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Abstract

Chronic pain is known to alter the brain's network dynamics. These dynamics are often demonstrated by identifying alterations in the brain network topology. A common approach used for this purpose is graph theory. To date, little is known on how these potentially altered networks in chronic pain relate to the symptoms reported by these patients. Here, we applied a graph theoretical approach to identify network changes in patients suffering from chronic neck pain, a group that is often neglected in chronic pain research. Participants with chronic traumatic and non-traumatic neck pain were compared to healthy pain-free controls. They showed higher levels of self-reported symptoms of sensitization, higher levels of disability and impaired sensorimotor control. The brain suffering from chronic neck pain furthermore showed altered network properties in the posterior cingulate cortex, amygdala and pallidum compared to the healthy pain-free brain. These regions have been identified as brain hubs (i.e. regions that are responsible for orchestrating communication between other brain regions) and are therefore known to be more vulnerable in brain disorders including chronic pain. We were furthermore able to uncover associations between these altered brain network properties and the symptoms reported by patients. Our findings indicate that chronic neck pain patients reflect brain network alterations and that targeting the brain in patients might be of utmost importance.

Keywords: Whiplash; chronic neck pain; idiopathic neck pain; Graph Theory; Hub Disruption Index (HDI); Network topology; Connectomics

Chronic neck pain has been nominated as the 6th leading cause of disability among people world-wide [90]. Chronic neck pain can be subdivided in traumatic (whiplash associated disorders; WAD) and non-specific non-traumatic neck pain (idiopathic neck pain;

INP) [35]. Both are associated with pain, and impaired motor control, but as WAD originates from a trauma, they are characterized by more severe impairments compared to INP [25,56,63,68,71]. Patients with WAD suffer for example from general hypersensitivity of the central nervous system [56,67], a symptom attributed to altered brain dynamics [18]. Consequently, during the further unraveling of the pathophysiological processes underlying these pain disorders, the brain has been nominated as a primary target. Unfortunately, the representation of pain in the brain tends to be complex and dynamic by nature [23,27,51,52], which makes inference on this matter challenging.

Previous studies in chronic musculoskeletal pain have particularly focused on functional connectivity within the pain neuromatrix, a set of regions known to be involved in the sensation of pain [30,91]. These initial studies involved narrow region of interest (ROI)-based approaches [16,49], although many of these regions also participate in functions beyond pain processing [27,87]. Recent advances have indeed identified the involvement of regions outside the pain matrix in numerous pain disorders [8], further necessitating the examination of the brain as a whole [27]. To this end, the brain can be conceptualized as a network constituted of densely connected regions (often called network nodes) with reciprocal information flow between these nodes [27,36,52]. Graph theory provides a theoretical framework to examine these complex networks, and might reveal information about the local and global organization of functional networks [15,37,76]. A handful of studies have tried to explore these functional brain networks in chronic musculoskeletal pain [7,17,58,59,97], of which none in chronic neck pain. Furthermore, only a minority has assessed the association between topological alterations and self-reported symptoms of pain [17,59,97], although there are reasons to assume a relationship between the patient's clinical presentation, including pain and sensorimotor symptoms, and the topology of the patient's brain network [41,42].

Although, local network alterations were identified as essential indicators embodying chronic musculoskeletal pain in the brain, these measures are unfortunately inherently data-rich and complex, which might hinder the identification of robust network changes [57]. The hub disruption index (HDI) was therefore introduced recently as a reliable and sensitive global graph measure that reflects nodal differences within a graph [2,86].

Here, using a GT approach, our goals were to (1) quantify difference in global network measures between INP, WAD and healthy pain-free controls (HC), using the novel HDI metric, and (2) assess the associations between potential network disruptions and clinical symptoms including motor impairment and self-reported symptoms of pain. Based on previous findings of changes in brain network organization in chronic musculoskeletal pain [58,59], we hypothesized that (1) local topological alterations are present on a global scale in patients with INP and WAD, and that (2) the degree of these alterations is associated with the degree of motor impairment and self-reported pain.

METHODS

I. *Participants*

This study involves participants that have taken part in a previously published study on brain morphology [69]. In total, 35 HC, 39 patients with INP and 37 patients with WAD were included in the present study. All participants (n = 110) were female, Dutch native speakers aged between 18 and 65 years, who were recruited via internet, flyers and posters. Inclusion criteria for patients with WAD and INP were persistent neck pain (> 3 months) with an average pain intensity of more than 3/10 on the Verbal Numeric Rating Scale (VNRS), mild/moderate to severe pain-related disability (≥ 10/50 on the Neck Disability Index (NDI)) [89], and stability of pain medication for at least 4 weeks prior to study participation. Patients

with CWAD were only included if they were classifiable as WAD II A, B or C according to the modified Quebec Task Force Scale [81,84], and if they did not report loss of consciousness during or after the trauma to exclude possible mild traumatic brain injury. Healthy pain-free women (HC) were included if they met the following inclusion criteria: (i) pain-free on the test day (VNRS < 2/10), had no history of neck-shoulder-arm pain for more than 8 consecutive days during the last year (average VNRS ≥ 2/10), a score of less than 8 out of 50 on the NDI, no medical consultation for neck-shoulder-arm pain during the last year and no history of a whiplash trauma.

General exclusion criteria for all participants were psychiatric illness, neurologic, metabolic, cardiovascular disorders, inflammatory conditions, fibromyalgia, chronic fatigue syndrome, and a history of neck or shoulder girdle surgery. Furthermore, pregnant women and women 1 year postnatal were excluded. All participants were asked to stop intake of non-opioid analgesics 48 hours prior to study participation. In addition, participants were asked not to undertake heavy physical exertion, and to refrain from consuming alcohol, caffeine and nicotine on the day of testing. Ethical clearance was received from the Ghent University Hospital ethical committee under registration number EC/2013/1053. Written informed consent was obtained from each participant prior to participation.

II. Clinical assessment

Self-reported pain, sensitization, and disability measures

Participants scored their neck pain intensity on a VNRS, a usable and valid pain rating scale [40], with scores ranging from 0 to 10, with 0 reflecting ‘no pain’ and 10 reflecting ‘the worst pain imaginable’. Self-reported disability was assessed with the Dutch version of the NDI [89], which has demonstrated high reliability and validity [4,46]. The scale includes 10

items: pain intensity, personal care, lifting, reading, headache, concentration, work, driving, sleeping, and recreation, whereby each of item has 6 response categories ranging from 0 to 5 (with 0 “no disability” and 5 “excessive disability”), resulting in a total score ranging up to 50. Higher scores indicate increased self-reported disability [89]. Finally, participants completed the Dutch version of the Central Sensitization Inventory (CSI), a reliable self-report screening instrument to measure clinical symptoms of central sensitization in chronic pain populations [50,61]. Higher CSI scores denote a higher degree of central sensitization symptoms.

Motor control

Maximal strength (Newton, N) was measured using a Hand-held dynamometer (MicroFET 2, Hoggan Health Industries Inc., Biometrics, The Netherlands), an apparatus with good reliability [85]. The subject was seated with the thorax stabilized. The hand-held dynamometer was placed on the forehead (frontal bone), the occiput, and just above the left and right ear (parietal bone) for respectively flexion, extension, and left and right side bending. The maximum of three consecutive trials with a 10 seconds rest-interval was retained.

Postural control was assessed with an AMTI ACG portable forceplate (50 cm x 50 cm) (Advanced Medical Technology, Inc., Watertown, MA). Participants were standing on a firm surface, feet placed at hip width, and eyes closed to measure postural control under high sensory load. CoP-data was acquired via three consecutive measurements of 90 seconds using a sampling frequency of 100 Hz in order to obtain reliable results [78]. Using MATLAB R2015a (Mathworks, Inc), the raw data were filtered using a 4th order low pass digital Butterworth filter with a cut-off frequency of 5 Hz. Changes in displacement of the Center of Pressure (CoP) were recorded and the following CoP parameters were computed: mean sway

velocity (cm/s), and sway area as the 95% confidence ellipse area (cm²). An increased sway area reflects worse postural control.

Neuromuscular control, which reflects the capability to contract a specific muscle, was assessed with the craniocervical flexion test (CCFT) and the scapular holding test (SHT). The CCFT has been shown to be valid [26] and reliable [94] method. Information on the validity and reliability of the SHT is not yet available. Both tests consist of a form with specific criteria on neuromuscular control, movement control and endurance. This results in a score ranging from 0 to 10 with a lower score indicating worse neuromuscular control (for details, see Appendix A, available as supplemental digital content at http://links.lww.com/PAIN/A918).

Based on the scores for strength and neuromuscular control a scaled average was computed to provide an overall indication of strength and neuromuscular control. A higher score reflects a higher strength or a better performance in neuromuscular control.

III. Neuro-imaging

MRI data acquisition

A Siemens 3T TimTrio scanner (located at Gifmi, Ghent University Hospital, Ghent, Belgium) and a standard 32-channel head coil was used for MRI data acquisition. High-resolution whole-brain T1-weighted anatomical scans were obtained with a 3D-T1 MPRAGE sequence with following parameters, voxel size = 1.00 x 1.00 x 1.00 mm, repetition time (TR) = 2250 ms, echo time (TE) = 4.18 ms, flip angle = 3°, 176 coronal slices, FoV-matrix = 256 x 256 mm, acquisition time (TA) = 5.14 min. High-resolution whole-brain T2*-weighted images (voxel size of 1.00 x 0.70 x 3.00 mm, TR of 839 ms, TE of 18.6 ms, flip angle of 20°, 33 transversal slices, FoV of 230 x 230 x 230 mm, and a TA of 3.48 min) were obtained to

assess potential micro-haemorrhages by an experienced neuroradiologist. No participants were identified with micro-haemorrhage and none were therefore excluded from further analyses. Finally, resting state fMRI was administered using a T2*-weighted EPI sequence with the following instruction: "Close your eyes, do not think about anything in particular, and do not fall asleep", and with the following parameters: TR = 2000ms, TE = 29ms, flip angle = 90°, number of slices = 40, slice thickness = 3.0 mm, FoV read = 192 mm x 192 mm, Bandwidth BW = 2694 Hz, and 300 volumes, and TA=10.12 min. None of the patients reported falling asleep during the resting state fMRI scanning procedure.

Analysis of brain imaging data

High resolution T1 data preprocessing

High-resolution T1-weighted scans were processed using FreeSurfer version 5.3.0 (http://surfer.nmr.mgh.harvard.edu) T1-using the default processing pipeline, which includes intensity normalization, skull stripping, removal of non-brain tissue, brain mask generation, cortical reconstruction, segmentation of subcortical white matter and deep gray matter volumetric structures, cortical tessellation of the gray matter/white matter and gray matter/pial boundary, construction of a probabilistic atlas based cortical parcellation into 68 regions according to gyral and sulcal structure, and segmentation of deep gray matter structures into 16 subcortical regions summing to a total of 84 ROIs [24,28]. All FreeSurfer output was visually inspected, and in case of surface-deformation, the subject was excluded for further analyses. We did not perform any corrections to the FreeSurfer segmentation [62]. A listed overview of the different regions together with the average and standard deviation estimates of the brain volume in the different segments can be found in Appendix B (available as supplemental digital content at http://links.lww.com/PAIN/A918).

Resting-state fMRI data preprocessing

Preprocessing of each subject's functional MRI data was performed using the FMRIB Software Library v5.0 (FSL, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki [95]) and AFNI [20]. In particular, preprocessing encompassed the following steps: skull extraction using BET, motion correction, slice time correction, temporal filtering with a band-pass frequency range from 0.009 Hz to 0.08 Hz, and detrending of the signal by removal of linear and quadratic trends. Functional images were then coregistered to the individual's structural space and normalized to the MNI standard template using the linear and non-linear registration algorithms provided by FSL (FLIRT and FNIRT [5,44,45,95]). Next, segmentation of the anatomical data was performed using FAST [96] and covariates, consisting of six head motion parameters, the white matter signal and cerebrospinal fluid signal, were regressed out of the fMRI signal. Of note, we did not perform smoothing for the following reasons: (i) noise suppression was already taken into account during the averaging step (see below); (ii) to avoid a shift in ROI consistencies [48] . As an additional quality parameter, the framewise displacement was calculated to evaluate the head motion during the scanning time [72,73]. Next, the FreeSurfer cortical parcellation obtained in the previous step was mapped to the subject's functional space. Specifically, fMRI images were linearly registered to the subject's raw high-resolution T1-weighted images using the epi_reg function of FSL FLIRT [44,45]. Then, the inverse of this transformation matrix was applied to transform the FreeSurfer parcellation scheme into the subject's functional space. Average BOLD signal time series for each region were then generated by computing the spatial mean for all voxel time-series of each region. Lastly, connectivity matrices were constructed by calculating the Fisher z-transformed Pearson correlation coefficient between all pairs of regions. The same procedure was repeated for the Automated Anatomical Labeling (AAL)-atlas [88] to evaluate the robustness of our analysis.

Graph theoretical analysis

Graph construction

Individual functional brain networks, i.e. graphs, were constructed using the 84 regions of the FreeSurfer parcellation scheme as nodes and region-wise functional connectivity between each pair of nodes as edges. To define a graph, each connectivity matrix was thresholded to create an adjacency matrix where each element is either 1 if the value of the correlation is greater than a given threshold or 0 otherwise. Since the value of this threshold is crucial to define the graph density (i. e. the amount of edges in graphs over the total amount of possible edges) [93], each graph was thresholded at different threshold. These thresholds were particularly chosen to avoid unreliability of graph metrics and the presence of disconnected networks when the network is too sparse (< 30%) [86] and to avoid biological implausible networks that are too dense (> 70%) [47,74]. Graph characteristics were therefore computed for all individual brain networks at various network densities ranging from 30% to 70% with density steps of 10%. In addition to the individual networks, 100 random graphs were constructed with the same number of nodes and edges to serve as a baseline for comparison. All graphs were constructed with the Brain Connectivity Toolbox (BCT) [77].

Characterization of the network: global and nodal graph measures

Based on the connectivity matrix, topological properties can be examined by graph metrics provided by the framework of graph theory. These metrics can be categorized into measures covering segregation (i.e. the ability for specialized processing to occur within densely interconnected groups of regions), integration (i.e. the capacity of the network to rapidly combine specialized information from distributed regions), and centrality (i.e. the importance of network brain regions to the global network functioning) [77]. In particular, we computed clustering coefficient (a measure for segregation), and global efficiency (a measure

for integration) to infer on the global network properties. Small-worldness, a key common feature of complex network structures [83,92], was additionally calculated as the tradeoff between network segregation and integration [43]. A value for small-worldness that is greater than 1 is believed to reflect an optimal balance between segregation and integration [1]. Besides global graph measures, clustering coefficient, degree and betweenness centrality (measures for centrality) were computed at the nodal level. For more details on the definitions of graph metrics, the interested reader is referred to Rubinov and Sporns (2019) [76]. All aforementioned and hereafter presented graph measures were estimated with the BCT [77].

Characterization of the network: modular organization

The modular structure of a network can be revealed by subdividing the network into modules by maximizing the number of within-group links and minimizing the number of between-group links [31,34]. The modularity statistic quantifies the degree to which the network may be subdivided into such clearly delineated modules [13]. This statistic was identified through modularity maximization across 100 iterations, and as an additional check, the stability of this modular decomposition was calculated across 100 iterations per subject. In particular, we calculated (per subject) how often any 2 nodes were grouped within the same module. Then, we computed the average stability across all nodes. Results showed relatively high stability (average across subjects = 68 %, SD = 15 %). Finally, based on the modularity structure of the network, the intra-modular degree and participation coefficient were calculated.

Characterization of the network: hubs

Of particular interest are nodes that play a central role in the organization of this complex network [82]. These nodes are identified as brain hubs, and are believed to feature high centrality measures, including betweenness centrality [38,82]. The examination of these

nodes is of special interest as they are involved in establishing and maintaining efficient communication, a key feature of the healthy human brain [12,39]. In a community-structured network, a similar reasoning was followed for the identification of hubs. Modular hubs can either be provincial hubs or connector hubs. Provincial hubs provide efficient communication within a subnetwork and are characterized by a low participation coefficient (i.e. a relatively low inter-module connectivity compared to its intra-module connectivity). Connector hubs provide connection of different modules in the network and are characterized by a high participation coefficient (i.e. a relatively high inter-module connectivity compared to its intra-module connectivity) [38,82]. Of note, the participation coefficient, module degree, and modularity were calculated using the same modular decomposition. Considering these definitions, hubs were classified into provincial hubs and connector hubs based on a participation coefficient respectively lower than the 15th quartile or higher than the 85th quantile. To study a change in hub properties, the mean differences in betweenness centrality, module degree and participation coefficient were calculated between each group for each hub in the network (patients with WAD versus HC, patients with INP versus HC, and patients with WAD versus INP). Hubs displaying an absolute between group difference greater than two standard deviations were identified as disrupted hubs.

Characterization of the network changes: Hub Disruption Index

Lastly, to overcome the shortcoming of traditional global network metrics, we computed the **Hub Disruption Index** (**HDI, κ**), a global index sensitive to the differences of nodes within a graph [86]. The HDI yields an estimate for the magnitude of differences between a group of interest or an individual patient and a reference (e.g. the average value in pain-free healthy controls) for a particular nodal graph measure. Specifically, the HDI of a subject corresponds to the slope of a linear regression line between the mean local network measure of a reference group as dependent variable (i.e the healthy pain-free controls) and the

difference between that reference group and the subject/group under study as independent variable. In line with other graph metrics, the HDI was calculated for degree, clustering coefficient, betweenness centrality, participation coefficient, and module degree at network densities ranging from 30% to 70% [2,86].

Statistical analysis

Normality and equality of variance of all variables within each group was formally assessed with Shapiro-Wilk and Levene's tests, respectively, and visually inspected with QQ-plots and histograms. When normality and equality of variance could be assumed in each group, group differences of demographic and clinical variables were estimated using an ANCOVA model with age as a covariate, because of its between-group significance. In case of non-Gaussian distributed data, data was log-transformed in an attempt to achieve normality and equality of variance. Variables on medication use were evaluated by a Chi-square test at $\alpha = 0.05$, and reported exact P-values were calculated based on a Monte-Carlo simulation. Graph measures were analyzed by estimating a random-intercept model (REML) with group as fixed variable of interest, and age as fixed variables of no interest. A random-intercept model was applied to model the observations across multiple graph densities within one subject (graph density of 30%, 40%, 50%, and 60%). The best fitting model was selected based on the AIC and a Likelihood Ratio Test between models. Significant group effects were evaluated by a permutation test consisting of 1000 permutations [54]. Pairwise post-hoc Tukey-HSD adjusted comparisons were performed in case of a significant group effect, supplemented with permutation-based P-values of the pairwise comparisons. were adjusted comparisons Similarly, associations between clinical variables and graph metrics were analyzed by building a random-intercept model with age and the clinical variable of interest as fixed factors. Group-specific association were assessed by the significance of the interaction group*variable. Interactions were only kept in the model in case of a significant

contribution of the interaction to the model's likelihood. Lastly, the R^2 of the model was calculated following the Nakagawa and Schielzeth approach [53,64]. All statistical analyses were carried out with R[75] (version 3.4.3) at a significance level of $\alpha = 0.05$.

RESULTS

Demographics and self-reported symptoms

As shown **table 1**, the F-test for between group-differences was significant for age, but only patients with WAD were on average 7.2 (±3.6) years older compared to HC. For pain duration, no significant difference was observed between patient-subgroups. Patients with INP reported higher amounts of disability and symptoms of central sensitization compared to HC. Patients with WAD reported significantly higher pain intensity compared to patients with INP, and higher amounts of self-reported disability and self-reported symptoms of central sensitization compared to HC and patients with INP. For pain medication intake, between-group differences were observed for regular intake of NSAIDs and paracetamol, and not for the intake of opioid medication. However, participants were asked to refrain from the intake of non-opioid medication 48 hours prior to testing. Full demographic and clinical details can be consulted in **table 2A and 2B**.

Motor performance

As can be seen in **table 1**, patients with INP only performed worse on neuromuscular control compared to HC. Patients with WAD performed worse on neuromuscular control, strength, sway area, and sway balance compared to HC, and showed a smaller amount of strength compared to patients with INP. No differences were identified between patient-subgroups for neuromuscular control, sway area and sway velocity, neither did we identify differences between patients with INP and HC for strength, sway area and sway velocity.

Quality assessment of rsfMRI

The average (SD) framewise displacement per group was estimated to be 0.08 (0.042) for HC, 0.11 (0.051) for INP and 0.10 (0.050) for WAD. There were no significant between-group differences ($F = 1.795$; $P = 0.171$), indicating that patients with WAD or INP did not move significantly more or less compared to HC.

Graph measures

Characterization of the network: traditional global graph measures

As depicted in **figure 1**, no significant differences were found between groups in terms of clustering coefficient, global efficiency, modularity or small-worldness across all graph densities. Noticeably, all groups showed small-world characteristics with values for small-worldness higher than 1. Global network characteristics thus do not appear to be different between chronic neck pain patients and healthy controls.

Characterization of the network changes: Hub Disruption Index

Figure 2 represents the estimates of the group-based HDI for betweenness centrality, clustering coefficient, degree, module degree, and participation coefficient, and their respective 95% confidence intervals. The HDI was calculated by taking the average value of the respective nodal graph measures in the HC as reference. Nodal graph measures in the group under study are considered to be different from the reference group if the HDI significantly differs from zero (i.e. the reference line). Patients diagnosed with INP or WAD showed on average a significantly negative value for the HDI of betweenness centrality compared to HC across all graph densities, indicating that regions that have a high degree of betweenness centrality in HCs have a low degree of betweenness centrality in patients and vice versa. Similarly, a significantly negative value for the HDI of module degree in patients compared to HC across all graph densities. In contrast, patients showed a higher value for the

HDI of degree and clustering coefficient for densities above 0.5 and densities between 0.4 and 0.6, respectively. Only patients who were diagnosed with INP showed a positive value for the HDI of participation coefficient. A visual example of the HDI for all graph measures at a density of 0.5 is given in **figure 3**. If the reference group of healthy controls is considered typical in the population, then a negative value for an HDI (e.g. degree) in a subject corresponds with higher values of the HDI at typically low value nodes and a lower value at typically high value nodes.

Table 3 shows the results of subject-specific HDIs for each group for degree, clustering coefficient, betweenness centrality, participation coefficient, and intra-modular degree (i.e. the HDI was calculated for each subject with the HC as reference group). Patients with INP showed a significantly lower HDI of module-degree compared to HC, but not compared to WAD. Similarly, patients with WAD showed a significantly more negative HDI of betweenness centrality and intra-modular degree compared to HC, but not to INP (post-hoc Tukey HSD corrected). No difference was observed for the HDI of betweenness centrality between patients with INP and HC. Unlike betweenness centrality and intra-modular degree, no significant group effects were observed for the HDI of participation coefficient, clustering coefficient or degree. Interestingly, we were able to identify similar findings when using the AAL-atlas as a parcellation scheme to construct the different networks. The results regarding the traditional global graph metrics and the HDI-metric can be consulted in Appendix C (available as supplemental digital content at http://links.lww.com/PAIN/A918).

Characterization of the network: hubs

Cortical areas were predominantly identified as connector hubs (e.g. bilateral superior temporal gyrus, left superior frontal gyrus, left posterior cingulate gyrus), and subcortical areas as provincial hubs (e.g. bilateral Pallidum, and bilateral amygdala). **Table 4** displays these connector and provincial hubs identified in the reference network of HC. Only regions

that were identified consistently across all 5 densities were retained. Nodal between group differences in betweenness centrality and modular degree were assessed since only for these graph metrics the HDI showed significant between-group differences. Hubs that showed a consistent difference greater than 2 SD were identified as disrupted hubs (i.e. hubs that were identified across 3 or more graph densities). The left posterior cingulate showed a lower betweenness centrality in patients with WAD compared to HC. This indicates that in patients with WAD fewer nodes have connections to other nodes that pass via the left posterior cingulate, i.e. the left posterior cingulate may have a less prominent role in patients with WAD. Contrarily, brains of patients with WAD and INP showed a higher intramodular degree in the right Amygdala and left Pallidum compared to HC, indicating an increase in the subnetwork importance of these regions. Lastly, the right temporal pole showed only an increase in intra-modular degree in brain of patients with WAD compared to HC. No differences were observed between patient-subgroups.

Associations of the HDI with clinical parameters

As can be seen from **table 5**, a negative association was found between the HDI of betweenness centrality and both self-reported disability and self-reported symptoms of central sensitization. A more negative HDI for betweenness centrality, which reflects higher nodal changes of the subject's network compared to the reference network, coincides with higher values of self-reported disability and symptoms of central sensitization. A similar association was observed between the HDI for modular degree, where a more negative HDI for intramodular degree coincides with higher values of self-reported disability and symptoms of central sensitization, and lower performance on neuromuscular control. No group-specific associations were identified, nor did we identify associations between betweenness centrality or intra-modular degree and other clinical variables.

DISCUSSION

We questioned if difference in brain network topology exist between the healthy pain-free brain and the brain under chronic neck pain. Therefore, we applied the novel HDI metric to identify brain network alterations and associated these changes with self-reported symptoms and signs of motor impairment. Our key findings were (1) the most prominent network topology changes are in centrality properties including intra-modular degree and betweenness centrality, (2) the hubs of the brain that are mostly affected in a brain suffering pain include the post cingulate cortex, amygdala and pallidum, (3) the variability in network topology measures for centrality properties can be partly explained by self-reported systems of central sensitization, self-perceived disability and neuromuscular control. To our knowledge, this study is the first to demonstrate nodal differences of brain network topology in patients with chronic neck pain using the novel HDI metric and find associations with self-reported symptoms and neuromuscular control.

Self-reported symptoms and motor performance

We were able to observe similar between-group differences compared to previously published research regarding self-reported symptoms [56,79] and motor impairment [25,63,80] in patients with chronic neck pain. Patients with WAD show a high variability in symptoms [84] which might be a result from the traumatic event that originates WAD [19,71]. The symptoms in WAD are furthermore similar to those reported by patients with mild traumatic brain injury [19,22], which has led to the hypothesis of more extreme brain alterations in patients with WAD compared to INP. However, previous studies were unable to reveal micro-hemorrhages [70], nor is there strong evidence for the presence of microstructural white matter alterations in patients with WAD [19]. The underlying pathophysiology remains thus partly enigmatic.

Graph metrics

We observed no group-differences for traditional global graph measures, which suggests a similar – averaged - global network topology in patients with chronic neck pain compared to HC on the level of clustering coefficient, global efficiency, small-worldness, and modularity. These findings are consistent with previously published research in other chronic pain disorders [7,59,97]. In the presence of chronic pain, the pattern and the number of links between brain regions shifts, which might indicate a local reorganization of the network topology inside the brain based on the observed differences [27]. Computing averages might fade out the changes in local differences [57]. Unlike naively calculating averages of nodal graph metrics, the HDI is able reflect nodal topological differences of graph measures in a reliable fashion [86]. Based on this novel metric, we were able to demonstrate consistent local group-based network topology differences (i.e. across all network densities) for betweenness centrality and intra-modular degree. These observed group differences are extendable to subject-specific disruptions in the HDI of betweenness centrality, specifically in patients with chronic traumatic neck pain, and subject-specific disruptions in the HDI of intra-modular degree in all chronic neck pain patients. Interestingly, the shift in nodal network topology seems to be mainly reflected in nodal measures for centrality properties, including betweenness centrality and intra-modular degree. In contrast, no consistent changes were identified in nodal integration, nor nodal segregation in the current study. Indeed, brain topology alterations have predominantly been identified in the centrality properties of different brain disorders [3,21]. Brain hubs express high levels of such central properties and are typically more vulnerable. Therefore, they should be regarded as key-nodes in all brain disorders, including chronic pain. The identification of these so-called brain hubs is similar to previously described methods [7,38,82]. By analyzing these hubs, we were able to detect differences for betweenness centrality between healthy controls and patients with WAD for

the left Posterior cingulate gyrus. This might indicate a less prominent role for directing communication between different brain regions in WAD. The posterior cingulate cortex is known to be involved in pain by being part of the default mode network (DMN) [17,29], a network that is crucial in mind wandering away from pain [51,52]. Indeed, acute pain sensation seems to correlate negatively with the activation pattern of the posterior cingulate gyrus [91]. This result partly coincides with the results from the study conducted by Baliki et al. 2014, in which a fragmentation of the DMN was shown across different pain conditions [10]. In contrast, the Amygdala and Pallidum express higher levels of intra-modular degree was found in both chronic neck pain patient-subgroups. Both regions have emerged as important centers for the emotional-affective dimension of pain and pain modulation [65,66]. They are furthermore particularly well situated to mediate interactions between pain and pleasure [14,55]. Functional alterations in the amygdala and posterior cingulate cortex have already been reported in a similar musculoskeletal chronic pain disorder (i.e. chronic low back pain) [9], while changes to the pallidum are not directly evident in chronic musculoskeletal pain. Considering the complexity and dimensionality of pain, it is not surprising that some brain alterations are disorder-specific, inducing a distinct set of regions that might be affected in distinct chronic pain disorders [11,27]. Interestingly, the HDI has also been successfully applied in conditions outside the chronic pain framework, such as in stroke and comatose patients [2,86], where it was correlated with a variety of clinical measures. Therefore, the HDI measure is not specific to chronic pain, but might serve as a general measure for brain pathology.

Associations of the HDI with clinical parameters

Here, we identified an association between the subject-specific HDI for betweenness centrality and self-reported disability and self-reported symptoms of central sensitization. More specifically, a greater shift in nodal network topology in comparison to the reference

"pain-free" network is associated with higher self-reported symptoms of central sensitization and disability. This is consistent with earlier studies that assessed the association between brain network properties and clinical variables of pain [17,59,97]. Given that the HDI of betweenness centrality only differed between patients with WAD and HC, one can argue that only in patients with more severe symptoms a clear difference in network topology is detectable. More severe pain symptoms often relate to hyper-responsiveness of the central nervous system often called central sensitization, a state that has only been identified in WAD and not in INP [56,67]. Unlike the HDI of betweenness centrality, the HDI of intra-modular degree not only showed associations with disability and central sensitization, but also with neuromuscular control. Topological alterations in intramodular degree furthermore occurred in both patient-subgroups. The link between pain and neuromuscular control might occur in the brain, where altered brain dynamics caused by pain, could induce an altered neuromuscular control strategy [42]. These changes in intramodular degree were furthermore observed more clearly in the pallidum and amygdala, regions that are both (in)directly involved in the selection-process of the most appropriate motor response [32,33]. Targeting the brain in the treatment of patients with chronic pain might not only diminish self-reported disability and symptoms of central sensitization, but might also improve motor control by normalizing neuromuscular control.

Strengths and limitations

This study included a large sample of participants and is the first to report functional network changes in patients with chronic non-specific neck pain. The methodology used in this paper follows the recommended guidelines reported by different methodological papers, including a proper preprocessing pipeline [6], and applying a subject-specific cortical parcellation scheme in contrast to a general segmentation scheme. Furthermore, the calculated traditional and novel global network topology characteristics together with their association

with self-reported disability, symptoms of central sensitization and motor performance were analyzed at different graph densities. Some limitations are however inherent to this paper: we were unable to formally prove differences in graph properties at the nodal level, the clinical interpretation of the HDI remains complex, and direct inference on this network measure is harsh. The graph theoretical approach only covers one piece of the underlying puzzle in the brain disorder that entails chronic pain. Future studies might as well focus on other aspects of network topology. Lastly, based on the current analysis, we were unable to infer on the causal relationship between brain topology and disability, sensitization and motor impairment. Longitudinal studies should explore causality and assess the predictability of chronic pain based on brain network topology, since the cross-sectional design restricts the inference on causal relationships between the HDI and chronic pain. Choosing appropriate regions of interest, including a large sample size, and construction of graph at different network densities is of utmost importance for the stability of calculated graph measures [60]. Although the results between the FreeSurfer- and AAL-atlas were in general overlapping, there are some minor differences. Therefore, future studies should empower our current findings by running a similar analysis on a different sample of patients. These studies should as well consider including more objective measures to evaluate pain. In addition, future research should evaluate the network properties of different subnetworks in addition to the global network based on a parcellation scheme that includes a larger number of brain regions.

Conclusions

We identified local changes in network topology of the brain in chronic neck pain patients. More specifically, these changes occur in local centrality properties, indicating differences in the functioning of so-called brain hubs. These changes furthermore correlate with levels of self-reported central sensitization, self-reported disability, and neuromuscular control. A larger difference in central network properties is reflected by increased symptoms

and greater impairments in neuromuscular control. Targeting the brain in the therapy of patients with chronic neck pain might be crucial in the healing-process of chronic pain.

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FIGURES

Figure 1: Between group comparisons of global graph measures across different graph densities (30% to 70%).

Figure 2: (a) Changes in HDI (κ) of patients with INP and WAD compared to pain free individuals (reference line: y = 0) across different graph densities (30% to 70%). The error bars represent the 95% CI around the estimated mean. **Abbreviations**: HC: healthy controls; INP: idiopathic neck pain; WAD: whiplash-associated disorder; κ: Hub Disruption Index (HDI).

Figure 3: Visual representation of the HDI of the corresponding graph measures of **figure 2**, calculated as the slope of the regression line between the graph measure values in the control group (as independent variable) and the difference in the graph measure values between the reference control group and individual subjects (as dependent variable) at a graph density of 50%. **Cave**: These lines represent the best fitting lines as calculated in the HDI, hence not all calculated points will fall exactly on these lines. **Abbreviations**: HC: healthy controls; INP: idiopathic neck pain; WAD: whiplash-associated disorder.

Table 1: Results from ANCOVA and post-hoc pairwise comparison for demographics, self-reported symptoms and motor performance of study participants.

		ANCOVA			Pairwise comparison					
					INP - HC		WAD - HC		WAD - INP	
		F-value	df	P-value	*MD [95% CI]*	*P-value*	*MD [95% CI]*	*P-value*	*MD [95% CI]*	*P-value*
DEMOGRAPHICS										
Age	Group	3.472	2	**0.035**	6.73 [-0.67; 14.13]	0.083	**7.22 [0.12; 14.32]**	**0.045**	0.49 [-6.55; 7.53]	0.985
Pain duration (months)†	Group	0.116	1	0.116	NA				0.10 [-0.48; 0.66]	0.734
SELF-REPORTED SYMPTOMS										
Self-reported pain (VNRS)	Group	26.77	1	**<0.001**	NA				**2.92 [1.79; 4.05]**	**<0.001**
	Age	0.18	1	0.672						
Self-reported disability (NDI)	Group	62.626	2	**<0.001**	**13.52 [10.26; 16.78]**	**<0.001**	**20.18 [17.24; 23.11]**	**<0.001**	**6.65 [3.56; 9.75]**	**<0.001**
	Age	3.959	1	0.050						
Self-reported sensitization (CSI)	Group	136.470	2	**<0.001**	**17.93 [11.80; 24.05]**	**<0.001**	**27.08 [21.27; 32.89]**	**<0.001**	**9.15 [3.34; 14.96]**	**<0.001**
	Age	2.132	1	0.148						
MOTOR PERFORMANCE										
Neuromuscular control	Group	14.471	2	**<0.001**	**-0.70 [-1.19; -0.22]**	**0.003**	**-1.05 [-1.52; -0.58]**	**<0.001**	-0.035 [-0.81; 0.11]	0.172
	Age	2.224	1	0.140						
Strength	Group	19.793	2	**<0.001**	-0.37 [-0.86; 0.11]	0.166	**-1.20 [-1.68; -0.73]**	**<0.001**	**-0.83 [-1.29; -0.36]**	**<0.001**
	Age	2.263	1	0.137						
Sway area	Group	7.996	2	**<0.001**	1.04 [-0.36; 2.44]	0.186	**2.23 [0.89; 3.58]**	**<0.001**	1.20 [-0.15; 2.54]	0.090
	Age	4.353	1	0.043						
Sway velocity	Group	3.492	2	**0.036**	0.16 [-0.05; 0.38]	0.175	**0.22 [0.02; 0.43]**	**0.032**	0.06 [-0.15; 0.27]	0.761
	Age	6.667	1	0.012						

Abbreviations: df: degrees of freedom; INP: idiopathic neck pain, HC: healthy controls; WAD: whiplash-associated disorders; MD: mean difference; 95%-CI: 95% confidence interval; VNRS: verbal numeric rating scale; NDI: neck disability index; CSI: central sensitization inventory. †Log-scaled due to non-normality.

Table 2A: Descriptive statistics of demographics, self-reported symptoms and motor performance.

	HC			INP			WAD		
	Mean (SD)	***Median***	***Range***	***Mean (SD)***	***Median***	***Range***	***Mean (SD)***	***Median***	***Range***
DEMOGRAHICS									
Age	30.4 (12.3)	24.5	18-62	37.1 (12.2)	36.0	18-62	37.6 (12.0)	38.0	21.0-59.0
Pain duration (months)*		NA		85.2 (82.1)	60	4-288	88.9 (89.4)	60	3-444
SELF-REPORTED SYMPTOMS									
Self-reported pain (VNRS)		NA		2.87 (2.15)	3	0-6	5.79 (2.20)	6	1-10
Self-reported disability (NDI)	2.31 (1.49)	2	0-6	15.8 (4.87)	15.5	10-27	22.5 (6.58)	22	10-37
Self-reported symptoms of sensitization (CSI)	20.8 (6.44)	21	9-35	38.7 (8.84)	39	22-54	47.8 (12.3)	48	13-67
MOTOR PERFORMANCE									
Neuromuscular control	0.62 (0.65)	0.60	-0.38-2.24	-0.08 (0.78)	0.05	-1.71-1.40	-0.43 (0.77)	-0.45	-1.50-1.40
Strength	0.57 (0.55)	0.61	-0.57-1.82	0.20 (0.61)	0.22	-1.16-1.29	-0.63 (0.95)	-0.66	-2.47-1.18
Sway area	1.74 (0.63)	1.74	0.57-2.98	2.77 (1.83)	2.11	0.95-8.18	3.97 (2.72)	3.68	0.89-13.70
Sway velocity	0.77 (0.18)	0.81	0.39-1.03	0.93 (0.40)	0.83	0.50-2.06	0.99 (0.31)	0.95	0.55-1.73

*Log-transformed; **Abbreviations**: HC: healthy controls; INP: idiopathic neck pain; WAD: whiplash-associated disorders; SD: standard deviation in the population; VNRS: verbal numeric rating scale; NDI: neck disability index; CSI: central sensitization inventory.

Table 2B: Results from Chi-square test for comparison of between-group medication use.

		Absolute frequency (Relative frequency)			Significance
		HC	***INP***	***WAD***	
NSAID	No	30 (100 %)	30 (97 %)	29 (78 %)	$X^2 = 11.216$
	Yes	0 (0%)	1 (3 %)	8 (22 %)	P = 0.004
Paracetamol	No	30 (100 %)	29 (94 %)	27 (73 %)	$X^2 = 12.678$
	Yes	0 (0%)	2 (6 %)	10 (27 %)	P = 0.003
Opiods	No	30 (100 %)	31 (100 %)	35 (95 %)	$X^2 = 3.336$
	Yes	0 (0%)	0 (0 %)	2 (5 %)	P = 0.317

Abbreviations: HC: healthy controls; INP: idiopathic neck pain; WAD: whiplash-associated disorders; NSAID: non-steroidal anti-inflammatory drugs.

Table 3: Results from LMM and post-hoc pairwise comparison for graph centrality metrics based on the HDI (across different densities).

BETWEEN GROUP COMPARISON											
	Random Intercept model					Pairwise comparison					
						HC - INP		HC - WAD		INP - WAD	
	AIC	**Est.**	**X^2-value**	**df**	**Permuted P-value**	***MD (± S.E.)***	***P-value (permuted*)***	***MD (± S.E.)***	***P-value (permuted*)***	***MD (± S.E.)***	***P-value (permuted*)***
Betweenness centrality	-52.146	Group	6.662	2	**0.032**	0.11 (± 0.05)	0.107 **(0.038)**	0.12 (± 0.05)	**0.044 (0.016)**	0.02 (± 0.05)	0.943 (0.752)
		Age	12.369	1	**0.014**						
Clustering coefficient	978.48	Group	0.364	2	0.850				NA		
		Age	9.104	1	**0.004**						
Degree	-789.98	Group	0.371	2	0.820				NA		
		Age	9.285	1	**0.007**						
Participation coefficient	493.93	Group	0.803	2	0.694				NA		
		Age	3.366	1	0.063						
Intra-modular degree	-392.12	Group	14.995	2	**0.003**	0.13 (± 0.04)	**0.002 (< 0.001)**	0.12 (± 0.03)	**0.002 (< 0.001)**	-0.01 (± 0.03)	0.998 (0.999)
		Age	9.065	1	**0.003**						

Abbreviations: df: degrees of freedom; INP: idiopathic neck pain, HC: healthy controls; WAD: whiplash-associated disorders; MD: mean difference; S.E.: standard error of the mean; Est.: estimate; AIC: Akaike information criterion.

Table 4: Identification of central brain hubs

	CONNECTOR		**PROVINCIAL HUB**	
HUBS identified in the reference network	Inferior temporal gyrus (lh) Middle temporal gyrus (lh) Superior frontal gyrus(lh) Lateral orbitofrontal gyrus (rh) **Posterior cingulate gyrus** (bil.) Superior temporal gyrus (bil.)		Entorhinal (bil.) **Temporal pole** (bil.) Accumbens area (bil.) **Amygdala** (bil.) **Pallidum** (bil.) Putamen (rh)	
HUB ALTERATIONS				
	BETWEENNESS CENTRALITY		***MODULE DEGREE***	
BETWEEN GROUP DIFFERENCES LARGER THAN 2 SD	HC > WAD	HC < WAD	HC > WAD	HC < WAD
	Posterior Cingulate (lh)			Temporal pole (rh) Amygdala (rh) Pallidum (lh)
			HC > INP	HC < INP
				Amygdala (rh) Pallidum (lh)

Abbreviations: SD: standard deviation; INP: idiopathic neck pain, HC: healthy controls; WAD: whiplash-associated disorders; lh: left hemisphere; rh: right hemisphere; bil.: bilateral.

Table 5: Associations between the HDI and clinical symptoms.

ASSOCIATION BETWEEN HDI AND CLINICAL SYMPTOMS									
					PARAMETERS				
	AIC	X^2-value	df	P-value	Inter.	Beta (S.E.)	P-value	Age (S.E.)	P-value	R^2
BETWEENNESS CENTRALITY									

Pain Duration (months)	-87.230	8.461	2	**0.015**	0.165	-0.038 (0.025)	0.118	-0.005 (0.002)	**0.040**	0.06
Disability (NDI)	-143.51	17.847	2	**<0.001**	0.133	-0.005 (0.002)	**0.024**	-0.005 (0.002)	**0.003**	0.11
Central sensitization (CSI)	-134.38	8.079	2	**0.004**	0.194	-0.004 (0.001)	**0.004**	-0.004 (0.002)	**0.015**	0.13
Self-reported Pain (VNRS)	-64.563	6.825	2	**0.032**	0.037	0.007 (0.011)	0.419	-0.006 (0.002)	**0.017**	0.06
Neuromuscular control	-23.625	9.605	2	**0.008**	0.078	0.030 (0.030)	0.310	-0.005 (0.002)	**0.010**	0.08
Strength	-24.544	10.524	2	**0.005**	0.073	0.038 (0.028)	0.163	-0.005 (0.002)	**0.010**	0.07
Sway area	-16.984	10.725	2	**0.005**	0.130	-0.015 (0.013)	0.246	-0.006 (0.002)	**0.008**	0.10
Sway velocity	-15.706	9.447	2	**0.009**	0.128	-0.024 (0.091)	0.790	-0.006 (0.002)	**0.005**	0.08
INTRAMODULAR DEGREE										
Pain Duration (months)	-211.04	5.384	2	0.068			NA			
Disability (NDI)	-354.85	20.76	2	**<0.001**	0.086	-0.005 (0.002)	**0.005**	-0.004 (0.001)	**0.004**	0.13
Central sensitization (CSI)	-353.55	9.328	2	**0.002**	0.137	-0.003 (0.001)	**0.002**	-0.003 (0.001	**0.008**	0.14
Self-reported Pain (VNRS)	-203.55	4.436	2	0.109			NA			
Neuromuscular control	-331.30	24.84	2	**<0.001**	0.031	0.066 (0.019)	**<0.001**	-0.004 (0.001)	**0.004**	0.16
Strength	-323.09	16.634	2	**<0.001**	0.051	0.036 (0.019)	0.056	-0.004 (0.001)	**0.001**	0.11
Sway area	-255.16	15.196	2	**<0.001**	0.097	-0.008 (0.008)	0.362	-0.005 (0.001)	**<0.001**	0.12
Sway velocity	-255.65	15.686	2	**<0.001**	0.050	0.065 (0.0577)	0.251	-0.006 (0.001)	**<0.001**	0.12

Abbreviations: df: degrees of freedom; INP: idiopathic neck pain, HC: healthy controls; WAD: whiplash-associated disorders; MD: mean difference; S.E.: standard error of the estimate; Est.: estimate; AIC: Akaike information criterion; VNRS: verbal numeric rating scale; NDI: neck disability index; CSI: central sensitization inventory; Inter.: intercept.