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SHORT COMMENTARY

Understanding the interaction between clinical, emotional and psychophysical outcomes underlying tension-type headache: a network analysis approach

César Fernández-de-las-Peñas[1,2,10] · María Palacios-Ceña[1,2] · Juan A. Valera-Calero[3,4] · Maria L. Cuadrado[5,6] · Angel Guerrero-Peral[7] · Juan A. Pareja[8] · Lars Arendt-Nielsen[2,9] · Umut Varol[4]

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Abstract

Objective Evidence supports that tension-type headache (TTH) involves complex underlying mechanisms. The current study aimed to quantify potential multivariate relationships between headache-related, psychophysical, psychological and health-related variables in patients with TTH using network analysis.

Methods Demographic (age, height, weight), headache-related (intensity, frequency, duration, and headache-related disability), psychological and emotional (Hospital Anxiety and Depression Scale, Pittsburgh Sleep Quality Index), psychophysical (pressure pain thresholds [PPTs] and myofascial trigger points) and health-related variables (SF-36 questionnaire) were collected in 169 TTH patients. Network connectivity analysis was unsupervised conducted to quantify the adjusted correlations between the modelled variables and to assess their centrality indices (i.e., the connectivity with other symptoms in the network and the importance in the modelled network).

Results The connectivity network showed local associations between psychophysical and headache-related variables. Multiple significant local positive correlations between PPTs were observed, being the strongest weight between PPTs over the cervical spine and temporalis area (ρ: 0.41). The node with the highest strength, closeness and betweenness centrality was depressive levels. Other nodes with high centrality were vitality and headache intensity.

Discussion This is the first study applying a network analysis to understand the connections between headache-related, psychophysical, psychological and health-related variables in TTH. Current findings support a model on how the variables are connected, albeit in separate clusters. The role of emotional aspects, such as depression, is supported by the network. Clinical implications of the findings, such as developing TTH treatments strategies targeting these most important variables, are discussed.

Keywords Tension-type headache · Depression · Pressure pain · Network analysis

✉ César Fernández-de-las-Peñas
cesar.fernandez@urjc.es

1 Department of Physical Therapy, Occupational Therapy, Rehabilitation and Physical Medicine, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain

2 Department of Health Science and Technology, Center for Neuroplasticity and Pain (CNAP), Faculty of Medicine, SMI, Aalborg University, Aalborg, Denmark

3 Department of Physiotherapy, Faculty of Health, Camilo José Cela University, Villanueva de la Cañada, Madrid, Spain

4 VALTRADOFI Research Group, Department of Physiotherapy, Faculty of Health, Camilo Jose Cela University, Madrid, Spain

5 Department of Neurology, Hospital Clínico San Carlos, Madrid, Spain

6 Department of Medicine, School of Medicine, Universidad Complutense de Madrid, Madrid, Spain

7 Headache Unit, Hospital Clínico Universitario de Valladolid, Valladolid, Spain

8 Department of Neurology, Hospital Quirón Pozuelo, Madrid, Spain

9 Department of Medical Gastroenterology, Mech-Sense, Aalborg University Hospital, Aalborg, Denmark

10 Facultad de Ciencias de la Salud, Universidad Rey Juan Carlos, Avenida de Atenas s/n, 28922 Alcorcón, Madrid, Spain

Introduction

Tension-type headache (TTH) is probably the most prevalent headache disorders with an estimated worldwide point prevalence of 42% and 1-year prevalence of 21% [1]. Despite its prevalence, TTH is the most neglected primary headache, which may be partly because its mechanisms are not fully understood and not found to be associated with specific neurological findings [2].

Current theories support the presence of several complex mechanisms behind potential pathogenesis of TTH [3]. Among these mechanisms, pressure pain hyperalgesia [4], emotional–psychological factors [5], sleep disorders [6], genetics [7], and humoral/immune responses [8] could be involved in TTH in a complex matrix. Supporting these associations, some previous studies have reported different interactions and mediation effects between headache features, emotional/psychological, and psychophysical variables in people with TTH [9, 10]. However, these studies used Pearson's Product-Moment Correlations or linear regressions to determine the associations between the outcomes [9, 10]. It should be noted that Pearson's Product-Moment Correlation ignores the potential for pairwise associations to arise from their interaction with another variable (e.g., a common cause for both variables) whereas linear regressions ignore the possibility of bidirectional relationships between the variables [11].

Network analysis techniques permit a better understanding of complex relationships addressing the aforementioned limitations [12]. Network analysis can provide a method to identify the most important variables in the associated complex network, which could be used to potentially design better therapeutic strategies [13]. From a network perspective, TTH can be viewed as a complex condition sustained by mutual interactions between clinical, emotional/ psychological, and physiological systems. Network analysis has previously been used to better understand the complexity of chronic pain syndromes [14, 15], but so far, no study has applied network analysis in TTH research. As the current TTH framework considers the reciprocal interactions between biological and emotional factors, this type of analysis could add precision to research on TTH and development of more targeted management procedures. The main objectives of the present study were: (1) to apply a network connectivity analysis including demographic, clinical, emotional/psychological and psychophysical variables in individuals with TTH; and (2) to illustrate the potential of a network analysis for understanding underlying features of TTH, generating new research questions, and improving options for developing more targeted treatment strategies.

Methods

Study design

An observational cross-sectional study following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [16] was conducted. The study design was approved by the Local Human Ethical Committees (URJC 23/2081, HRJ 07/18). All participants read and signed a written consent form before being included in the study.

Participants

Patients with headache attending three different university-based hospitals between January 2017 and December 2019 were screened for eligibility criteria. The diagnosis of TTH was made according to the current criteria of the International Classification of Headache Disorders, third edition (ICHD-3), either the beta version [17] or the final version [18], by neurologists with more than 20 years of clinical experience. Participants were excluded if any of these circumstances were present: 1, any other primary or secondary headache; 2, previous cervical or head trauma; 3, cervical herniated disk on medical records; 4, active systemic medical disease; 5, fibromyalgia syndrome; 6, change of medications in the previous 6 months; or, 7, pregnancy.

Assessments were conducted when patients had no headaches or, in those with a high frequency of headaches, when headache intensity on the day of assessment was ≤ 3 points on the numerical pain rating scale (NPRS). Participants were asked to avoid any analgesic or muscle relaxant 24 h before their examination.

Headache-related variables

A 4-week diary was used to obtain the headache features [19]. Participants recorded in the diary the number of days with headache (days/week), the duration of the headache attack (hours/day), and the intensity of pain of each attack on an 11-point NPRS (0: no pain; 10: the worst imaginable pain). The headache diary was collected those 4 weeks before assessment.

Headache-related disability was assessed with the Headache Disability Inventory (HDI)—a questionnaire including 25 items about the impact of headache on emotional functioning and daily activities [20] which has exhibited good test–retest reliability [21]. Thirteen items evaluate the emotional burden (HDI-E, score 0–52), and the remaining 12 items evaluate the physical burden

(HDI-P, score 0–48) of headache. A higher score indicates a greater headache-related burden.

Emotional/psychological variables

The Hospital Anxiety and Depression Scale (HADS) was used to determine the presence of anxiety/depressive symptoms. Seven items assess anxiety (HADS-A, 0–21 points) and the other seven assess depressive symptoms (HADS-D, 0–21 points) [22]. Each question is scored on a 4-point scale ranging from 0 to 3 points (total score of each scale 0–21 points) where a higher score indicates greater symptoms. The HADS has shown good internal consistency in patients with headache [23].

The sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI) [24]. This 24-item self-reported questionnaire evaluates the quality of sleep of the previous month by asking questions, such as usual bedtime, usual wake-up time, actual number of hours slept, and number of minutes to fall asleep. All questions are answered on a Likert-type scale (0–3). The total score ranges from 0 to 21 where a higher score indicates worse sleep quality [24].

Neurophysiological variables

Since widespread pressure pain hyperalgesia is a known feature of TTH [4], pressure pain thresholds (PPTs) were bilaterally assessed over a trigeminal/symptomatic (temporalis muscle belly), an extra-trigeminal (C5–C6 joint), and two remote pain-free (second metacarpal, tibialis anterior muscle) points with an electronic pressure algometer (Somedic® Algometer, Sollentuna, Sweden, 1 cm^2 probe, set to 30 kPa/sec pressure increase). The mean of 3 trials on each point, with a 30 s resting period for avoiding temporal pain summation, was calculated. The order of assessment was randomized. As no side-to-side differences were observed (Student's *t* test), the mean of both sides was used for each point in the network.

Another feature of TTH is the finding of myofascial trigger points (TrPs) [25], so the total number of TrPs detected in the examination of each subject was also recorded. The presence of TrPs was looked for bilaterally in temporalis, masseter, suboccipital, upper trapezius, sternocleidomastoid, and splenius capitis muscles according to international guidelines [26]: 1, painful spot in a palpable taut band in the muscle; 2, local twitch response on palpation of the taut band, and 3, referred pain on palpation. TrPs were classified as active or latent, depending on whether or not the referred pain pattern reproduced the patient's usual complaint [25, 26].

Health-related quality of life

Health-related quality of life was assessed with the Medical Outcomes Study Short Form 36 (SF-36) questionnaire [27]. This questionnaire includes the following 8 domains: physical functioning, physical role, bodily pain, general health, vitality, social function, role-emotional, and mental health. Each domain has a score ranging from 0 (the lowest quality of life) to 100 (the highest quality of life) [28].

Sample size calculation

An adequate sample size for network analyses is based on 5–6 individuals per potential node [29]. In the current network, a total of 25 nodes were included. Accordingly, a minimum of 150 participants were required.

Network analysis

Software and packages

Data were analyzed with R software v.4.1.1 for Windows 10. The following packages were used: Qgraph (v.1.6.9) and Glasso (v.1.11) for network estimation, Igraph (v.1.2.6) for community detection, Huge (v.1.3.5) for variable transformation, MissForest (v.1.4) for missing data imputation, and Bootnet (v.1.4.3) for stability analysis [30–32].

Missing value imputation

After conducting an exploratory data analysis on the dataset, missing values were found in 25 variables divided into 5 attributes: sociodemographic (sex, age); psychological/emotional (anxiety, depression, sleep quality, mental health, emotional role); headache-related (years with pain, disability, and headache intensity, duration and frequency); health-related quality of life (physical and social function, physical role, general health, vitality and bodily pain) and psychophysical (active and latents TrPs and PPTs). Removal of the missing values resulted in loss of 19.5% of the data (33 records) involving a reduced sample size which may introduce bias and result on incorrect conclusions [33]. Considering that missing data did not depend on any other variable, a data imputation was performed using missForest.

The missForest tool is a Random Forest-based iterative imputation method that can handle mixed continuous or categorical data in presence of complex interactions and non-linearity without assuming normality or requiring specification of parametric models unlike standard imputation approaches [34]. Therefore, missForest has been found to be competitive [33] and able to outperform other imputation methodologies [31], e.g., k-nearest neighbors (kNN) and mice [35], by consistently producing the lowest imputation

error [34, 36] when the missing data are missing at random. Thus, the summary statistics for each variable subject to imputation were checked before and after the operation to ensure there were no drastic shifts in the distribution.

Network estimation

Network theory is used to represent and explore complex systems. Networks are made up of nodes (vertices) and edges. The nodes in the current network were made from 25 variables, 24 as continuous (age, psycho-physical, psychological, headache and health-related variables) and 1 included as categorical (sex). Edges constituted the links connecting the nodes and interpreted as "the remaining association between two nodes after controlling for all other information possible [11]". Edges in the network were represented by qgraph providing the magnitude (thickness) and direction (red color for negative associations and green color for positive associations) of the partial correlations with both the weights and colors.

After imputation of the missing data, a non-paranormal transformation was applied to the entire data set to ensure that the 25 variables (y) were multivariate normally distributed, which is a requirement for the estimation of the Gaussian Graphical Gaussian Model (GGM) [32].

Given that y is distributed as multivariate normal, $y \sim N(0, \Sigma)$ where Σ is variance–covariance matrix. Following, K was defined as the inverse of Σ (Σ^{-1}) and standardized to obtain the partial correlation coefficient between variable y_i and y_j, after conditioning on all other variables $y_{-(i,j)}$ as follows [11]:

$$\mathrm{Cor}\left(y_i, y_j | y_{-(i,j)}\right) = -\frac{K_{ij}}{\sqrt{K_{ii}}\sqrt{K_{jj}}}$$

For the network estimation, the graphical least absolute shrinkage and selection operator (LASSO) was used to draw out a sparse model. Given that S represents the variance–covariance matrix, LASSO aims to estimate K by maximizing the penalized likelihood function [30]:

$$\log\det(K) - \mathrm{trace}(S\,K) - \lambda \sum\nolimits_{<i,j>} \cdot |K_{ij}|$$

As LASSO seeks to maximize specificity (aims to include as few false positives as possible), estimated network ends up to be sparse, i.e., includes fewer edges compared to a saturated model [30], which makes the model easier to interpret [11]. LASSO utilizes a tuning parameter λ to control the level of sparsity in the network that directly penalizes the likelihood function for the sum of absolute parameter values [30]. In addition, careful selection of the tuning parameter becomes important for "creation of a network structure that minimizes the number of spurious edges while maximizing the number of true edges [11]". Selection of the LASSO tuning parameter was performed by minimization of Extended Bayesian Information Criterion (EBIC) since it has been shown to perform well in retrieving the true network structure, featuring high specificity (i.e., not including edges that are not in the true network) but a varying sensitivity (i.e., estimating edges that are existent in the true network) based on the true network structure and sample size [11]. The graphical LASSO was run for 100 values of λ logarithmically spaced between the maximum value of the tuning parameter at which all edges are zero ($\lambda_{max} = 0.824$), and $\lambda_{max}/1000$. The EBIC is computed under different values for λ, and the network structure with the lowest EBIC is selected ($\lambda_{EBIC\,=\,3591.04} = 0.134$). For this practice, EBIC hyperparameter δ was set to 0.5, as suggested by [11] This methodology is explained in detail in previous tutorial papers [11, 37].

Node centrality

Not all nodes in a network are equally important for determining the structure. Centrality indices can be conceived as functions measuring a node's importance based on the pattern of connections of the node of interest. In network analysis, centrality indices are utilized to model or predict several network processes, such as the amount of flow that traverses a node or the tolerance of the network to the removal of selected nodes [38]. In this study, the following three centrality indices were calculated:

1. Strength centrality, which is defined as the sum of weights of edges (in absolute values) that are directly connecting the target node [39, 40]. Clinically, nodes with high strength centrality could be potentially good therapeutic targets since a change in their value can have a strong and direct influence on the other nodes in the network without considering the mediating role of other nodes [37]. Yet, it should be noted that node strength is a blunt measure that takes node's total level of involvement in the network and not the number of connections with other nodes. Thus, utilization of other centrality indicators together with strength centrality suitable to the study is important to derive accurate conclusions [41].
2. Closeness centrality, which is defined as the inverse sum of the distances of the shortest paths (inverse of the absolute value of the edge's weight) of the target node from all other nodes in the network [37]. This can be simply interpreted as the expected speed of arrival of something flowing through the network. Clinically, a node with high closeness centrality could be easily affected by changes in another node's value directly or through changes in other nodes [37]. Additionally, its

influence can reach (spread to) other nodes more quickly than the nodes that are peripheral thanks to the shortest paths connecting itself and other nodes [37] and, thus, it can constitute a potentially good therapeutic target.

3. Betweenness centrality, which is defined as the total number of shortest paths (between any couple of nodes in the graphs) that passes through the target node, moderated by the total number of shortest paths existing between any couple of nodes in the graphs. This can be considered as the percentage of shortest paths that must go through the target node. Clinically, a node with a high betweenness centrality would act as an intermediary in the transmission of information or resources between other nodes or even clusters of nodes in the network [38].

Network edge and node centrality variability

The variability of the edge weights and the centrality indices was assesed using bootstrapping [38]. This step plays an important role since the networks were built with a real-world clinical data with inherent sources of variation, which means the results may not generalize (i.e., yield same results with an independent dataset). In the present study, 2000 iterations were used to bootstrap 95% confidence intervals (CIs) of edge weights.

The edge weights bootstrapped CIs should not be interpreted as tests of a null relationship hypothesis but rather as accuracy of the estimated weights since LASSO regularization was used to preserve only the edges with non-zero weights. Wide confidence intervals would entangle the interpretation of the edge strength, yet not the presence since model selection is already performed by LASSO. Additionally, the sign of the edge (+ or −) can be interpreted independent of the CI width as LASSO rarely retains an edge that can be positive or negative in the model.

To get an overview of the variability of the centrality indices (CS-coefficient), i.e., whether the order of centrality indices remain the same after reestimation of the network with fewer records, participant-dropping subset bootstrap was utilized [38]. This approach drops a percentage of participants, reestimates the network and related three centrality indices. The CS-coefficient (correlation stability) reflects the maximum proportion of data that can be dropped to retain with 95% certainty a correlation of at least 0.7 with the original centrality indices [11]. Ideally, it has been suggested that this coefficient should be above at least 0.25, and better if above 0.5 [11, 38].

Community detection

Some nodes (variables) often form distinct groups where there are many relations in between compared to the others in the system. In network analysis, community detection is the process of identifying these relatively dense cluster of nodes [42], which constitutes a data clustering problem. There are various approaches for community detection and (i) spectral clustering-based techniques, and, (ii) network modularity optimization strategies have been widely investigated among them. In this study, Louvain community detection algorithm was utilized which is one of the most popular methods for identifying non-overlapping communities that iteratively uses modularity to optimize its partitions [43, 44].

Results

Descriptive statistics of the variables used in the network analysis (before and after missing value imputation) can be found in Table 1. Figure 1 displays the modelled network in the sample of 169 patients with TTH. Up to 99 correlations were found between and within the five groups of variables. For instance, multiple positive correlations between PPTs were observed among the locations (nodes 9 to 12), with correlations (ρ) ranging from 0.08 (hand and C5–C6 locations) to 0.41 (C5–C6 and temporalis locations). The strongest associations were those between the emotional and physical disability burden (ρ=0.6), psychological with health-related variables (ρ up to 0.24 for physical role and emotional role) and mental health with depression (ρ=− 0.38). The rest of correlations ranged from 0.01 to 0.23 (Fig. 1).

The variability associated with the weight of each edge is shown graphically in Suppl. Figure. As an illustration of the utility of this figure, the non-overlap of the 95% CI of the edge between PPTs at the hand and tibialis anterior locations (nodes 11 and 12) with the 95% CI of the edge between headache frequency and emotional burden due to headache disability (nodes 6 and 13) indicates that the strength of the former is greater than the latter.

The node with the highest strength, closeness and betweeness centrality was depressive levels (Fig. 2). Other nodes with higher centrality were vitality (strength centrality) or headache intensity (closeness and betweeness centrality centralities). The betweenness and closeness measures of the network were extremely unstable at $CS_{cor=0.7} = 0.0$, both. The strength centrality measure was found stable with $CS_{cor=0.7} = 0.36$ (Fig. 3).

Parallel to the visualization of the network, four clusters were found by the Louvain community detection algorithm. Most of the nodes from the same variable classification ended up in the same cluster, e.g., psychophysical variables (i.e., PPTs) were grouped within the green cluster, and most of the psychological/emotional and headache-related variables were grouped within the purple and blue clusters, respectively (Fig. 4).

Table 1 Values (mean ± standard deviation) of demographic, clinical, sensory-related, psychological and sensitivity variables of the total sample ($n = 169$)

Variable	Pre-imputation statistics	Missing values (n; %)	Post-imputation statistics
Gender (male/female, %)	46/123	0; 0	46/123
Age (years)	46.3 ± 14.5	0; 0	46.3 ± 14.5
Pain duration (years)	10.8 ± 11.8	2; 1.2	10.7 ± 11.7
Headache intensity (0–10)	6.1 ± 2.8	0; 0	6.1 ± 2.8
Headache duration (hours/day)	7.1 ± 4.5	8; 4.7	7.2 ± 4.4
Headache frequency (days/month)	16.7 ± 9.2	0; 0	16.7 ± 9.2
Active TrPs (n)	4.9 ± 2.9	3; 1.8	4.8 ± 2.9
Latent TrPs (n)	1.9 ± 2.4	3; 1.8	1.8 ± 2.4
PPT C_5C_6 (kPa)	186.8 ± 86.8	0; 0	186.8 ± 86.8
PPT temporalis (kPa)	193.0 ± 83.7	0; 0	193.0 ± 83.7
PPT hand (kPa)	238.5 ± 99.1	0; 0	238.5 ± 99.1
PPT tibialis (kPa)	381.3 ± 182.5	0; 0	381.3 ± 182.5
HDI-E (0–52)	19.1 ± 13.2	0; 0	19.1 ± 13.2
HDI-P (0–48)	22.8 ± 12.3	0; 0	22.8 ± 12.3
Physical function (SF-36, 0–100)	77.9 ± 25.2	0; 0	77.9 ± 25.2
Social function (SF-36, 0–100)	65.2 ± 25.7	0; 0	65.2 ± 25.7
Bodily pain (SF-36, 0–100)	49.4 ± 22.6	0; 0	49.4 ± 22.6
General health (SF-36, 0–100)	55.1 ± 22.7	0; 0	55.1 ± 22.7
Physical role (SF-36, 0–100)	51.6 ± 40.5	0; 0	51.6 ± 40.5
Vitality (SF-36, 0–100)	48.9 ± 22.2	0; 0	48.9 ± 22.2
Emotional role (SF-36, 0–100)	60.8 ± 41.5	0; 0	60.8 ± 41.5
Mental health (SF-36, 0–100)	55.8 ± 22.6	1; 0.6	55.8 ± 22.6
Sleep quality (PSQI, 0–21)	8.2 ± 4.6	19; 11.2	8.0 ± 4.4
HADS-D (0–21)	7.9 ± 4.4	0; 0	7.9 ± 4.4
HADS-A (0–21)	9.9 ± 4.7	0; 0	9.9 ± 4.7

HADS Hospital Anxiety and Depression Scale; *HDI* Headache Disability Index; *TrP* Trigger Points; *PPT* Pressure Pain Thresholds; *PSQI* Pittsburgh Sleep Quality Index

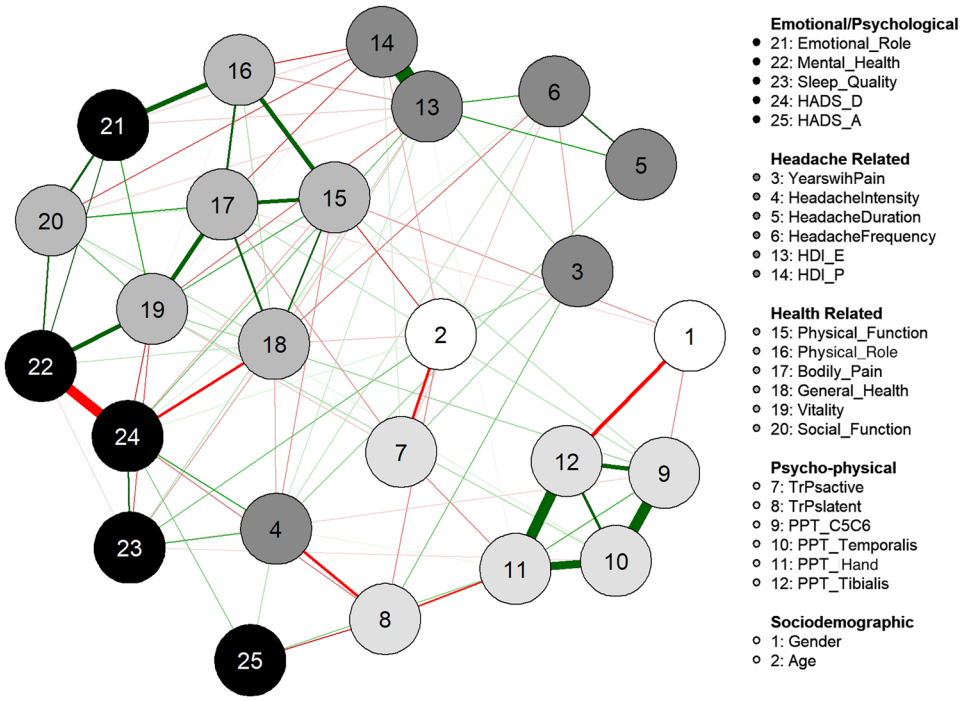

Fig. 1 Network analysis of the association between demographic, headache-related, psychological, heatlh-relatedm and psycho-physical/neurophysiological measures. Edges represent connections between two nodes and are interpreted as the existence of an association between two nodes, adjusted for all other nodes. Each edge in the network represents either positive regularized adjusted associations (green edges) or negative regularized adjusted associations (red edges). The thickness and color saturation of an edge denotes its weight (the strength of the association between two nodes)

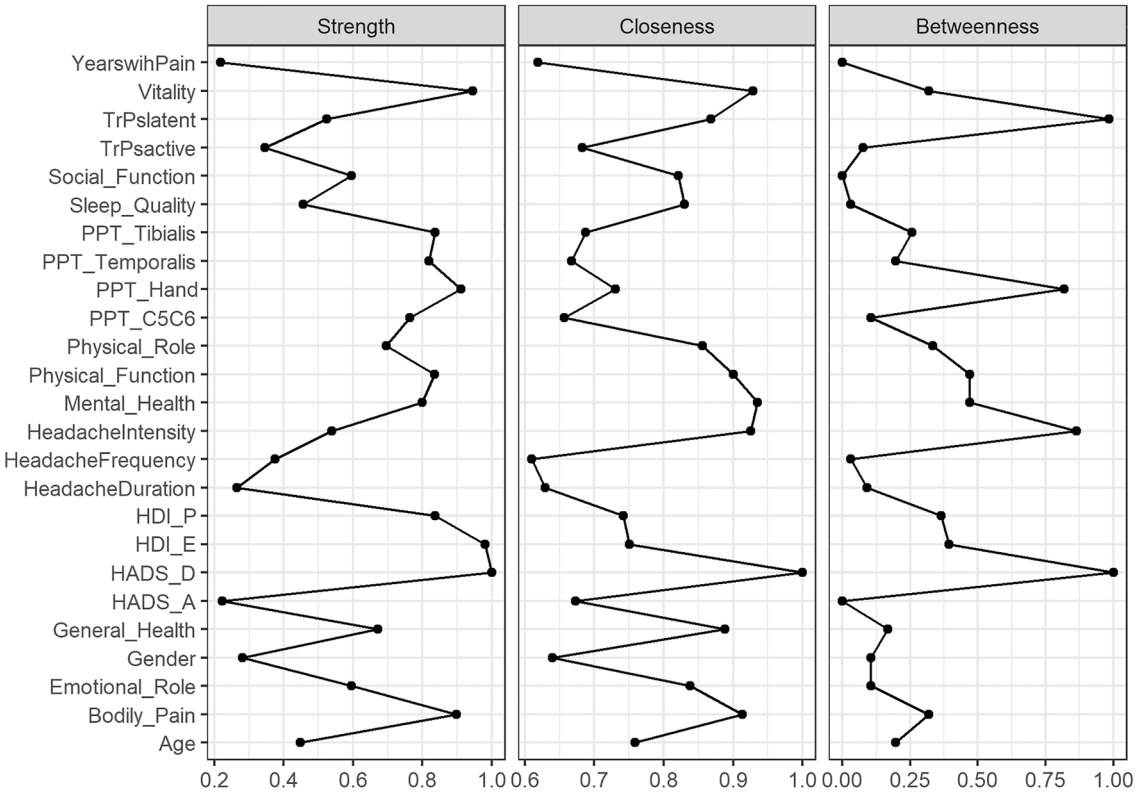

Fig. 2 Centrality measures of Strength, Closeness, and Betweenness of each node in the network. Centrality value of 1 indicates maximal importance, and 0 indicates no importance

Discussion

Current understanding supports the presence of several linked biopsychosocial mechanisms underlying the pathogenesis of TTH [45]. This study applied network connectivity analysis to understand the multivariate interaction between headache-related, psychological, health-related or psycho-physical variables in TTH. Consistent with modern theories on TTH features, the identified network supports a complex model where headache-related, psychological, health-related, and psycho-physical variables interact but also grouped in different clusters.

The first identified cluster (Fig. 4, green cluster) grouped PPTs and sex. The topic of widespread pressure pain hyperalgesia in individuals with TTH and more pronounced in female sex has been extensively reported in former headache literature [4]. In fact, the edge with the strongest weight was PPTs at the cervical spine and trigeminal area (temporalis muscle) supporting that pressure pain hyperalgesia is greater in the trigemo-cervical nucleus caudalis as it has been previous reported [46]. The network did not identify significant association of widespread PPTs with headache-related clinical parameters. This lack of association agrees with previous data, suggesting no linear associations between PPTs and pain and related disability outcomes in chronic pain [47]. Nevertheless, it is important to consider that lower PPTs predict future pain and disability in musculoskeletal pain conditions [48]. It is postulated that PPTs reflect aspects of peripheral or central sensitisation of the central nervous system, whereas headache-related variables are the clinical manifestation of pain; therefore, a non-linear, rather than linear, influence would be expected.

The data showed that TrPs and PPTs were grouped into different clusters (Fig. 4; red and green clusters, respectively), despite the fact that pressure pain hyperalgesia has been observed to be associated with a higher number of TrPs [25]. It has been postulated that prolonged nociception generated in peripheral tissues, specifically in muscles, could trigger sensitisation mechanisms and thus promoting the evolution of episodic to chronic TTH [49]. However, the clinical relevance of the musculoskeletal disorders found in TTH patients, including the presence of muscle TrPs, has not been fully elucidated [50]. Recently, it has been hypothesised that TrPs may be more relevant in certain subgroups of TTH patients [51].

The network identified that depressive levels showed the highest strength, closeness and betweeness centrality. In this scenario, mood disorders seem to play a key role

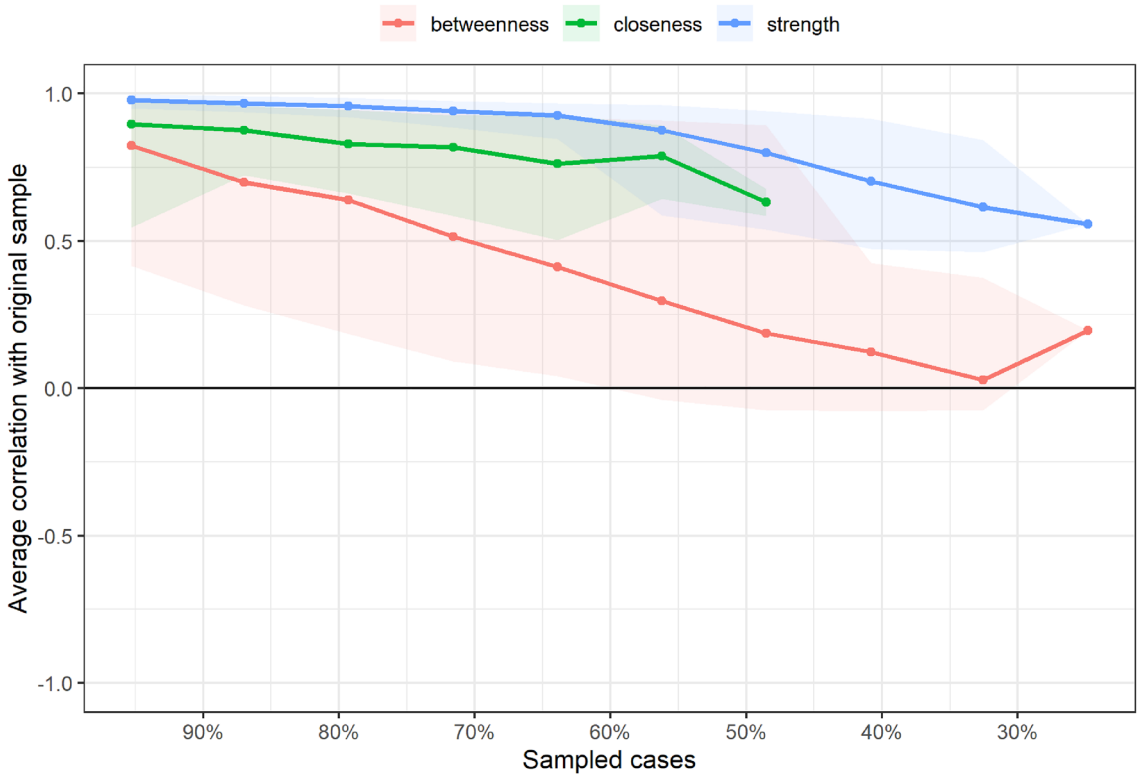

Fig. 3 Average correlations between centrality indices of networks sampled with persons dropped and networks built on the entire input dataset, at all follow-up time points. Lines indicate the means and areas indicate the range from the 2.5th quantile to the 97.5th quantile

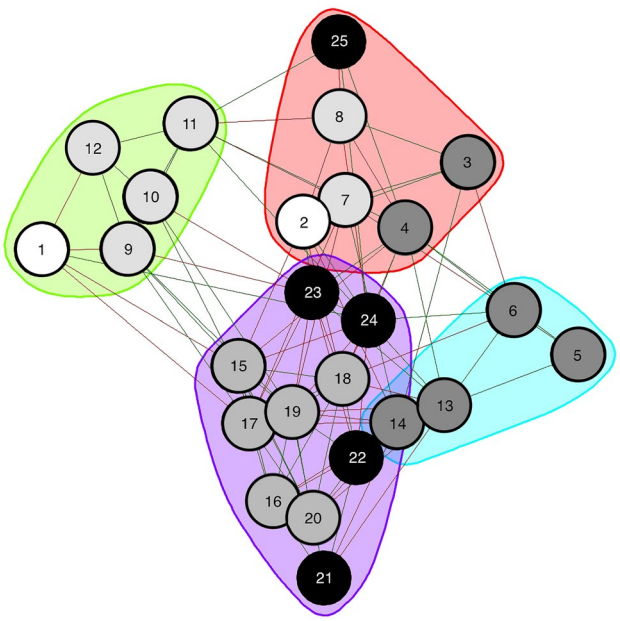

Fig. 4 Clusters identified found by the Louvain community detection algorithm. Blue cluster: headache-related variables; Green cluster: neurophysiological (PPTs) variables; Red cluster: trigger points and headache pain features; Purple cluster: Health-related as well as psychological/emotional variables

in TTH, so if clinicians want to influence other variables, e.g., those related to headache or quality of life, the best variable to focus treatment on would be depressive levels. Previous studies observed that depression, but not anxiety, is an important mediating factor of headache frequency and headache-related burden in people with TTH [10, 52]. This hypothesis would support why interventions, such as education or cognitive behaviour therapy, have been found to be effective for the management of TTH [53, 54]. The relevance of depressive levels is in line with the finding that the vitality domain also showed a high centrality of strength, since depression tends to decrease self-reported vitality. Another node that showed high closeness centrality and betweeness centrality was headache intensity, a variable that showed a small association with depressive levels in our network.

Overall, the results further reinforce theories suggesting that management of patients with TTH should include multimodal therapeutic approaches targeting headache-related pain and function (i.e., physical therapy approaches), psychological aspects (i.e., cognitive behavior, relaxation interventions), health-related (i.e., exercise programs) and also psychophysical pain mechanisms (i.e., pain neuroscience education programs) [55].

Although this is the first study using network analysis in TTH, and despite the positive aspects of its use, some

limitations should be recognized. First, conditional independence relationships as encoded by the edge weights in the network cannot be a source of confirmatory causal inference, but may provide indicative potential causal pathways [11]. In other words, biological plausibility between the connected variables is needed from a clinical point of view to determine the viability of the analysis. This assumption is supported in those relationships identified in the network. Second, the sample of patients with TTH was recruited from different university-based headache centers; therefore, it may be not representative of general population of headache sufferers. In fact, patients attending specialized headache centers are usually those who have a poor control of their headache. Similarly, quality of life of these patients may be lower than the headache general population and they may have more comorbidities, especially depressive levels.

Conclusion

The application of network connectivity analysis in a sample of patients with TTH revealed a model where headache-related, psychological, health-related, and psycho-physical variables interact but grouped in different clusters, with small associations between them. The network showed that depressive levels were the node with the highest centrality measures, supporting a relevant role of mood disorders in the model. These findings support that management of patients with TTH should include multimodal therapeutic approaches targeting all the aspects identified in the clusters.

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Data availability All data derived from this study are presented in the text.

Declarations

Conflicts of interest The authors declare no conflict of interest.

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