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EDITORIAL

With Great Brain Hub Connectivity Comes Great Vulnerability

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Theoretical and empirical studies have begun to explore the structure and function of the human brain from a system perspective, using network science to abstractly model the brain as a set of nodes (e.g., brain regions) and edges (e.g., structural or functional connections) [1]. Within this framework, many studies have identified a small set of highly connected network nodes, referred to as hubs, primarily located in the medial and lateral frontal and parietal cortices. These hubs exhibit higher rates of cerebral blood flow and metabolism activity and mediate long-distance connections between brain modules to allow for efficient communication across remote regions [2–4].

The central embedding of the hubs supports their diverse roles across a broad range of cognitive behaviors. For instance, the communication capacities of hubs are significantly associated with individual intellectual and cognitive-control abilities [4,5] and can predict neuropsychological outcomes after brain injury [6]. A hypothesis that naturally follows is that those brain disorders that clinically present with significant cognitive impairments might result from the pathological lesions to the network hubs.

In a recent elegant study, Crossley et al. [7] provided compelling evidence for this hypothesis. They first employed diffusion imaging tractography to build healthy human brain structural networks in which nodes represent gray-matter (GM) regions, and edges represent white-matter connections linking these nodes. Highly connected hub regions were identified from the network. Then, GM lesion maps of 26 different brain disorders were generated by carrying out meta-analyses on the structural MRI data of 392 published studies. Two significant findings emerged from this comprehensive analysis. First, a commonality across almost all brain disorders was that the GM lesions were more likely to be anatomically located in hubs of healthy brain networks. Second, distinct subsets of brain hubs were disrupted in different disorders. Take an example, the hubs in the frontal and temporal lobes were specifically associated with higher lesion probability in schizophrenia, whereas the medial temporal and parietal hubs were mainly affected in Alzheimer's disease. For the commonality observation, there are two possible explanations that are not mutually exclusive. One is that the hubs are topologically centralized in terms of global brain communications and play key roles in a variety of cognitive functions, especially for "higher order" cognitive tasks and adaptive behaviors; therefore, lesions in hubs, relative to those in nonhubs, are more likely to lead to clinical symptoms associated with cognitive impairments. It is also possible that brain hubs are biologically costly and therefore are particularly vulnerable to pathogenic processes of brain disorders. That is, it is either that hub lesions tend to be more visible due to its stronger behavioral consequences, or that hubs are just more likely to be damaged, or both. The differences in terms of the specific hubs being involved indicated differences in disease pathogenetic processes: Disorder-specific factors may determine which brain hubs are primary targets and how neurodevelopmental and neurodegenerative processes then propagate along the network structure. Together, Crossley et al. [7] provide an empirical framework for a hub perspective toward understanding the pathophysiological mechanisms of brain disorders, which in turn generates crucial clinical implications about how connectivity patterns of brain hubs could serve as potential biomarkers for early diagnosis and treatment targets for therapeutic intervention (e.g., the optimized locations of brain stimulation). Meanwhile, this study raises several critical questions that warrant further attention.

The GM volume or density reduction was used as the signature of brain disorders [7], which might reflect synaptic and neuronal loss. However, there are many other signatures for brain disorders such as synaptic dysfunction, glucose hypometabolism and abnormal axonal projections. These pathological features might exhibit different sensitivities across regions and/or disorders and could also appear prior to GM loss. For instance, white-matter damages or structural dysconnectivities are one of the main pathologies for multiple sclerosis, whereas functional connectivity abnormalities in specific regions may represent an early marker of Alzheimer's disease. Thus, it would be interesting to examine whether the brain hubs are also abnormal while using other hallmarks as brain signatures such as functional and structural connectivity rather than focal GM lesions.

Another important concern is that Crossley et al. [7] demonstrated GM lesions in brain disorders primarily located at healthy network hubs. However, whether the hubs in the actual brain networks in patients were targeted remains to be elucidated. Moreover, very little know whether there exist possible compensatory mechanisms that the brain goes through after hub damage. By constructing whole-brain functional connectivity networks derived from resting-state functional MRI data, we reported disrupted connectivity strength of brain hubs (e.g., the medial prefrontal and parietal cortices) in Alzheimer's disease [8]. Brain network analyses of autism spectrum disorders and attention-deficit/hyperactivity disorder revealed shared functional disconnectivity in the precuneus hubs and distinct connectivity disruptions in the medial frontal hubs [9]. In the future, it would be important to map connectivity patterns of disorder-specific hubs using empirical structural and functional data in patients. Moreover, computational modeling of brain network data [10] that incorporate the hub lesion information and associated disease propagation patterns over network could be a powerful tool to deepen the understanding of the biological mechanisms of brain disorders.

Finally, how are the hubs defined in the brain networks? Brain hubs generally reflect the importance of regions in terms of their information communications, which can be defined using different measures (e.g., nodal degree and betweenness centralities and

participation coefficient) in structural and functional networks [4]. While interrelated, these metrics quantify different aspects of nodal roles in the network: nodal centrality metrics capture global brain communication while nodal participation coefficient captures the integrity ability between different brain modules. Thus, the hub locations are dependent on different definitions. Although Crossley et al. [7] used multiple nodal measures to identify the brain hubs and observed compatible results, it remains open as to which hub measure(s) is the most sensitive, specific and reliable index to quantify the brain network changes for each disorder? Charting the patterns of hub disruption using different nodal measures and imaging modalities would be a potentially productive topic for future studies.

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Conflict of Interest

The authors declare no conflict of interest.

References

1. Bullmore E, Sporns O. Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci* 2009;**10**:186–198.
2. Liang X, Zou QH, He Y, Yang YH. Coupling of functional connectivity and regional cerebral blood flow reveals a physiological basis for network hubs of the human brain. *Proc Natl Acad Sci USA* 2013;**110**:1929–1934.
3. Tomasi D, Wang GJ, Volkow ND. Energetic cost of brain functional connectivity. *Proc Natl Acad Sci U S A* 2013;**110**:13642–13647.
4. van den Heuvel MP, Sporns O. Network hubs in the human brain. *Trends Cogn Sci* 2013;**17**: 683–696.
5. Cole MW, Yarkoni T, Repovs G, Anticevic A, Braver TS. Global connectivity of prefrontal cortex predicts cognitive control and intelligence. *J Neurosci* 2012;**32**:8988–8999.
6. Warren DE, Power JD, Bruss J, et al. Network measures predict neuropsychological outcome after brain injury. *Proc Natl Acad Sci USA* 2014;**111**:14247–14252.
7. Crossley NA, Mechelli A, Scott J. The hubs of the human connectome are generally implicated in the anatomy of brain disorders. *Brain* 2014;**137**:2382–2395.
8. Dai Z, Yan C, Li K. Identifying and mapping connectivity patterns of brain network hubs in Alzheimer's disease. *Cereb Cortex* 2014. doi: 10.1093/cercor/bhu246. [Epub ahead of print].
9. Di Martino A, Zuo XN, Kelly C, et al. Shared and distinct intrinsic functional network centrality in autism and attention-deficit/hyperactivity disorder. *Biol Psychiatry* 2013;**74**:623–632.
10. Raj A, Kuceyeski A, Weiner M. A network diffusion model of disease progression in dementia. *Neuron* 2012;**73**:1204–1215.