Systematic Review

Graph Measure Based Connectivity in Chronic Pain Patients: A Systematic Review

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Background: Chronic pain affects 20 to 30% of the adult population worldwide and is consequently the leading cause of disability. Current developments in brain imaging technology are increasing the understanding of the pathophysiology of (chronic) pain and enabling the possibility to objectify pain. As a result, our view of the brain has evolved from a static organ to a dynamic organ that constitutes an adaptable network of linked regions. Graph theory has emerged as a framework to analyze such networks and can be applied to investigate a range of topological properties of both the functional and structural brain network or connectome, thus providing meaningful information about the organization of human brain networks.

Objectives: The aim of this systematic review is to determine whether connectivity differs between chronic pain patients and healthy controls by integrating previous studies that performed graph analyses on structural or functional connectivity. A secondary aim was to determine whether graph measures correlate to clinical outcomes.

Study design: Systematic review.

Methods: Relevant articles were searched for in PubMed and Web of Science. These were screened against certain criteria and assessed for quality.

Results: On a global level the transitivity, betweenness centrality, intramodular degree, and rich club organization differed between chronic pain patients and healthy controls, but the path length, modularity, degree, and (Hub Disruption Index [HDI] of) participation coefficient did not differ between both groups, along with the small-worldness. Conflicting evidence still remains about a number of global graph measures, namely the global efficiency, local efficiency, clustering coefficient, and HDI of degree. Significant correlations were found between several nodal and global graph measures on one hand, and clinical outcomes related to pain, disability, and motor control on the other hand.

Limitations: No clear conclusions could be made about the majority of the nodal measures, as they were often based on single studies.

Conclusion: Differences between chronic pain patients and healthy controls were mostly observed for the global graph measures. Future research is still needed to validate the obtained findings and to expand this knowledge to the chronic pain populations that were not discussed in the included papers.

Key words: Chronic pain, connectivity, graph theory, brain imaging, MRI, EEG

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Chronic pain is the leading cause of disability, affecting 20 to 30% of the adult population worldwide (1,2). As a result, millions of people suffer from ongoing pain and significant sensory, cognitive, and affective abnormalities (3,4). It goes without saying that new insights in the understanding of the pathophysiology of these disorders are urgently needed. While chronic pain is defined as pain that

is present for more than 3 months, or beyond the expected period of healing without having the warning function of acute pain, current developments in (brain) imaging technology are enabling the possibility to objectify pain (5-10). The expansion of insights into brain mechanisms of chronic pain is not only the gateway to understanding the pathophysiology of chronic pain, but it could also improve clinical practice (9,11). Moreover, developing a brain-based biomarker for pain, which is defined as "an unpleasant sensory and emotional experience" by the International Association for the Study of Pain (IASP), would enable the addition of an objective measure to the subjective self-report measures that are currently in use to assess pain (9,12-14). Several studies have already reported a relationship between brain structure or function and pain intensity or disease severity (15-18). Other studies have shown that certain brain properties might be able to predict the transition from acute to chronic pain (19,20).

Our view of the brain has evolved over the past decades from a static organ, in which change is irreversible, to a dynamic organ that constitutes an adaptable network of linked regions. To date, a vast amount of research in the form of meta-analyses and systematic reviews is available that shows altered morphology and function in different brain regions, of patients suffering from a variety of pain conditions (18,21-29); however, previous studies mostly focused on specific pain conditions or on specific brain regions, while in reality pain is a result of the coordinated collaboration between several brain regions. Recently, a neurological signature of (heat induced) physical pain was found, which could be seen as a pain network, which indicates that pain is the result of the simultaneous activation of several brain regions (10).

Graph theory has emerged as the framework to analyze such networks, which are represented by nodes (brain regions) and edges (connections between brain regions) (30-32). Graph theory can be applied to investigate a range of topological properties of both the functional and structural brain network or connectome, and thus provide meaningful information about the organization of human brain networks (31-33). In the functional connectome (FC), edges are defined as correlations between time series of brain activation of 2 nodes. Edges in the structural connectome (SC) can be defined as the correlation between grey matter metrics (such as cortical thickness or surface area) of 2 nodes, or as connectivity strength measures of white matter (such as fractional anisotropy or streamline count) between 2 nodes. The edges between the nodes can be weighted or unweighted (binary), with weighted edges representing the strength of the connection between 2 nodes (34). Binary networks on the other hand apply a threshold to a weighted network to define the presence or absence of an edge between 2 nodes.

The outcome measures resulting from graph analyses can be clustered into certain properties of the brain network, which include integration, segregation, and centrality (35). Measures of integration provide an estimate of the ease with which brain regions communicate by rapidly combining specialized information from distributed brain regions (31). Segregation refers to the ability for specialized processing to occur within densely interconnected groups of brain regions. Measures of centrality define the importance of network nodes and edges in the organization of the functional and structural connectome. Finally, graph metrics can be computed on a global network level, resulting in a single value for each network. Nodal measures on the other hand refer to network properties of individual nodes, resulting in a value for every node in the connectome.

The topology, or organization, of a certain network is of high relevance to its function, as it can influence the efficiency and content of the information transfer among nodes (36,37). This is reflected in the fact that these brain network properties have been shown to be altered in patients with brain disorders, such as Alzheimer's disease, epilepsy, etc (38-41). A previous meta-analysis has for example shown that patients suffering from brain disorders showed grey matter alterations that occurred especially in highly connected nodes, typically referred to as hubs (42). These hubs are more functionally valuable, as they play an important role in integrative information processing and adaptive behavior. They are often involved in "higher-order" cognitive tasks and adaptive behavior, which explains why lesions in these hubs are more likely to be symptomatic than lesions in non-hubs (43,44). As a result of hub lesions, the global efficiency degrades, which is associated with clinically significant cognitive impairments (42); however, different disorders will not necessarily involve an identical set of hubs. Instead disorder-specific factors are probably responsible for the determination of the brain regions that are affected first and how different neurodevelopmental and neurodegenerative disease processes then propagate over the network architecture.

The topology of brain connectomes has been investigated extensively in a healthy population and altered network properties have been shown in patients with brain disorders, but a clear overview of (alterations in) those graph measures in chronic pain patients is still missing. Therefore, this systematic review aims to determine whether connectivity differs between chronic pain patients and healthy controls by integrating all previous studies that performed graph analyses on structural or functional connectivity.

As a secondary outcome measure, the relationship between these graph measures and self-reported clinical outcomes will be investigated, as this would enable integration of neuroimaging findings into clinical practice and further unravelling of the underlying mechanisms of persistent pain (45).

Methods

Protocol and Registration

This systematic review was conducted following the preferred reporting items for systematic reviews and meta-analysis guidelines (PRISMA) (47). It was registered with the number CRD42020177930 (https://www.crd.york.ac.uk/PROSPERO).

Information Sources and Search

The databases PubMed (www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (www.webofknowledge.com) were searched for relevant articles. The following search strategy was constructed and employed for both databases: (Chronic Pain) AND (Functional OR Structural) AND (Network* OR Connect* OR graph). In addition, hand searching was performed to identify additional relevant articles.

Eligibility Criteria and Study Selection

To formulate an adequate search strategy, the following PICO approach was applied: "What are the differences in graph based connectivity metrics (O) between chronic pain patients (P) and healthy controls (C), measured with MRI or EEG (I)?". Based on this research question, different inclusion and exclusion criteria were formulated and can be found in Table 1.

A first screening of all obtained articles consisted of the examination of the title and abstract of each article performed by 2 independent researchers, DL and RDP. Articles were only retained if they complied with the predefined inclusion criteria. A consensus meeting was held in case of conflicts, and if necessary, the opinion of a third independent researcher, BC, was consulted. The full texts of the remaining articles were screened against the same predefined inclusion criteria during a second screening round. The decision process was constructed in a similar manner as the first screening.

Risk of Bias Assessment

Based on the 8 items of the Newcastle - Ottawa quality assessment scale, which is recommended for case-control studies and has been proposed by the Cochrane Collaboration (www.cochrane.org), all included articles were assessed for risk of bias (46,47).This scale evaluates 8 items spread over 3 categories, namely selection (case definition, representativeness of cases, selection of controls, definition of controls), comparability of cases and controls (gender and age), and exposure (ascertainment of exposure, method of ascertainment, nonresponse rate). One star was assigned for each of these items that were considered as a low risk of bias. For each of the 8 criteria one star could be obtained, with the exception of the criterion regarding comparability, where 2 stars could be awarded when studies controlled for age and gender, resulting in a

Table 1. *Inclusion and exclusion criteria.*

	Inclusion	Exclusion
Population	Adults (18-65 years old) suffering from chronic pain (> 3 months)	-Children or elderly -Healthy patients -Pain duration < 3 months
Intervention	-Magnetic resonance imaging -Electro-encephalography	-No brain imaging -Magneto-encephalography -Positron emission tomography -Single-photon emission computed tomography
Controls	Healthy adults	-Children or elderly -People suffering from any pain condition
Outcome	Graph measures of connectivity (both structural and functional)	-No investigation of connectivity -Connectivity based on non-graph measures
Study Design	Comparative studies	-(Systematic) review/ meta-analysis -Preliminary data/pilot study/case reports -Other study designs
Language	Dutch, English, French	Other languages

maximum total score of 9 stars, which indicated the highest methodological quality (46).

Based on the risk of bias assessment and the study design of the included articles, a certain level of evidence was attributed to each article, which was determined according to the 2005 classification system of the Dutch Institute for Healthcare Improvement CBO (http://www.cbo.nl/). This level of evidence ranged from A1 (a systematic review of at least 2 independent studies of evidence level A2) to D (an opinion of experts). A level A2 was allocated for randomized double-blinded comparative clinical research of good quality and efficient size, whereas comparative research without the needed characteristics for A2 (including patient-control and cohort research) received a level B and non-comparative research was attributed a level C.

This risk of bias assessment was independently performed by the 2 researchers, DL and RDP., and finalized after a consensus meeting. In case of uncertainty, the opinion of a third independent researcher, BC, could be consulted.

Data Extraction

Following a consensus meeting between DL and RDP, a table of evidence was constructed. First author, year of publication, investigated pathology, and characteristics of the patients and healthy control population (including number of patients, gender distribution, age, duration of disability, weight, length, and body mass index [BMI]) were chosen and represented in the Table of Evidence (Supplemental Table 1). Data extraction was independently performed by the authors DL and RDP and afterwards compared, to obtain a consensus. An additional table was constructed with the first author, year of publication, population, imaging method, analysis toolbox, applied density threshold, number of nodes, used atlas, definition of the edges, results concerning the global graph measures, and the correlations between these measures and clinical outcomes.

Results

Study Selection

The search strategies were last inserted into PubMed and Web of science on the 3rd of March, 2020 and led to a total of 2,336 results, of which 1,100 were obtained in PubMed and 1,236 in Web of Science. Removal of duplicates resulted in a total number of 1,831 unique articles, to which 2 additional articles were added as a result of the hand search. Following the first screening round based on title and abstract, 58 articles were retained. A full text screening of these 58 results revealed 37 articles that did not fulfil the inclusion criteria. Of these 37, 18 did not describe graph measures of connectivity as an outcome, 7 discussed a population other than chronic pain patients, another 7 included a non-comparative study design and for 5 of those articles no full-text could be obtained. As a result, 21 articles were included in this systematic review and were assessed for risk of bias. The flowchart of the study selection can be found in Fig. 1.

Risk of Bias Assessment

The risk of bias assessment of all included articles resulted in identical outcomes for 172 of the 189 items (91%). To resolve the existing conflicts, a consensus meeting was held and the opinion of a third independent researcher, BC, was consulted if needed. Of the 21 included articles, 15 had a potential risk of selection bias and 13 did not report how the healthy controls were selected, or selected them from a hospital. Moreover, 10 articles did not base the case definition on independent validation, and 9 articles did not include the absence of a history of disease in the inclusion criteria of their healthy controls. Due to the case-control design of all included articles, a level of evidence B was attributed to each one of them. A more detailed representation of the quality assessment can be found in Table 2.

Study Characteristics

Study Design

All included studies had a case-control design.

Diagnosis

Chronic back pain patients were included in 5 studies (48-52), as well as patients suffering from chronic migraine (CM) (53-57), whereas 2 studies discussed chronic osteoarthrosis (OA) (50,52), fibromyalgia (FM) (58,59), or irritable bowel syndrome (IBS) (60,61). Only one study covered patients suffering from chronic neck pain (CNP) (62), chronic pelvic pain syndrome (CPPS) (63), primary dysmenorrhea (PDM) (64), trigeminal neuralgia (TN) (65) and burning mouth syndrome (BMS) (66). One study did not specify the included chronic pain population (11). Full information about the diagnosis is represented per study in the Table of Evidence, which can be found in appendix.

Demographics

In total, 1,325 chronic pain patients and 1,205 healthy controls were included with a mean age (± standard deviation) of respectively 41.9 (± 9.2) and 37.9 (± 9.2) years. Of those patients, 67% were women in the patient group and 65% in the healthy control group. The mean duration of the pain complaints ranged from 2.72 – 15.71 years across the different included chronic pain populations. Further demographic information can be found in the Table of Evidence.

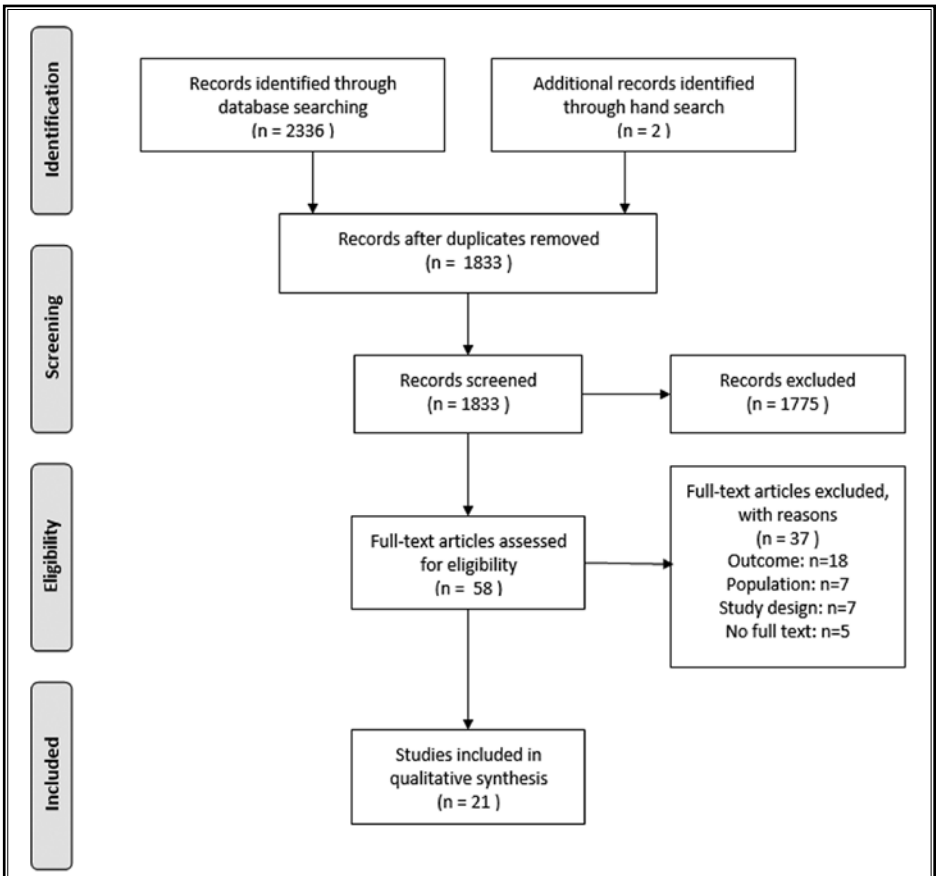

Fig. 1. *PRISMA 2009 flow diagram.*

Graph Measures

Global graph measures were discussed in 16 of the included studies (11,48,51-53,55-57,59-62,64-67), whereas nodal graph metrics were described in all but one of them (61).

Neuroimaging Method

Functional magnetic resonance imaging (fMRI) was used in 16 of the included studies (48-52,54,55,57,59-65,67), whereas diffusion tensor imaging (DTI) was applied in 2 of them (56,66), and a T1 structural MRI scan was applied in 2 others (53,58). Electro-encephalography (EEG) was the neuroimaging method of choice in only one of the included papers (11).

Graph Metrics in Chronic Pain Patients

The general framework of graph theory provides a rich array of graph metrics, which can largely be classified into measures of integration, segregation, and centrality (31). Definitions of the included graph measures can be found in Table 3. For further explanation of these measures we refer the reader to Rubinov et al (31). A visual representation of the clustering coefficient, path length, betweenness centrality and degree can be found in Fig. 2. A visual representation of small-worldness is shown in Fig. 3.

Based on these graph metrics, the hub disruption index (HDI) can be computed, which is the slope of the linear regression model, between the mean nodal metric value of a reference group and the differential nodal metric value between a given patient or control and that reference (68). By doing so, the HDI summarizes graph metric changes at the nodal level in a single value and is thus a global index capturing changes at the nodal level.

To construct the HDI, for example for the degree, the mean nodal degree from a healthy group should be subtracted from the degree of the corresponding node in an individual before plotting this individual difference against the mean of the healthy group (68). The HDI is then the slope of the regression line computed on this scatter plot. If a subject's values are close to those of the reference group, the value of the HDI will be close to 0.

Table 2. *Risk of bias assessment*.

Author and Year of publication	Case Definition[1]	Case Description[2]	Selection Controls[3]	Definition Controls[4]	Comparability[5]	Exposure Ascertainment[6]	Same Method[7]	Non-response Rate[8]	Level of Evidence
Berger et al 2014	-	-	-	+	++	+	-	-	B
Davis et al 2016	-	-	-	-	++	+	+	+	B
De Pauw et al 2020	-	+	+	+	++	+	+	-	B
DeSouza et al 2020	-	+	+	+	++	+	+	+	B
Gupta et al 2019	-	-	-	-	+ (*)	+	+	+	B
Huang et al 2019	+	-	-	+	++	+	+	+	B
Hyungjun et al 2015	+	-	-	-	++	+	+	+	B
Kaplan et al 2019	+	-	-	+	++	+	-	+	B
Labus et al 2014	+	+	+	-	+ (¥)	+	+	+	B
Lee et al 2018	+	-	-	+	++	+	+	+	B
Liu et al 2011	+	-	+	+	++	+	+	+	B
Liu et al 2013	-	-	+	+	++	+	+	+	B
Liu et al 2015	-	-	+	+	+ (¥)	+	+	+	B
Mano et al 2018	-	-	-	-	++	+	+	+	B
Mansour et al 2016	-	-	+	-	++	+	+	+	B
Mi Ji et al 2019	+	+	-	+	++	+	+	+	B
Qi et al 2015	+	+	+	+	++	+	+	+	B
Ta Dinh et al 2019	+	-	-	-	++	+	+	+	B
Tsai et al 2019	-	+	-	+	++	+	+	+	B
Tu et al 2019	+	-	-	-	++	+	+	+	B
Wada et al 2017	+	-	-	-	++	+	+	+	B

Newcastle-Ottawa Quality Assessment Scale: + = score fulfilled; - = score not fulfilled
[1]Is the case definition adequate? (Independent validation: > 1 person/record/time/process to extract information, or reference to primary record source such as x-rays or structured injury data); [2]Representativeness of cases (All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined team/competition/sport, or a random sample of those cases); [3]Selection of controls (Controls selected from the same source population as the cases); [4]Definition of controls (Explicitly stated that controls have no history of this outcome); [5]Comparability (Controlled for the most important confounders [age* and gender ¥]); [6]Ascertainment of exposure (Structured injury data, e.g., record completed by medical staff or structured interview where blinded to case/control status); [7]Same method of ascertainment for cases and controls; [8]Non-response rate (Same for both groups).

Table 3. *Definitions of graph measures.*

Graph Measure	Definition	Interpretation of a Higher Value
Measures of integration		
Characteristic path length	Average shortest path length between all pairs of nodes in the network.	Lower efficiency
Global efficiency	Average inverse shortest path length between all pairs of nodes in the network.	Stronger potential for integration
Measures of Segregation		
Clustering coefficient	Number of connections between the direct neighbors of a node, as a proportion of the maximum number of possible connections.	More clustered connectivity around individual nodes
Transitivity	An alternative to the clustering coefficient: the ratio of triangles to triplets in the network.	More clustered connectivity around individual nodes
Modularity	The presence of densely interconnected groups of nodes, along with an estimation of the size and composition of these individual groups.	Stronger subdivision of the network into modules
Local efficiency	Similar to global efficiency, but computed on the node's neighbors	Higher efficiency
Measures of Centrality		
Degree	The number of edges connected to a given node.	Nodes are interacting with many other nodes in the network
Intramodular degree	Localized, within-module version of degree.	Nodes are interacting with many other nodes in the network
Participation coefficient	Diversity of intermodular interconnections of individual nodes.	Nodes have a higher likeliness to facilitate global intermodular integration
Betweenness centrality	Fraction of all shortest paths in the network that pass-through a given node.	More central nodes facilitating integration
Closeness centrality	How close a node is to all other nodes in the network (average of the shortest path length from the node to every other node in the network).	Less central nodes
Eigenvector centrality	Measure of a node's importance while giving consideration to centrality of its neighbors.	Highly influential nodes
Nodal connection strength	The nodal mean connection distance multiplied by the nodal degree	Higher number of edges incident to a node which was connected with many long-distance connections
Other		
Small-worldness	Balance between functionally specialized (segregated) modules with a robust number of intermodular (integrating) links, supported by shorter path lengths.	Simultaneously highly segregated and integrated network
Rich club organization	High degree nodes are more densely interconnected than expected by chance among themselves than lower-degree nodes in the network.	High-degree nodes form a core network

All results from the global graph measures are represented in Table 4.

Measures of Integration

Measures of integration estimate the ease with which brain regions communicate by rapidly combining specialized information from distributed brain regions (31). Sequences of specific nodes and edges form paths, which represent potential routes of information flow between pairs of brain regions in brain networks.

Global Integration Measures

The characteristic path length was reported to be similar in chronic pain patients and healthy controls in 4 of the included articles, 3 of which reported the structural characteristic path length (52,55,58), whereas only one described the functional path length (63).

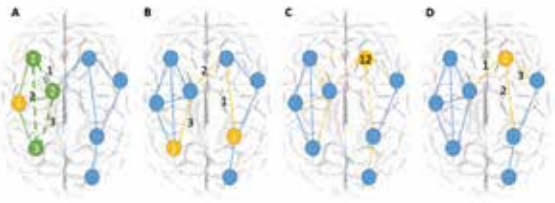

Fig. 2. *A graph represented by 8 nodes and 11 edges (the connections between nodes). (A) The clustering coefficient of node i provides information about the level of connectedness in the graph and is given by the ratio of the number of connections between the direct neighbors of node i and the maximum number of possible connections between the neighbors of node i (here depicted as 1 since the number of maximal connections between the neighbors of node i is 3 and the number of connections between these neighbors also equals 3, hence 3 divided by 3 equals 1). (B) The path length of node i reflects how close node i is connected to all other nodes in the network. It is related to distance between the i and those nodes, and the distance between node i and node j reflects the amount of connections that have to be crossed to arrive at node j from i (here the path length between node i and j is depicted as 3). (C) The level of betweenness centrality of a node i indicates how many of the shortest paths between the nodes include node i (here depicted as 12). (D) The degree of node i is defined as the total amount of connections to i (here depicted as 3).*

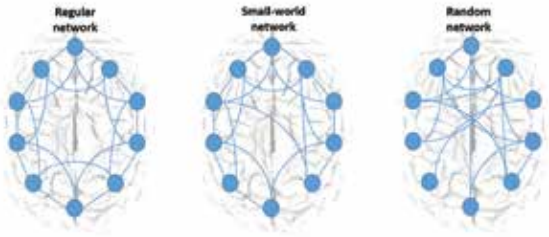

Fig. 3. *A continuum from regular network topology to random network topology with in-between the hypothesized optimum of a small-world network topology. A small-world network topology reflects an optimal balance between segregation (relatively high clustering) and integration (relatively short characteristic path length). Small-world network show a shorter characteristic path length compared to a regular network, and a higher clustering compared to random networks. (Adapted from Watts et al. (33))*

Ten of the included articles reported the global efficiency, of which the majority stated that no difference between chronic pain patients and healthy controls could be found (50,51,58,59,61,63,65), and 3 reported significant differences, characterized by lower global efficiency in the chronic pain population (11,53,61). All of these articles discussed functional networks, with the exception of one article that did not find any differences in structural global efficiency (66), and one that did report a significantly decreased global efficiency in chronic migraine patients (53).

In conclusion, it is likely that both the structural as functional path length does not differ between chronic pain patients and healthy controls, and there is conflicting evidence for a lower (structural and functional) global efficiency in chronic pain patients.

Nodal Integration Measures

Structural nodal path length of the insula, limbic network (PCC, rostral ACC, isthmus), temporal pole, and frontal network (frontal pole, medial OFC) was described in one article (53), and functional nodal efficiency of the mPFC/rACC was discussed in another (49). All of these were found to be higher in chronic pain patients than in healthy controls. The entorhinal and occipital path length however, were found to be decreased in chronic pain patients (53).

In conclusion, whereas one study provided indications for an increased functional nodal efficiency in chronic pain patients, another study provided evidence for an increased structural nodal path length.

Measures of Segregation

Segregation refers to the ability for specialized processing to occur within densely interconnected groups of brain regions (31). The quantification of such groups, known as clusters or modules within the network, forms the base for measures of segregation.

Global Segregation Measures

No significant differences in the clustering coefficient could be found in 7 of the included studies (11,52,59,60,62,64,66). This was mostly investigated for the functional clustering coefficient, as only one study reported the structural clustering coefficient (66). Two other studies did report significant differences between both groups, one of which found a decrease in chronic back pain based on functional networks (50), whereas the other found an increase in CM patients based on structural networks (55).

The HDI of the functional clustering coefficient was determined in 2 of the included studies, but they did not reach consensus either, as one of them reported no significant differences between chronic pain patients and healthy controls (62), whereas the other did report lower HDI in patients with chronic pain (67).

Table 4. *Global graph measures*.

Study	Population	Method	Toolbox	Density	Nodes	Edges	Integration			Segregation						Centrality								SW	RCO	Correlations
							L	Ge	S	C	Ch	T	Le	M	S	B	Bh	D	Dh	Di	P	Ph	S			
Berger et al 2014	9 CBP, 18 HC	fMRI	BCT	-	HOA 110 regions	W	-	-	-	-	-	-	-	≈	≈	-	-	-	-	-	-	-	-	-	-	-
De Pauw et al 2020	39 CINP, 37 CWAD, 35 HC	fMRI	BCT	30 to 70%	Freesurfer 84 regions	B	-	≈	≈	≈	≈	-	-	≈	≈	-	↓	-	≈	↓	-	≈	δ	≈	-	Bh ~ NDI and CSI: negative association Di ~ NDI and CSI: negative association Di ~ NMC: positive association
DeSouza et al 2020	52 CM, 48 HC	T1	BRAPH	5 to 40%	Desikan-Killiany atlas 83 regions	B	≈	↓	δ	-	-	↓	↓	≈	δ	-	-	≈	-	-	-	-	≈	≈	-	-
Huang et al 2019	68 LDH (Discovery group), 68 LDH (Validation group), 157 HC	fMRI	BCT	2 to 10%	256 regions	B	-	≈	≈	↓	-	-	-	-	δ	↓	-	-	↓	-	↓	-	δ	≈	-	Dh ~ pain-related components: not significant Men (high educational level): Dh ~ pain intensity (inversely correlated)
Kaplan et al 2019	40 FM, 46 HC	fMRI	BCT	5 to 40%	Conn Toolbox 264 regions	B	≈	≈	≈	≈	-	-	-	≈	≈	-	-	-	-	-	-	-	-	≈	-	C ~ clinical pain ($r > 0.3$, $P < 0.05$)
Labus et al 2014	82 IBS, 119 HC	fMRI	GAT	0,05 to 0,45	LPBA 40 + HOA 62 regions	B	-	≈	≈	≈	-	-	-	≈	≈	-	-	-	-	-	-	-	-	≈	-	-
Lee et al 2018	57 PDM, 62 HC	fMRI	BCT	0,03 to 0,40	AAL 90 regions	B	≈	≈	≈	≈	-	-	≈	≈	≈	-	-	-	-	-	-	-	-	≈	-	-
Liu et al 2011	38 CM, 38 HC	fMRI	-	15 to 25%	AAL 90 regions	B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	↑	-	SW in women CM ~ duration of migraine ($r = 0.53$, $P = 0.02$).
Liu et al 2013	26 CM, 26 HC	DTI	-	25%	AAL 90 regions	W	≈	-	≈	↑	-	-	-	≈	δ	-	-	-	-	-	-	-	-	≈	-	C ~ migraine duration ($r = 0.65$, $P = 0.0004$) SW ~ migraine duration ($r = 0.6$, $P = 0.001$) M: No significant correlation
Liu et al 2015	108 CM, 30 HC	fMRI	-	Variable densities	AAL 90 regions	W	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	δ	RCO ~ migraine duration

Table 4 (cont). *Global graph measures*.

Study	Population	Method	Toolbox	Density	Nodes	Edges	Integration			Segregation						Centrality								SW	RCO	Correlations
							L	Ge	S	C	Ch	T	Le	M	S	B	Bh	D	Dh	Di	P	Ph	S			
Mano et al 2018	75 CBP, 90 HC	fMRI	BCT	10%	Brain-VISA sulci atlas + AAL 140 regions	B	-	-	-	-	↓	-	-	-	δ	-	↓	-	δ	-	-	-	δ	-	-	-
Mansour et al 2016	40 CBP, 40 OA, 22 CRPS, 75 HC	fMRI	BCT	10 to 50%	HOA + AAL 90 regions	W	-	≈	≈	≈	-	-	-	≈	≈	-	-	-	↓	-	-	-	δ	≈	-	Density 10%: Dh ~ pain intensity (Strong negative correlation) Density 10-50%: Dh ~ pain intensity when networks exhibited SW properties
Qi et al 2015	31 IBS, 32 HC	fMRI	GRETNA	-	AAL 20 regions	B	-	↓	δ	-	-	-	≈	-	≈	-	-	-	-	-	-	-	-	≈	-	-
Ta Dinh et al 2019	101 CP, 84 HC	EEG	Fieldtrip + BCT	10%	64 electrodes, 10-20 system Reference: Cz; Ground: AFz	B	-	↓	δ	≈	-	-	-	-	≈	-	-	-	≈	-	-	-	≈	≈	-	Ge & Dh~ pain intensity, pain duration, pain disability, mental and physical quality of life, depression, medication quantification scale: no significant correlation
Tsai et al 2019	25 TN, 20 HC	fMRI	-	-	Shen Brain Atlas 205 regions	B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	≈	-	≈	-	-	P of the DMN at baseline ~ treatment effect score ($r = 0.42$, $P < 0.05$)
Wada et al 2017	14 BMS, 14 HC	DTI	BCT	-	Freesurfer 83 regions	W	-	≈	≈	≈	-	-	-	-	≈	-	-	≈	-	-	-	-	≈	≈	-	-

Population: BMS, burning mouth syndrome; CBP, chronic back pain; CINP, chronic diopathic neck pain; CM, chronic migraine; CP, chronic pain; CRPS, complex regional pain syndrome; CWAD, chronic whiplash associated disorders; FM, fibromyalgia; HC, healthy controls; IBS, irritable bowel syndrome; LDH, lumbar disk herniation; OA, osteoarthritis; PDM, primary dysmenorrhea; TN, trigeminal neuralgia. Method: DTI, Diffusion tensor imaging; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; T1, T1 weighted anatomical scan. Toolbox: BCT, brain connectivity toolbox; BRAPH, Brain Analysis using Graph Theory; GAT, Graph Analysis Toolbox; GRETNA, Graph Theoretical Network Analysis Toolkit. Nodes: AAL, Automated anatomical labelling atlas; HOA, Harvard-Oxford atlases. Edges: B, binary; W, weighted. Graph Theory Outcomes: Integration: L, path length; Ge, global efficiency; S, summary. Segregation: C, clustering coefficient; Ch, clustering coefficient hub disruption index; T, transitivity; Le, local efficiency; M, modularity; S, summary. Centrality: B, betweenness centrality; Bh, betweenness centrality hub disruption index; D, degree; Dh, degree hub disruption index; Di, intramodular degree; P, participation coefficient; Ph, participation coefficient hub disruption index; S, summary. SW, small worldness. RCO, rich club organization. Symbols: δ, significant difference; -, not investigated; ≈, no significant difference; ↓, decreased in patients; ↑, increased in patients.
Correlations: CSI, central sensitization inventory; DMN, default mode network; NDI, neck disability index; NMC, neuromuscular control.

A collectively normalized classical variant of the clustering coefficient, known as the transitivity (31), was found to be significantly lower in the structural connectome in CM patients than in healthy controls (53).

Of the included studies, 7 agreed that no difference in modularity could be observed between chronic pain patients and healthy controls (52,53,56,59,60,62,64). Only 2 of these studies discussed the structural modularity (53,56), whereas all others discussed functional networks.

The functional local efficiency was found to be similar between chronic pain patients and healthy controls in 2 of the included studies (61,64), whereas the structural local efficiency was reported to be significantly lower in CM patients in one study (53).

In conclusion, there is conflicting evidence for differences in the structural and functional clustering coefficient and in the HDI of the functional clustering coefficient. Moreover, it is likely that there is no difference in structural and functional modularity between chronic pain patients and healthy controls; however, there are indications that the structural transitivity is lower in CM patients than in healthy controls.

It is likely that the functional local efficiency does not differ between chronic pain patients and healthy controls, but there are indications that the structural local efficiency would be lower in patients.

Nodal Segregation Measures

The functional clustering coefficient was determined in 3 of the included studies, of which 2 reported the absence of significant differences in clustering between chronic pain patients and healthy controls (11,64). A decreased functional clustering coefficient was found in the middle temporal network, whereas an increased coefficient was obtained for the cingulate, caudate node, and hippocampus (60). The structural clustering coefficient was found to be decreased in the medial orbitofrontal node, cuneus, rostral ACC (66), and limbic network (caudal ACC, parahippocampal) (53).

The functional local efficiency was only discussed in one study and was found to be similar between chronic pain patients and healthy controls (64). The structural local efficiency on the other hand was also investigated by one study and was decreased in limbic nodes (caudal ACC, parahippocampal) and the insula of chronic pain patients (53).

Functional modular connectivity was only discussed in one study and was found to be altered in the nucleus accumbens and medial temporal lobe of chronic back pain patients (48).

In conclusion, there is conflicting evidence about the functional clustering coefficient, whereas it is likely that the structural clustering coefficient would be decreased in chronic pain patients.

Whereas there are indications that the functional local efficiency does not differ between chronic pain patients and healthy controls, the structural local efficiency would be decreased in chronic pain patients. Lastly, there are indications that the functional modular connectivity is altered in chronic pain patients.

Measures of Centrality

The importance of specific network nodes and edges in the functioning of the network is described in measures of centrality (31).

Global Centrality Measures

Based on 2 of the included studies, no differences in structural global degree could be found between chronic pain patients and healthy controls (53,66). Assessment of the HDI of the functional global degree resulted in more ambiguous results, as 2 studies reported an absence of differences in global degree (11,62), whereas 3 studies did report significant differences between chronic pain patients and healthy controls (51,52,67).

The functional intramodular degree and its HDI were only computed in one study, where they were found to be significantly lower in CNP patients than healthy controls (62).

The functional participation coefficient was found to be similar in chronic pain patients and healthy controls, both for the participation coefficient (51,65) on its own and for the HDI of the participation coefficient (62).

Lastly, the functional betweenness centrality was found to be significantly lower in chronic pain patients (51). So was the HDI of betweenness centrality (62,67).

In conclusion, it is likely that the structural global degree does not differ between chronic pain patients and healthy controls, but there is conflicting evidence concerning the HDI of the functional global degree. It is equally likely that the functional participation coefficient does not differ between both groups and it is also likely that the same conclusion can be made for the HDI of that participation coefficient. However, it is likely that the HDI of the functional betweenness central-

ity differs between chronic pain patients and healthy controls, and there are indications that the same can be said for the functional betweenness centrality on its own. Moreover, there are indications that the HDI of the functional intramodular degree is lower in CNP patients than in healthy controls.

Nodal Centrality Measures

Functional nodal degree was reported in 8 of the included studies, of which only 2 did not find any differences between chronic pain patients and healthy controls (11,64). An increased functional and structural nodal degree in chronic pain patients was found in the limbic network (hippocampal, parahippocampal, ACC) (49,52,58,60,66), as well as in other nodes (functional: primary sensory, motor, visual, frontoparietal, prefrontal, medial frontal, orbitofrontal, nucleus accumbens, thalamus, and peri-aquaductal grey; and structural: cerebellar, supramarginal gyrus, orbitofrontal, inferior parietal) (49-52,57,58,60,66), whereas a decreased nodal degree in chronic pain patients was found in a number of, partly overlapping, regions (functional: the sensorimotor cortex, frontal gyrus, opercular gyrus, angular gyrus, cingulate gyrus, fusiform, precuneus, frontoparietal, subcortical, limbic, and supplementary motor areas; and structural: postcentral gyrus, gyrus rectus, orbitofrontal, inferior frontal) (50-52,58,60). The functional intramodular degree was only reported in one study and was found to be higher in the right amygdala, left pallidum, and right temporal pole of chronic pain patients (62). Similarly, the functional degree centrality indicated a stronger connectivity in the dorsolateral prefrontal cortex, insula, ACC, thalamus, precuneus, supramarginal gyrus, premotor cortex, and cerebellum of chronic pain patients (54).

The functional betweenness centrality was investigated in 5 studies and showed a decrease in chronic pain patients in the cingulate cortex, insula, (para) hippocampus, precentral gyrus, dorsolateral superior frontal gyrus, orbital inferior frontal gyrus, and inferior temporal areas (49,55,60,62,63), along with an increase in the caudate nucleus, angular gyrus, cingulate gyrus, thalamus, medial prefrontal cortex, and ACC (49,60,63).

Structural closeness centrality was found to be higher in entorhinal areas but lower in the insula, limbic structures (posterior cingulate cortex, isthmus, rostral ACC), medial orbitofrontal cortex, temporal areas, and brainstem (53).

Functional eigenvector centrality was reported to be higher in the insula, superior temporal gyrus, primary motor cortex, right inferior parietal lobule, precuneus, and posterior cingulate of chronic pain patients, but lower in its mid temporal gyrus, medial prefrontal cortex (59).

In one study, the functional participation coefficient of the sensorimotor network and default mode network was shown to be lower in chronic pain patients (65). The structural nodal connection strength of the insula, amygdala, cingulate gyrus, hippocampus, parahippocampal gyrus, putamen, thalamus, dorsolateral prefrontal cortex, precentral gyrus, inferior parietal gyrus, occipital cortices, and temporal cortices was altered in chronic pain patients (56).

In conclusion, there is conflicting evidence about the presence of a significant difference in functional nodal degree, whereas it is likely that the structural nodal degree does differ between both groups with the direction of change depending on the brain region. There are indications that the functional intramodular degree and degree centrality are higher in chronic pain patients.

It is likely that the functional betweenness centrality differs between chronic pain patients and healthy controls, with the direction of that difference depending on the brain region. Similarly, there are indications that the structural closeness centrality and functional eigenvector centrality differ between chronic pain patients and healthy controls, but that the direction of that difference depends on the brain region. In addition, there are indications that the functional participation coefficient is lower in chronic pain patients and that the structural nodal connection strength is altered in this population.

Small-worldness

The need of the network to satisfy the opposing demands of functional integration and segregation is reflected by small-world attributes (70). Optimal functioning of the brain requires a suitable balance between functionally specialized (segregated) modules with a robust number of intermodular (integrating) links supported by shorter path lengths. This small-worldness was assessed in 12 of the included articles for both functional and structural networks (11,51-53,55,56,59-62,64,66), of which only one found significant differences in functional networks between CM patients and healthy controls (55). However, these differences were only found at specific sparsity values, namely at 20, 23 and 24% for CM patients who were men and at 15, 16 and 17% for CM patients who were women.

In conclusion, it is likely that small-worldness does not differ between chronic pain patients and healthy controls, but there is some contradicting evidence about the functional small-worldness at specific sparsity thresholds.

Rich Club Organization

Nodes with a high degree, which indicates that they are rich in connections, are more likely to form tight and well-interconnected subgraphs (clubs), than low-degree nodes (71). A rich club exists in a network if those nodes are more densely interconnected among themselves than expected by chance. In other words, the high-degree nodes form a club. The functional rich club organization was found to be significantly different in CM patients, when compared to healthy controls, in one of the included studies (57). A formation of an abnormally strong interconnected organization could be observed in the CM group.

In conclusion, there are indications that the rich club organization in functional networks differs between CM patients and healthy controls, characterized by a stronger interconnection in the CM group.

Correlations between Graph Measures and Clinical Outcomes

The correlation between pain intensity on one hand and functional global degree (52) and thalamus degree (50) on the other hand was found to be significant. So was the correlation between HDI for functional degree and pain sensitivity (51). Clinical pain also correlated with the rich club membership and eigenvector centrality (59) and symptom severity correlated with global efficiency (61).

Pain duration was shown to be correlated with functional and structural small-worldness (55,56), structural clustering (56), functional connection strength (57), and functional nodal centrality of the precentral gyrus and anterior cingulate gyrus (55), but did not show a significant correlation with functional degree centrality or modularity (54,56).

Self-reported disability and symptoms of central sensitization correlated with betweenness centrality and intramodular degree. The latter also correlated with motor control (62).

In conclusion, it is likely that there are significant correlations between graph measures and clinical measures such as pain intensity, pain duration, disability, symptoms of central sensitization, and motor control. There are however indications that this is not the case for degree centrality and modularity.

Discussion

Chronic pain is believed to reflect a multimodal brain signature on different levels. Graph theory has emerged as a recent framework to evaluate the brain on its network-level. The current review aims to determine whether brain network connectivity, based on global and nodal graph measures, differs between chronic pain patients and healthy controls.

Overall, findings seemed more consistent for the global measures compared to nodal levels and indicated a lack of evidence for differences in most of the global graph measures between chronic pain patients and healthy controls. This was the case for the structural and functional path length, structural and functional modularity, structural global degree, and the (HDI of the) functional participation coefficient. Significant group differences between chronic pain patients and healthy controls were found for some of the global graph measures. The functional betweenness centrality was shown to be lower in chronic pain patients compared to healthy controls, which represents the presence of less central nodes facilitating integration in chronic pain patients. Moreover, the HDI of the functional intramodular degree of CNP patients and structural transitivity of chronic migraine patients would be lower than those outcomes in healthy controls.

Measures of Integration

At a global level, measures of integration did not show to be different among patients with chronic pain compared to healthy controls, which reflects the absence of changes in efficiency of white matter structural or functional connections. These findings are in contrast to findings in other pathologies, where differences in integration were detected (72,73); however, chronic pain might reflect a specific state of the brain rather than a structural pathology, since most studies found only subtle structural differences among chronic pain patients (74). Therefore, the differences in integration might be more subtle compared to disorders with clear anatomical lesions, such as stroke (42).

Obvious differences in measures of integration could not be observed between chronic pain patients and healthy controls. A consensus was not reached about the global efficiency of functional and structural networks, while no differences were found in the functional characteristic path length, although both are measures of integration. Whereas the path length is primarily influenced by long paths, the global efficiency is primarily influenced by short paths (31). Some

authors have argued that this may make the global efficiency a superior measure of integration (75).

Measures of Segregation

One measure of segregation, namely the structural transitivity, was shown to be decreased in chronic pain patients. The transitivity is a classical variant of the clustering coefficient, but cannot be disproportionately influenced by nodes with a low degree because it is normalized collectively (76). Concerning the clustering coefficient, conflicting evidence was obtained from the included articles for both functional and structural networks. Similarly, no consensus was reached for the functional local efficiency, which is a third measure of segregation. Given the strong link between transitivity and clustering coefficient, based on the combined results of the 2 measures, no clear differences could be observed between chronic pain patients and healthy controls.

Measures of Centrality

Differences between chronic pain patients and healthy controls were observed in betweenness centrality and structural nodal degree, with the direction of change depending on the brain region. Based on single studies, the structural clustering coefficient, structural nodal connection strength, structural path length, structural closeness centrality, functional modular connectivity, functional intramodular degree, functional degree centrality, functional nodal efficiency, functional eigenvector centrality, and functional participation coefficient seem to differ between chronic pain patients and healthy controls. All of these were found to be higher in chronic pain patients, with the exception of the closeness centrality and participation coefficient.

Hub Disruption Index

In contrast to the aforementioned measures of global and local network-properties, the HDI is able to reflect a global shift at the nodal level (68). The HDI is sensitive to detection if the degree of one node in network would increase (e.g., the node plays a more central role), while the degree of another node would decrease (e.g., the node plays a less central role). In contrast, these opposite changes (an increase and a decrease) would have no impact on the average nodal degree within the network (68). Differences between the chronic pain patients and healthy controls were found for the HDI of the functional betweenness centrality and for the HDI of the functional intramodular degree, which is a localized measure for the importance of a node. Both of these measures were shown to be decreased in chronic pain patients. The interpretation of these findings is the same as described above for betweenness centrality, namely the presence of less central nodes facilitating integration in chronic pain patients and an interaction with less other nodes in the network in these patients, due to the lower intramodular degree.

Conflicting evidence was found about the HDI of both the functional clustering coefficient and functional global degree. It must however be said that all studies that did report a difference in the HDI of global degree included a chronic back pain population; therefore, this result might be population dependent.

Other Measures

The presence of an optimal balance between functional integration and segregation, reflected by small-worldness, probably does not differ between chronic pain patients and healthy controls. The small-worldness, global efficiency, global path length and clustering are all interconnected. Whereas the small-worldness equals the ratio of clustering over path length, the global efficiency equals the inverse of path length. The absence of obtained differences in global path length, as well as in the majority of the studies investigating the clustering coefficient, are therefore in line with the lack of differences in small worldness between healthy controls and chronic pain patients.

One study showed a significantly different rich club organization in the functional networks of chronic pain patients, characterized by a strong connection among the insula (mainly), orbitofrontal cortex, and primary and secondary somatosensory cortices (57). Interestingly, the level of rich club organization was similar between chronic pain patients and healthy controls, but the specific membership of the rich club differed. This implies that the information flow across brain networks differs on a qualitative level, rather than on a quantitative level.

Nodal versus Global Measures

As expected, a discrepancy was identified between nodal and global graph measures. Nodal differences or shifts do not necessarily correlate with differences in global graph measure, but might be captured by the HDI. In addition, multiple pain populations were included and discussed. Given the complexity and dimensionality of pain, it is not surprising that certain brain alterations could be disorder-specific; because of

this, a distinct set of brain regions could be affected in distinct chronic pain populations (22,77). Moreover, differences in number of investigated brain regions and used atlas could further explain these differences in findings. Lastly, some of the included studies did not correct for multiple comparisons or did not state clearly whether they did. This can induce type I errors and lead to profound consequences for the interpretation of significant findings (78).

One similarity between local and global graph measures could be observed. Although only one study presented a decreased functional global betweenness centrality in chronic pain patients, this was backed up by 5 other studies that found a decreased functional nodal betweenness centrality; however, on a nodal level these findings were region specific, as 3 studies reported increases in betweenness centrality in certain brain regions.

Clinical Implications

Overall, some changes were found at a global level, but most of the obtained differences were computed on a nodal level or on the basis of a HDI, which is a global index capturing changes at the nodal level (68,79). Both of these findings support the theory of the presence of a shift in important brain regions contributing to graph properties in chronic pain patients, rather than a global change in network properties.

Identifying this shift might be an important predictive or prognostic biomarker in the identification of the chronic pain phenotype and lead to a potential clinical pathway for the patient. With a better understanding and identification of the organizational structure of the brain, targeted and tailored treatments might be within scope.

Due to an insufficient number of articles per patient population, results were not presented separately for each of the included patient groups; however, 5 of the included studies discussed CM and 5 others chronic back pain (48-52). Only 2 outcome measures were evaluated in several papers for CM, which agreed that no differences with healthy control could be found in structural modularity or small-worldness (with the exception of one paper that did obtain significant differences between healthy control and CM patients in small-worldness at specific sparsity thresholds). Findings within the different studies examining chronic back pain were in line with each other, characterized by significant differences in both global and nodal degree and by the absence of differences with healthy control in small-worldness.

Although not the primary aim of this study, multiple correlations between clinical outcomes and graph measures were investigated. The alteration in rich club organization was strongly related to migraine duration and shows that the discovered connections of long-distance short-cuts between functional diverse brain circuits reflect altered functional integration as a result of long term pain experience (57). This may affect the normal organization of the network for transferring pain-related information through different brain circuits. Additional significant correlations were found between pain-related measures, motor control, disability and graph measures of integration, segregation, and centrality. All of these correlations were positive, with the exception of nodal centrality, and indicated that greater disturbances in graph measures were related to worse clinical outcomes. This contributes to the hypothesis that the properties of a clinical condition could reshape the brain by adapting to changing cognitive/emotional demands, such as the experience of chronic pain (80). Moreover, this contributes to the hypothesis that chronic pain may modulate brain functions in ways that may be maladaptive and that these alterations may extend beyond the pain system itself, affecting the patients' daily experience (49). Consequently, this indicates that central pain processing mechanisms of the brain play a role in the persistent pain complaints of chronic pain patients, which could contribute to the recommendation to include biopsychosocially-driven rehabilitation for these patients (45).

Limitations

The findings of this review should be interpreted in the light of several limitations and strengths.

Firstly, due to the many different included populations and a large diversity in discussed graph measures, a meta-analysis was not indicated. Secondly, no exclusion criteria were determined based on matching of patient and control group, neither on the number of investigated brain regions, nor applied atlas. Thirdly, the majority of the included studies performed functional MRI to investigate the graph measures. As a result, conclusions are mainly based on functional connectome studies, as structural connectome studies were underrepresented. Structural and functional results were presented separately, due to the absence of a strong link between functional and structural graph measures (81-83).

Lastly, although a hand search was added to the search strategies to include all relevant articles, it could

be more comprehensive to include more databases such as Embase.

This review discussed an innovative topic, which explains the low number of studies per patient population and the inability to apply more strict inclusion criteria. Hence, innovation entails certain limitations, but also identifies the opportunities for future research.

Several methodological strengths apply to this review. Firstly, the applied search strategies were formulated in a very broad manner, ensuring that relevant articles would definitely be found. Secondly, the quality of this systematic review was ensured by performing blinded evaluations for the inclusion process, as well as for the quality assessment and data extraction. Thirdly, all of the included studies were published recently, reducing the probability of including outdated findings.

Some of the included studies already included an HDI or combined a discovery group with a validation group to obtain and validate their findings, which provides more reliable an robust conclusions that can be generalized more easily to the population at large (20,84).

Recommendations for Future Research

The determination of the HDI and the use of a combination of a discovery group and a validation group should be included in future studies to provide more reliable results. Moreover, unweighted networks were most frequently used, but weighted network analyses could provide more specific information (85); therefore, future studies should include weighted network analyses more often.

Given the fact that this is a rather new domain, future research is needed to validate the obtained findings in all of the included populations, as most of the included patient groups were only covered by one or 2 studies. Moreover, similar research should still be performed in other chronic pain patients that were not included in this review due to a lack of studies, such as chronic fatigue syndrome, chronic tension-type headache, etc.

Conclusion

Graph theory provides meaningful information about the organization of human brain networks by quantifying the brain networks based on how brain regions are connected at both global and local levels. As a result of this systematic review, it can be concluded that on a global level the transitivity, betweenness centrality, intramodular degree, and rich club organization differ between chronic pain patients and healthy controls, but that the path length, modularity, degree, (HDI of) participation coefficient, and small-worldness did not differ between both groups. Conflicting evidence still remains about a number of global graph measures, namely the global efficiency, local efficiency, clustering coefficient, and HDI of degree. No clear conclusions could be made about the majority of the nodal measures, as they were often based on single studies.

Finally, significant correlations were found between several nodal and global graph measures and clinical outcomes related to pain, disability, and motor control, indicating the relevance of looking at the brain of chronic pain patients on a network level. These associations substantiate the recommendation to target the brain during the treatment of chronic pain patients by involving and addressing biopsychosocial components.

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Supplemental Table 1. *Table of evidence.*

Author, year of publication	Pathology Diagnostic criteria	Number of participants (N); Gender (% women); Age (years): mean(SD) or (SEM)*; Duration of disability mean(SD) or median (range)*; Pain: mean(SD) or (SEM)*	
		Patients	Healthy controls
Berger et al 2014	Chronic back pain (CBP)	CBP n = 9 Gender: 56% ♀ Age: 46.7 ± 6.0 Duration: NA Pain: NA	HC n = 18 Gender: 28% ♀ Age: 35.3 ± 5.6
Davis et al 2016	Chronic back pain (CBP) and osteoarthrosis (OA) Diagnosis: NA	Discovery group (CBP + OA) n = 42 Gender: 47% ♀ Age: 54.2 ± 8.8 Duration: 12.7 ± 9.9 Pain (VAS): 6.7 ± 1.8 Replication group (CBP + OA) n = 42 Gender: 52% ♀ Age: 53.6 ± 9.5 Duration: 14.8 ± 11.0 Pain (VAS): 6.7 ± 1.7	HC n = 88 Gender: 57% ♀ Age: 44.2 ± 12.6 Age and gender matched controls
De Pauw et al 2020	Chronic idiopathic neck pain (CINP) and chronic whiplash associated disorders (CWAD) Diagnosis: Self-report CWAD: modified Quebec Task Force grade A, B or C	CINP n = 39 Gender: 100% ♀ Age: 37.1 ± 12.2 Duration (months): 85.2 ± 82.1 Pain (NRS): 2.87 ± 2.15 Experienced StaffCWAD n = 37 Gender: 100% ♀ Age: 37.6 ± 12.0 Duration (months): 88.9 ± 89.4 Pain: 5.79 ± 2.2	HC n = 35 Gender: 100% ♀ Age: 30.4 ± 12.3
DeSouza et al 2020	Chronic migraine (CM) Diagnosis: International classification of headache disorders 3	CM n = 52 Gender: 81% ♀ Age: 38.5 ± 12.8 Duration (years): 9.8 ± 9.3 Headache intensity (NRS): 6.1 ± 1.8	HC n = 48 Gender: 63% ♀ Age: 37.1 ± 14.2
Gupta et al 2019	Urological chronic pelvic pain syndrome (UCPPS) Diagnosis: NA	UCPPS n = 85 Gender: 66% ♀ Age: 39.36 ± 12.8 Duration: NA Pain (Genitourinary Pain index-pain subscale): 15.41 ± 5.02	HC n = 86 Gender: 69% ♀ Age: 37.9 ± 12.23

Supplemental Table 1 (cont.). *Table of evidence.*

Author, year of publication	Pathology Diagnostic criteria	Number of participants (N); Gender (% women); Age (years): mean(SD) or (SEM)*; Duration of disability mean(SD) or median (range)*; Pain: mean(SD) or (SEM)*	
		Patients	Healthy controls
Huang et al 2019	Lumbar disc herniation (LDH) Diagnosis: Physical examination + MRI	Discovery group (LDH) n = 68 Gender: 37% ♀ Age: 44.0 ± 1.5* Validation group (LDH) n = 68 Gender: 35% ♀ Age: 44.0 ± 1.4* Duration (weeks): 104 (12; 1040)* Pain (NRS): 4.99 ± 0.18*	HC n = 157 Gender: 51% ♀ Age: 40.1 ± 1.0 Age and gender matched controls
Hyungjun et al 2015	Fibromyalgia (FM) Diagnosis: Wolfe et al. criteria + confirmation by physician and medical records	FM n = 42 Gender: 86% ♀ Age: 45.3 ± 11.6 Duration (years): 13.9 (11.6) Pain: NA	HC n = 63 Gender: 76% ♀ Age: 42.8 ± 13.7
Kaplan et al 2019	Fibromyalgia Diagnosis: American college of rheumatology 1990 criteria	n = 40 Gender: 100% ♀ Age: 39.03 ± 11.04 Duration: NA Pain (VAS): 4.88 ± 2.24	HC n = 46 Gender: 100% ♀ Age: 38.83 ± 12.18 Pain (VAS): 0.40 ± 0.90 Age and gender matched controls
Labus et al 2014	Irritable bowel syndrome (IBS) Diagnosis: Rome II or III symptom criteria assessed by gastroenterologists	IBS n = 82 Gender: 100% ♀ Age: 32.2 ± 9.6 Duration: 12.7 (8.9) Pain (21 point NRS): 9.5 ± 4.9	HC n = 119 Gender: 100% ♀ Age: 29.9 ± 10.3
Lee et al 2018	Primary dysmenorrhea (PDM) Diagnosis: By gynaecologist.	PDM n = 57 Gender: 100% ♀ Age: 23.1 ± 2.27 Duration (years): 8.8 ± 2.75 Pain (McGill pain questionnaire: present pain intensity: range 0-5): 3.1 ± 1.11	HC n = 62 Gender: 100% ♀ Age: 23.7 ± 2.4
Lee et al 2019	Chronic migraine (CM) Diagnosis: By 2 headache specialists	CM n = 18 Gender: 61% ♀ Age: 41.4 ± 10.9 Duration (years): 12.9 ± 9.9 Pain: NA	EM n = 44 Gender: 82% ♀ Age: 40 ± 10.22 Duration (years): 12.0 ± 9.0 Pain: NA Controls: episodic migraine patients (EM)
Liu et al 2011	Chronic migraine (CM) Diagnosis: ICHD criteria for migraine without aura	CM n = 38 Gender: 53% ♀ Age: 32.5 ± 8.2 Duration (years): 11.3 ± 6.7 Pain (NRS): 5.3 ± 1.6	HC n = 38 Gender: 53% ♀ Age: 32.6 ± 6.9 Age, gender, and education matched controls

Supplemental Table 1 (cont.). *Table of evidence.*

Author, year of publication	Pathology Diagnostic criteria	Number of participants (N); Gender (% women); Age (years): mean(SD) or (SEM)*; Duration of disability mean(SD) or median (range)*; Pain: mean(SD) or (SEM)*	
		Patients	Healthy controls
Liu et al 2013	Chronic migraine (CM) Diagnosis: ICHD II criteria	CM n = 26 Gender: 100% ♀ Age: 34.6 ± 4.5 Duration (years): 11.8 ± 5.7 Pain (NRS): 4.1 ± 0.8	HC n = 26 Gender: 100% ♀ Age: 33.3 ± 3.04 Age, gender and education matched controls
Liu et al 2015	Chronic migraine (CM) Diagnosis: ICHD III criteria for migraine without aura	CM n = 108 Gender: 100% ♀ Age: 30.2 ± 10.1 Duration (years): 12.2 ± 6 Pain: NA	HC n = 30 Gender: 100% ♀ Age: 26.3 ± 5.1 Gender and education matched controls
Mano et al 2018	Chronic musculoskeletal low back pain (CBP) Diagnosis: self-report	CBP – Japan cohort n = 24 Gender: NA Age (range): 21-66 Duration: 11.6 ± 9.2 Pain (VAS): 2.6 ± 2.4 CBP – UK cohort n = 17 Gender: NA Age (range): 20-61 Duration: 10.4 ± 7.5 Pain (VAS): 4.8 ± 2.8 CBP – US cohort n = 34 Gender: NA Age (range): 21-62 Duration: 15.7 ± 11.3 Pain (VAS): 6.7 ± 1.7	HC – Japan cohort n = 39 Gender: NA Age (range): 21-68 Pain: 0.3 ± 1.1 HC – UK cohort n = 17 Gender: NA Age (range): 20-62 Pain: 0.3 ± 0.7 HC – US cohort n = 34 Gender: NA Age (range): 21-64 Pain: 0 Age, gender, and IQ matched controls
Mansour et al 2016	Chronic back pain (CBP), complex regional pain syndrome (CRPS), osteoarthritis (OA) Diagnosis: NA	CBP n = 40 Gender: 38% ♀ Age: 48.87 ± 1.29* Duration: NA Pain: NA OA n = 40 Gender: 50% ♀ Age: 55.37 ± 1.01* Duration: NA Pain: NA CRPS n = 22 Gender: 82% ♀ Age: 42.41 ± 2.57* Duration: NA Pain: NA	HC n = 75 Gender: 59% ♀ Age: 44.16 ± 1.28* Age and gender matched controls

Supplemental Table 1 (cont.). *Table of evidence.*

Author, year of publication	Pathology Diagnostic criteria	Number of participants (N); Gender (% women); Age (years): mean(SD) or (SEM)*; Duration of disability mean(SD) or median (range)*; Pain: mean(SD) or (SEM)*	
		Patients	Healthy controls
Qi et al 2015	Irritable bowel syndrome (IBS) Diagnosis: By gastroenterologist, based on Rome III criteria	IBS n = 31 Gender: 19% ♀ Age: 29.23 ± 9.69 Duration (months): 32.67 ± 23.56 Pain (VAS): 30.47 ± 14.86	HC n = 32 Gender: 22% ♀ Age: 27.47 ± 8.64 Age, gender, and education matched controls.
Ta Dinh et al 2019	Chronic pain (CP) Diagnosis: Clinical diagnosis of chronic pain	CP n = 101 Gender: 69% ♀ Age: 58.2 ± 13.5 Duration (months): 121.9 ± 114.3 Pain (VAS): 5.7 ± 1.6	HC n = 84 Gender: 65% ♀ Age: 57.8 ± 14.6 Age and gender matched controls.
Tsai et al 2019	Trigeminal neuralgia (TN) Diagnosis: ICHD criteria for TN, 3rd edition	TN n = 25 Gender: 60% ♀ Age: 58.7 ± 6.0 Duration (months): 85.7 ± 86.1 Pain (VAS): 9.3 ± 0.7	HC n = 20 Gender: 65% ♀ Age: 55.7 ± 7.8 Matched controls
Tu et al 2019	Chronic low back pain (CLBP) Diagnosis: Clinical evaluation	1) Discovery group CLBP n = 50 Gender: 60% ♀ Age: 39.5 ± 23.0 Duration: NA Pain (VAS): 44.5 ± 29.7 2) Validation group CLBP n = 30 Gender: 47% ♀ Age: 35.0 ± 9.0 Duration: NA Pain (VAS): 32.6 ± 22.8	1) Discovery group HC n = 44 Gender: 43% ♀ Age: 36.9 ± 8.2 2) Validation group HC n = 30 Gender: 53% ♀ Age: 34.2 ± 2.5 Matched controls.
Wada et al 2017	Burning mouth syndrome (BMS) Diagnosis: ICHD 3 beta criteria	BMS n = 14 Gender: 100% ♀ Age: 50.9 Duration: NA Pain: NA	HC n = 14 Gender: 100% ♀ Age: 50.2 Age and gender matched controls.

HC, healthy controls; n, number; NA, not available; NRS, numeric rating scale; SD, standard deviation; SEM, standard error of the mean; VAS, visual analog scale