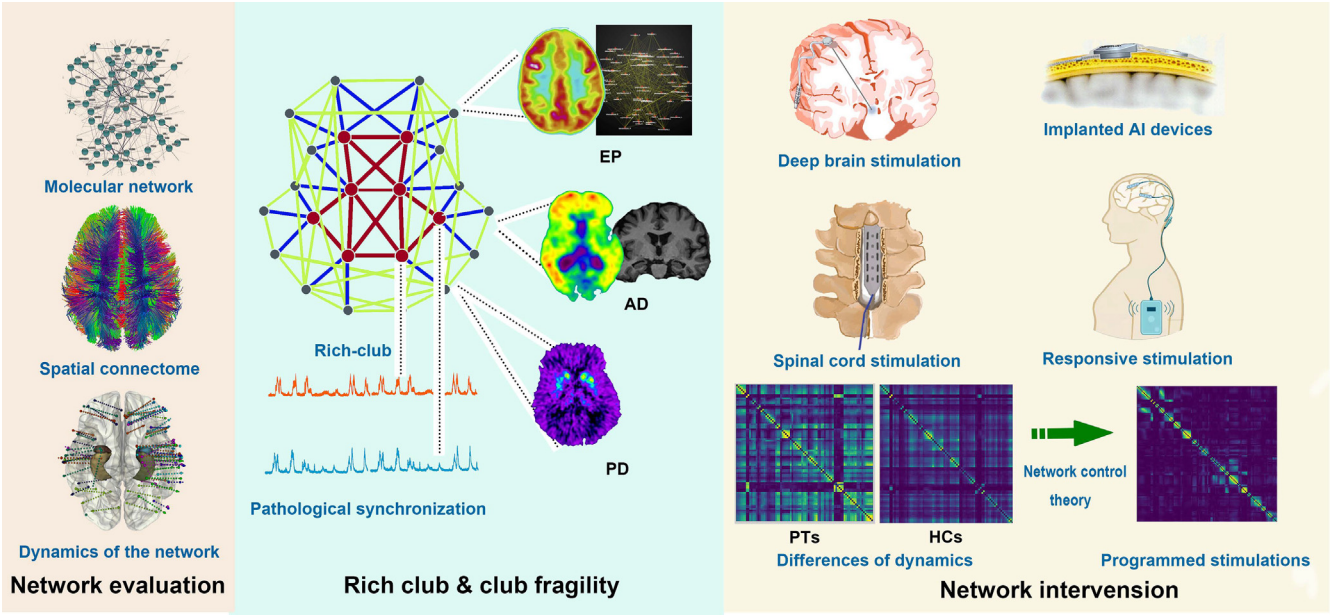


**Fig. 1.** The scope of network neurosurgery. The notion will be created for clinical practice from the evaluations to the intervention. The spectrum of network evaluation should cover molecular and neuron networks at the microscale to the connectomic and electrophysiological networks at the macroscale. The rich club within the neural network plays a vital role in the progression of various diseases. The activity shares the common pathological synchronization seen in EP, AD, and PD should be the target of elimination with network neurosurgery. With network control theory, it may be possible to restore normal levels of activity in the pathological network with approaches such as RNS, DBS, and SCS. PTs: patients; HCs: healthy controls.

programmed stimulation power at one or multiple hubs, depending on the complexity of the network. One of the long-term therapeutic goals here would be to redefine the connectivity strength between the nodes by moving them to a more physiological distribution range (Text S4 online).

The goal of delivering artificial electrical signals, therefore, would be treating the pathological brain activity that creates the symptoms of a variety of brain disorders. This technique may benefit in the future from the use of the so-called brain-machine-brain interfaces (BMBIs). In this variant of the classical brain-machine interface paradigm, the feedback component of the BMBI is generated through the delivery of artificial electrical stimulation, carrying, for instance, tactile information directly to the primary somatosensory cortex via cortical microstimulation. Considering the neural network perspective and inspired by the development of BMBIs, closed-loop RNSs have been introduced in the past two decades (Text S4 online).

With network neurosurgery, pushing the network back to normal and blocking pathological synchronization could prevent the symptoms of network disorders. For example, we can select the anterior thalamic nuclei as the target for DBS in patients with bilateral drug refractory temporal epilepsy, who do not have the opportunity for surgical treatment, to block the pathophysiological synchronization of the bilateral mesial temporal structures [17]. Likewise, RNS could lead to favorable seizure management outcomes by blocking pathological neuronal synchronizations at the onset of the seizure in EP patients more accurately. Facilitated by the consideration of the time domain in network surgery, the major innovation in RNS is that the electrical stimulation is delivered only when seizure activity is detected, and the stimulation stops only when the network activity returns to the physiological level. This innovation of network neurosurgery moves the focus of epilepsy surgery from "treating the epileptogenic focus" to "the elimination of epileptogenicity". This change would increase the size of the population to be treated, as for some patients, the epileptogenic focus might be the whole brain or involve important brain functions and cannot be removed (Text S5 online).

For PD patients, while DBS is already considered a method for surgically modifying network activities and could be recognized as a kind of network surgery, side effects such as depression, fatigue, confusion, and hypersexuality could still arise. In addition, DBS is less efficient in treating FoG. Therefore, the use of network neurosurgery could still improve the treatment outcome; for example, by resorting to network control theory and closed-loop stimulation, DBS could be triggered when pathophysiological synchronization occurs and stopped after the network is automatically judged to be normal. This would increase the specificity for treating the symptoms and reduce the side effects. Again, as SCS is effective for treating the DBS-refractory symptoms of FoG [13], any approaches that could eliminate pathological synchronization according to network neurosurgery should be developed and might open new windows for PD symptoms (Text S5 online).

Regarding AD patients, although fornix or Meynert nucleus DBS have been shown to be less effective, with long-term MEG data recording, increased delta-theta synchrony in the dorsal frontal and parietal cortices may predict the long-term outcome in the Mini-Mental State Examination. Therefore, disruption of this pathological neural activity may offer the best outcomes in the future.

In summary, network neurosurgery is a concept that simultaneously takes into consideration the spatial and temporal dynamics as well as the E/I balance of a targeted neural network. Disorders with functional abnormalities, such as AD, PD, and EP, may benefit from the employment of the same general neurosurgical strategy for modulating the pathological activity of functional hubs causing severe symptoms. Pathological synchronizations among these hubs are the most important pathophysiological component to be eliminated to induce much more favorable clinical outcomes and functional recovery.

## Conflict of interest

The authors declare that they have no conflict of interest.

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## Appendix A. Supplementary materials

Supplementary materials to this news & views can be found online at https://doi.org/10.1016/j.scib.2022.11.012.

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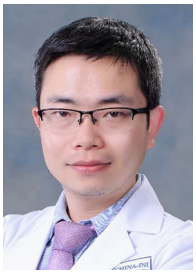

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