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Graph Metrics Reveal Brain Network Topological Property in Neuropathic Pain Patients: A Systematic Review

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Abstract: Neuropathic pain (NP) is a common and persistent disease that leads to immense suffering and serious social burden. Incomplete understanding of the underlying neural basis makes it difficult to achieve significant breakthroughs in the treatment of NP. We aimed to review the functional and structural brain topological properties in patients with NP and consider how graph measures reveal potential mechanisms and are applied to clinical practice. Related studies were searched in PubMed and Web of Science databases. Topological property changes in patients with NP, including small-worldness, functional separation, integration, and centrality metrics, were reviewed. The findings suggest that NP was characterized by retained but declined small-worldness, indicating an insidious imbalance between network integration and segregation. The global-level measures revealed decreased global and local efficiency in the NP, implying decreased information transfer efficiency for both long- and short-range connections. Altered nodal centrality measures involve various brain regions, mostly those associated with pain, cognition, and emotion. Graph theory is a powerful tool for identifying topological properties of patients with NP. These specific brain changes in patients with NP are very helpful in revealing the potential mechanisms of NP, developing new treatment strategies, and evaluating the efficacy and prognosis of NP.

Keywords: neuropathic pain, graph theory, brain network, magnetic resonance imaging

Introduction

Neuropathic pain (NP), one of the most distressing types of pain, is defined as pain caused by a lesion or disease of the somatosensory system by the International Association for the Study of Pain (IASP).[1] NP can result from various conditions or lesions of the peripheral or central nervous system, such as spinal cord injury (SCI), head trauma, stroke, herpes zoster, trigeminal neuralgia, or nerve lesion (such as lesion caused by trauma or surgery).[2,3] Epidemiologically, NP affects approximately 5% of the population.[2] Similarly, the pathophysiology varies and involves ectopic neural activity in adjacent or damaged nerves, central pathways, or dorsal root ganglia, which underlie the spontaneous pain.[3] Induced pain may spread to adjacent regions, involving central and peripheral sensitization.[3] Relevant nociceptive pathways alterations are related to ion channels, glial-derived mediators and activation of immune cells. Due to the intricate connections between injured nerves and the brain, the transmission of signals may be modulated or amplified at different levels, leading to more complex and diverse pain manifestations than other tissue injuries.[4,5] Moreover, chronic NP always leads to a wide range of emotional symptoms, including depression, anxiety, and social isolation, which markedly impacts quality of life and presents a significant personal and social burden.[6] Currently, the treatment of NP shows a huge unmet medical demand. Clinically, many patients respond poorly to conventional analgesics and do not receive sufficient pain relief from their mechanically targeted therapy regimen.[7,8]

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The successful development of targeted therapies requires further research on the underlying pathophysiology and the neural basis of NP perception.[3] Furthermore, clinical studies have suggested common underlying mechanisms for most neuropathic conditions.[9] With the development of neuroimaging technology, advanced neuroimaging offers a new impetus to explore the multiple dimensions of NP and enables the possibility of objectify pain.[10] Imaging methods have not only provided new insights into the pathophysiology of NP but have also improved clinical practice by developing mechanism-based therapeutics with optimized analgesic effect.[11] Several studies have reported relationships between brain structure or function and pain intensity or disease severity.[12,13] By identifying brain-based biomarkers for NP, an objective measure, rather than subjective self-reporting, can be added to the evaluations currently used to assess NP.

NP involves extensive structural and functional reorganization of brain regions, which cannot be clearly interpreted from the structural and functional changes in specific brain regions.[14] As a complex network connectome, the human brain continuously transmits and integrates information from multiple brain regions.[15] Similar to the microscopic neuronal level, a large-scale human brain network can be abstracted into a graph based on a graph theory analysis. The graph consists of two basic elements: nodes and edges representing brain regions, and connections between brain regions, respectively.[16] These nodes and their interacting edges were combined to form a network framework. Among them, the structural network (SN) constructed by diffusion tensor imaging (DTI) or structural magnetic resonance imaging (sMRI) employs the white matter fiber bundle or the correlation between the gray matter metrics of two nodes as edges.[17] A functional network (FN) is constructed using functional imaging technologies, such as blood oxygenation level-dependent (BOLD), in which the edges are defined as correlations in the time series of brain activation among the nodes.[17] Additionally, considering that structural connectivity may serve as the basis of functional execution, the two connections have been proposed to be studied in combination with SN-FN coupling analysis.[18,19]

Graph theory analysis builds a powerful framework to describe the potential disruption of the brain topology and connectome. The method analyses the topological features of regions of interest (ROIs) across networks associated with specific functions or the entire brain, different from seed-based analysis merely revealing the connectivity between one ROI and another.[20] Particularly, the brain network represents complex properties, such as small-world topology, modularity and highly connected hubs, which is of high relevance to its function.[16] In other words, global and local information transmission as well as the properties of individual nodes (brain regions) within the brain network are measured, illuminating the interrelationships between different brain regions and unveiling key pain circuits and core targets. Graph theory has been widely used to reveal altered brain network properties in neurologic and psychiatric disorders, such as Parkinson disease[21] and Alzheimer disease.[22] Pain perception has been found to be associated with a pain matrix in the brain network consisting of cortical and subcortical areas.[23] A recent graph theory research systematically analyzed the activation of a comprehensive structural pain network in the brain in response to pain stimuli.[24] The topological characteristics of the pain network were revealed, which proved the rationality of the network construction. And the network's vulnerability to attacks offers the possibility of relieving pain by targeting the most strongly connected areas in the network.

Taken together, graph theory suggests new ideas for advancing the pathophysiological mechanisms underlying NP and extracting potential therapeutic targets. However, a clear overview of these graphical measures in patients with NP is lacking. In this article, we review graph theory studies in multiple modalities (including structural and functional MRI in humans) that investigate diverse brain network changes in patients with NP. We aimed to determine which topological property changes are present in patients with NP based on a systematic search through suitable literatures and further reveal the underlying mechanisms of NP and clinical implications for graph theory.

Methods

Studies that explored topological property changes in patients with NP have been reviewed. A comprehensive strategy was used to search for relevant articles in PubMed and the Web of Science. No time period limitations or article type restrictions were used, and the most recent search was conducted on April 10, 2024. The search terms used were as follows: #1 AND #2 AND #3. #1: (neuropathic pain OR (spinal cord injury AND pain) OR ((head trauma AND pain) OR post-traumatic headache) OR (stroke AND pain) OR (multiple sclerosis AND pain) OR (trigeminal neuralgia) OR ((nerve lesion* AND pain) OR peripheral nerve injuries OR neuropathic injury) OR (painful neuropathy*) OR (post-herpetic neuralgia*) OR ((lumbar disc herniation AND pain) OR painful radiculopathy) OR (diabetic neuropathic pain

OR (diabetic peripheral neuropathy AND pain)) OR painful polyneuropathy OR carpal tunnel syndrome OR phantom limb pain). #2: (neuroimaging OR magnetic resonance imaging OR MRI). #3: (brain network* OR graph).

Articles screening was performed by two independent researchers. When necessary, the comment of a third researcher was sought. The essential features of the included cross-sectional studies are shown in Table 1 (including the first author, publication year, population, age, sex, modality, analysis toolbox, definition of the nodes and edges, findings concerning the global graph theoretical parameters, and correlations between these parameters and clinical characteristics).

Results

Study Selection

As presented in Figure 1, 1026 results (367 in PubMed and 659 in Web of Science) were found. After removing the duplicate records, 846 unique citations were retained. After screening titles and abstracts, 41 papers were identified for further screening. Among them, 27 papers did not fulfil the inclusion criteria: no graph measures were reported in 14 papers, pain other than NP in five papers, animal experiments in three studies, and five reviews. In summary, 14 articles were included in this review.

Study Characteristics

Twelve papers were cross-sectional studies and two were longitudinal studies. Of these, functional MRI (fMRI) was applied in nine studies, DTI was used in 3 of them, and a T1 structural MRI scan method was applied in three (one article revealed both functional and structural changes). Diagnostically, postherpetic neuralgia (PHN) patients were included in 4 studies,[27–29,36] whereas 3 studies discussed classic trigeminal neuralgia (CTN).[19,25,26] Two papers researched lumbar disc herniation (LDH).[32,33] Only one study included patients with neuropathic pain after spinal cord injury (SCI),[34] phantom limb pain (PLP),[35] post-traumatic headache (PTH),[37] painful diabetic neuropathy (PDN)[30] and carpal tunnel syndrome (CTS).[31]

Small-Worldness Alterations in NP Patients

Previous research has demonstrated that the human brain is characterized by a small-world network, which represents the need for a network to satisfy functional segregation and integration.[38] Small-worldness is vividly defined as a network topology in which most nodes are not adjacent to each other, but most nodes can be reached from any other node in a few steps.[16] Mathematically, in order to quantitatively determine whether a network has small-worldness, the clustering coefficient and shortest path length of the network are generally compared with the corresponding properties of random networks.[39] The small-worldness property reflects a suitable balance between local specialization (high levels of local clustering among nodes of a network) and global integration (short path lengths that link all nodes of the network).[38] An optimal balance ensures optimal brain function and is the outcome of natural selection.[40] Small-worldness was evaluated in eight of the included articles for brain networks, of which five found significantly decreased small-worldness in patients with NP compared with healthy controls (HCs). The five papers included one paper on functional networks,[25] two papers on DTI structural networks[19,30] and two papers on gray matter networks.[31,35]

Segregation Measures in NP Patients

Segregation refers to the ability of specialized neuronal processing to be carried out within densely functionally interconnected groups of brain regions.[41] Measures of segregation primarily include quantification of these groups (clusters or modules within the network).[39] Representative parameters, such as the clustering coefficient, local efficiency (E_{loc}), and modularity, have been generalized for graph metrics in the human brain network. Decreased E_{loc} was found in four of the included studies (two for functional E_{loc}[25,29] and two for structural E_{loc}[19,30]). Only one study reported a decreased structural clustering coefficient.[19] One study investigated the modular organization of brain resting-state networks.[26]

Table 1 Global Graph Measures

Study	Population	Age (Years)	Gender (F/M)	Modality	Toolbox	Nodes	Edges	Group	Integration			Segregation				s	Correlations
									λ	L	E_{glob}	C	E_{loc}	γ	M		
Zhang et al, 2022[19]	29CTN 34HCs	54.59 ± 10.82 54.97 ± 6.78	20/9 22/12	rs-fMRI, DTI	FSL,DTK, PANDA	Brainnetome Atlas 246 regions	W	SN	↑	↑	↓	↓	↓	≈	–	↓	Coupling of local connections↑~ VAS↑ coupling of feeder connections↑~ VAS↓
								FN	≈	≈	≈	≈	≈	≈	–	≈	–
Zhang et al, 2021[25]	41CTN 43HCs	56.34 ± 10.50 53.40 ± 9.73	23/18 24/19	rs-fMRI	GRETNA	59 ROIs	B	–	≈	↓	↓	≈	↓	↓	–	↓	s, γ, L↑~ duration↓ γ↑~ frequency↓
Tsai et al, 2019[26]	25CTN 20HCs	58.7 ± 6.0 55.7 ± 7.8	15/10 13/7	rs-fMRI	AFNI	Shen Brain Atlas 205 regions	B	–	–	–	–	–	–	–	–	–	–
Li et al, 2022[27]	50PHN 50HZ 50HCs	62.81 ± 13.59 60.25 ± 11.09 58.90 ± 6.15	20/30 21/29 28/22	rs-fMRI	GRETNA	Dosenbach 160 regions	W	–	≈	≈	↓	≈	≈	≈	–	≈	HZ~E_{glob}↑~ VAS↓
Qiu et al, 2021[28]	16PHN 38LBP	66 ± 7 59 ± 12	27/11 13/3	T1WI	GRETNA	AAL 90 regions	B	–	–	≈	≈	≈	≈	–	–	≈	PHN~ mean degree of left rectus gyrus↑~ VAS↑
Zhang et al, 2014[29]	16PHN 16HCs	68.1 68.6	8/8 8/8	rs-fMRI	SPM	AAL 90 regions	B	–	–	–	≈	–	↓	–	–	–	NE of right putamen and left inferior temporal gyrus↑~ VAS↑
Chao et al, 2022[30]	24PDN 13PLDN 27HCs	60.1 ± 10.6 57.5 ± 15.2 56.1 ± 10.7	9/15 5/8 17/10	DTI	FSL, BCT	HOA 110 regions	B	PDN~ PLDN	≈	–	↓	–	≈	≈	–	≈	–
								PDN~HC	≈	–	↓	–	↓	↓	–	↓	–
Li et al, 2021[31]	27CTS 19HCs	53.56 ± 8.50 56.89 ± 6.96	25/2 16/3	T1WI	BCT	Brainnetome Atlas 246 regions	B	–	–	≈	≈	≈	≈	–	–	↓	–

Zhang et al, 2022[32]	30LDH 30HCs	56.3 ± 9.7 55.0 ± 12.3	11/19 13/17	rs-fMRI	GRETNA	AAL 90 regions	B	–	≈	≈	–	≈	–	≈	–	≈	Degree centrality and efficiency of right inferior occipital gyrus↑~ODI↓
Huang et al, 2019[33]	68LDH 68HCs (Discovery group)	44.0 ± 1.5 43.7 ± 1.7	25/43 27/41	rs-fMRI	BCT	Brainnetome Atlas 246 regions	B	–	–	–	–	–	–	–	–	≈	–
Park, E et al, 2023[34]	41SCI-NP (24 mild NP, 17moderate-severe NP) 32HCs	49.87 ± 14.74 53.82 ± 12.18 50.12 ± 13.33	9/15 4/13 12/20	rs-fMRI	CONN	140 ROIs	B	–	–	–	–	–	–	–	–	–	E_{glob} and L of left MidFG↑~VAS↑ E_{glob} and L of left sLOC↑~VAS↑
Bao et al, 2023[35]	45PLP 45HCs	44.47 ± 8.86 45.16 ± 9.30	11/34 12/33	T1WI	BCT	HCP 360 regions	B	–	–	≈	≈	≈	≈	–	–	↓	–

Notes: Population: CTN, classic trigeminal neuralgia; HCs, healthy controls; PHN, postherpetic neuralgia; LBP, low back pain; PDN, painful diabetic neuropathy; PLDN, painless diabetic neuropathy; CTS, carpal tunnel syndrome; LDH, lumbar disc herniation; SCI-NP, neuropathic pain after spinal cord injury; PLP, phantom limb pain. Modality: rs-fMRI, resting-state functional magnetic resonance imaging; DTI, Diffusion tensor imaging; T1WI, T1 weighted imaging. Toolbox: FSL, FMRIB Software Library; DTK, Diffusion Toolkit; PANDA, Pipeline for Analyzing brain Diffusion images; GRETNA, Graph Theoretical Network Analysis Toolkit; AFNI, Analysis of Functional Neuro Images; SPM, statistical parametric mapping; BCT, brain connectivity toolbox; CONN, functional connectivity toolbox. Nodes: AAL, Automated anatomical labelling atlas; HOA, Harvard Oxford atlas; HCP, Human Connectome Project Atlas. Edges: W, weighted; B, binary. Group: SN, structural network; FN, functional network. Network measures: L, characteristic path length; λ, normalized characteristic path length; E_{glob}, global efficiency; C, clustering coefficient; E_{loc}, local efficiency; γ, normalized clustering coefficient; M, modularity; σ, small-worldness. Correlations: VAS, visual analog scale; HZ, herpes zoster; NE, nodal efficiency; ODI, Oswestry Disability Index; midFG, middle frontal gyrus; sLOC, superior lateral occipital cortex. Symbols: ↑, increased in patients; ↓, decreased in patients; ≈, no significant difference; –, not investigated.

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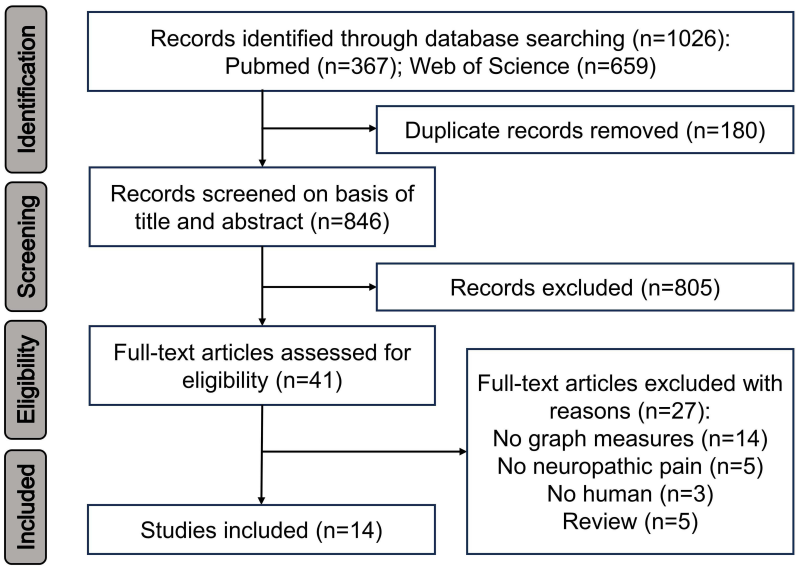

Figure 1 Flow chart of the conducted search.

Integration Measures in NP Patients

Functional brain integration is the ability to rapidly integrate specialized information from separate brain regions.[39] The measures of integration are frequently based on the concept of paths, which are characterized by sequences of diverse nodes and edges. Paths can reflect potential information streams among brain regions in anatomical networks.[16] Consequently, the shorter the path, the stronger is the potential for integration. Characteristic path length and global efficiency (E_{glob}) are common functional integration measures. In a network, the average shortest path length between all node pairs is called the characteristic path length of the network.[16] The latter was obtained by taking the average inverse of the former. The E_{glob} was reported to be decreased in NP patients compared with HCs in 4 of the included articles, 2 of which reported the structural E_{glob},[19,30] and 2 described the functional E_{glob}.[25,27] The characteristic path length was observed to decrease in one functional study[25] and increase in another structural study.[19]

Measures of Centrality in NP Patients

Some brain regions, often defined as hub regions, play a key role in interacting with other nodes.[39] Nodal centrality measures (such as betweenness centrality (BC), nodal degree, nodal efficiency, and clustering) evaluate the regional characteristics of whole networks and assess the importance of the individual nodes.[42] First, BC acts as an important measure of information flow, defined as the ratio of all the shortest information transfer paths in a network that passes through a specified node.[43] An increased BC indicates shorter paths that pass through the node and a role as an intermediate node in a network.[36] This sensitive measure has been naturally extended to connections to explore important functional or anatomical links. Second, in a network, node degree measures the total weighted number of direct links between a given node and all other nodes.[16] A higher node degree indicates that more edges are connected to a particular node. Third, nodal efficiency represents the average shortest path length between a certain node and all other nodes in a network.[32] A higher nodal efficiency describes a faster information transfer between one node and other nodes. Studies on NP have shown alterations in nodal metrics in specific brain regions, mostly involving pain regulation functions, and cognitive and emotional responses.

Discussion

Small-Worldness Alterations in NP Patients

The preservation of small-world properties in the brain network indicated that patients with NP still exhibited an efficient network architecture with an optimal balance between network integration and segregation. The results exhibited relative insidiousness of the brain network reorganization following NP, in contrast to other psychiatric or neurological disorders, such

as schizophrenia or Alzheimer's disease, in which disrupted brain structural integrity leads to the disappearance of the small-worldness property.[40] Additionally, a structural covariance network analysis revealed a weaker small-world property in patients with PLP, indicating decreased information processing and transmission efficiency.[35] The authors propose that further study is needed to explore whether decreased small-worldness is associated with a reduced desire to engage in social activities after amputation.[44] Importantly, the lower small-worldness metric suggested that brain networks in patients was topologically more similar to those of random networks and less economical.[16,40] Both functional and structural brain alterations confirmed these findings, based on the results of the included studies. Even so, Caeyenberghs et al recommended a combination of various graph indices to detect network integration and segregation rather than separate calculations of this measure.[42]

Segregation Measures in NP Patients

E_{loc} is predominantly associated with short-range connections between neighboring regions, which mediate the fault tolerance of a network or modularized information processing.[45] These results suggest that NP may be related to short-range connection impairment, which is consistent with previous findings suggesting preferential changes in local node interactions for chronic pain.[29] Notably, Zhang et al compared E_{loc} in patients with PHN before and after treatment with Lidoderm and found an increasing trend in E_{loc}.[29] The above observation indicated topological optimization of the brain network with treatment in patients with NP.

Modularity analysis is a more sophisticated measure of segregation, in which a network is subdivided into a set of nodes.[16] The modular structure is characterized by densely connected within-group links and sparsely connected nodes between-group links.[46] A graph theory modularity analysis in CTN patients found that a higher interaction between the default mode network (DMN) and other modules before surgery was associated with a better treatment response.[26] Distortion and atrophic patterns have been observed in severely or recurrently affected trigeminal nerves, accompanied by inflammation, edema, and progressive, demyelination.[47] Reduced communication between the DMN and other brain models may reflect more serious neural injury with stronger pain-related nerve impulses, leading to unsatisfactory therapeutic effects. Modularity analysis has implications regarding the potential pathophysiology of NP and could be a tool for risk stratification to predict the response of patients to treatment.

Integration Measures in NP Patients

Decreased E_{glob} represents decreased information transfer among remote brain regions, which is mainly combined to long-range connections.[15] Commonly, lost global integration is interpreted as moderate information flow in brain networks.[42] Chao et al observed lower E_{glob} of the white matter networks in PDN patients.[30] This finding may be attributed to the fact that due to chronic NP, brain networks became more fragmented, with more inefficient and indirect information exchanges within the networks. The metric change could be considered as a neural substrate of maladaptive plasticity following NP and contributes to further research on the recovery of the topological network after pain healing. The E_{glob} has been considered as a superior measure of disconnected networks integration compared with the characteristic path length.[48] When the path between disconnected nodes is defined as an infinite length, the corresponding efficiency is calculated as zero.[16] The view above was also supported by our findings that E_{glob} alterations shown higher consistency than characteristic path length.

Measures of Centrality in NP Patients

All of these measures of centrality describe the importance of the node in the information flow of the entire network. Graph theoretical approaches show the advantage of analyzing the importance of local nodes at the whole-brain level, which is not feasible with voxel-based analysis. For example, LDH-induced nerve compression syndromes show that functional nodal centralities increase in the opercular part of the inferior frontal gyrus and decrease in the orbital part of the inferior frontal gyrus, inferior occipital gyrus, and lingual cortex.[32] In a structural covariance network study based on gray matter volume, CTS patients presented lower nodal degrees in the pain neuromatrix (insula and thalamus) and higher BC in non-pain-related brain regions (lateral occipital cortex and dorsolateral middle temporal gyrus).[31] In a functional brain network study, abnormal nodal efficiencies were found in several regions of patients with PHN.[29] Specifically, the nodal efficiencies of the putamen and inferior temporal gyrus (ITG) were related to visual analog scale

(VAS) scores, presenting direct correlations with PHN pain. As part of the basal ganglia (BG), the putamen not only participates in the execution of cognitive, emotional, and motor activities, but is also involved in pain processing.[29] Importantly, the thalamocortico-BG loop has been found to integrate motor, cognitive, and emotional responses to pain.[49] The ITG was found to be activated during certain pain expectation.[50] Positive correlations indicated that the nodal efficiency of these regions increased with an increase in the VAS score. Centrality measures of brain networks may provide novel insights into how functional disturbances of neuronal circuits are connected with the pathophysiology of NP and might be used as clinical biomarkers for objective pain information evaluation. Additionally, Pei et al demonstrated that after rTMS treatment, patients with PHN showed significant changes in the brain areas related to sensorimotor, cognition, and affection, in terms of BC, nodal efficiency, and nodal degree.[36] These alterations at the regional level may serve as potential neural biomarkers for post-treatment evaluations.

Other Graph Metrics in NP Patients

In graph theory, the rich club with its high interconnection and the hub nodes within it contribute to global communication and efficient integration of the brain.[19] Zhang et al observed reorganization of a rich club in classic CTN patients compared to HCs. In particular, as a CTN-specific hub, the left postcentral gyrus (PoG) belongs to the lateral pain system, which encodes pain location, intensity, and duration, and transmits fast sharp pain signals.[19] The appearance of new hubs was interpreted as compensation for the functional overload of initial hubs against long-term and frequent facial attacks, with a demand for better information modulation and integration.[51] The research also revealed that the recombination of rich club memberships in NP patients may mirror the adaptive plasticity of brain function.

Suggestions for Future Research

We found that the application of graph theory parameters in the evaluation of treatment effects is valuable, and future research should focus on this tool by establishing an evaluation model. Given the limited number of studies included, our preliminary findings should be further confirmed in future studies. Moreover, considering the individual differences in brain network changes, personalized brain network intervention strategies should be developed according to the characteristics of the brain network changes in patients. For example, according to the characteristics of the brain network in different patients, diverse brain stimulation techniques (such as transcranial magnetic stimulation and transcranial direct current stimulation) are used to regulate brain network activity and reduce pain sensation.

Methodologically, binary networks are defined by the presence or absence of connections, whereas weighted networks contain additional information regarding the link strengths.[39] Only two researches included in our review employed weighted networks.[19,27] It is possible that binary networks tend to be easily defined as null models for statistical comparison and are easier to characterize under most conditions. However, although this does not spoil the calculations, it may lead to loss of detailed information. Additional observations from the weighted networks should be considered in future studies. Additionally, current research mainly focuses on a single brain imaging technology, which cannot fully reveal brain network changes in NP. Therefore, a multimodal approach combining multiple brain imaging techniques has been proposed to obtain more comprehensive and accurate information about brain networks in patients with NP.

Limitations

This study had several limitations. First, the most obvious limitation of the surveyed studies was the small cohort size. Second, owing to the many different included populations and the large diversity in the discussed graph measures, a meta-analysis was not indicated. Third, although most NP studies have reached a consensus on topological changes, significant inconsistencies still exist in our findings, and the possible impacts of the respective mechanisms may need to be further explored in conjunction with other technologies.

Conclusions

We reviewed graph theory research based on MRI findings in patients with NP. The findings suggest that NP was characterized by retained but declined small-worldness, indicating an insidious imbalance between network integration and segregation. The global-level measures also revealed decreased local and global efficiency in NP, implying decreased information transfer

efficiency on both long-range and short-range connections. Differences in nodal centrality measures between patients with NP and healthy controls were found in a variety of brain regions, mostly those associated with pain, cognition, and emotion. Graph theory is a powerful tool for discovering changes in the global and local topological properties of NP patients, revealing the underlying mechanisms, and contributing to the evaluation of the efficacy and prognosis of NP.

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Disclosure

The authors declare no conflicts of interest regarding the publication of this paper.

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