Title

Understanding the Psychophysiological Mechanisms related to Widespread Pressure Pain Hyperalgesia Underpinning Carpal Tunnel Syndrome: A Network Analysis Approach.

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Abstract

Objective: Current evidence suggests that carpal tunnel syndrome (CTS) involves widespread pressure pain sensitivity as manifestion of central sensitization. This study aimed to quantify mechanisms driving widespread pressure pain hyperalgesia in CTS by using network analysis. **Design:** Cross-sectional. **Setting:** Urban hospital. **Subjects:** 120 women with CTS who participated in a previous randomized clinical trial. **Methods:** Pain intensity, related-function, symptom's severity, depressive levels, and pressure pain threshold (PPTs) over median, radial and ulnar nerves, the cervical spine, the carpal tunnel, and the tibialis anterior were collected. Network analysis was used to quantify the adjusted correlations between the modelled variables, and to determine the centrality indices of each variable (i.e., the degree of connection with other symptoms in the network). **Results:** The estimated network showed several local associations between clinical variables and the psychophysical outcomes separately. The edges with the strongest weights were between PPT over the median and radial nerves (ρ: 0.34), function and depressive levels (ρ: 0.30), and PPT over the carpal tunnel and tibialis anterior (ρ: 0.29). The most central variables were PPT over the tibialis anterior (the highest Strength centrality), and PPT over the carpal tunnel (the highest Closeness and Betweenness centrality). **Conclusions:** This is the first study to apply network analysis to understand the multivariate mechanisms of individuals with CTS. Our findings support a model where clinical, depression, and widespread pressure pain sensitivity are connected, albeit within separate clusters. Clinical implications of current findings, such as developing treatments targeting these mechanisms, are also discussed.

Keywords: Carpal tunnel syndrome, pain, function, pressure pain, network analysis.

Understanding the Psychophysiological Mechanisms related to Widespread Pressure Pain Hyperalgesia Underpinning Carpal Tunnel Syndrome: A Network Analysis Approach.

Introduction

Carpal tunnel syndrome (CTS) is probably the most prevalent entrapment neuropathy of the upper extremity with an estimated lifetime prevalence of 3.1% and an estimated incidence rate of 1.73 per 1,000 person-year in the general population (1). Since CTS mainly affects middle-aged workers, it is associated with substantial health care costs and economic burden, particularly associated with loss of productivity (2).

Although CTS has been traditionally considered a localized peripheral neuropathy of the median nerve at the carpal tunnel, recent theories support the presence of more complex mechanisms involving the central nervous system (3). This theory is based on the presence of altered nociceptive pain and motor processing systems, manifested as generalized pressure (4) and thermal (5) pain hyperalgesia, enhanced wind-up (6), bilateral motor deficits (7), and reduced endogenous pain inhibition (8).

The presence of these central mechanisms may explain the heterogeneity in the clinical presentation observed in CTS patients. In fact, no direct association between clinical outcomes and electrodiagnostic findings is usually reported in this pain condition (9). In line with this hypothesis, previous studies have reported associations between clinical outcomes, e.g., pain and function, with psychological (e.g., depressive level) and psychophysical (i.e., pressure pain sensitivity) variables in women with CTS (10, 11) but of different strengths showing potential complex interactions between these variables.

Previous studies had used Pearson Product-Moment Correlation and linear regression to determine the associations between clinical, psychological, and psychophysical outcomes in CTS (10, 11). In fact, Pearson Product-Moment Correlation ignores the potential for pairwise associations to arise from their interaction with another variable (e.g. a common cause) (12).

Linear regression ignores the possibility of bidirectional relationships since the researcher is constrained to model the unidirectional relationship of the independent variables on the dependent variable. For example, one study investigated the relationships of function, finger motor force, and depressive levels on hand pain intensity (11). Such an analysis ignores the possibility that pain can itself impair motor performance, function, and alter depressive levels.

Network analysis provides a novel methodology to understand complex relationships that address the aforementioned limitations of Pearson product-moment correlations and linear regressions (13). Also, network analysis provides a method to identify the most important variables within the network, which could be used to potentially inform the design of novel therapeutic intervention studies (14). From a network perspective, CTS may emerge and be sustained by a collection of reciprocal interactions between complex psychological and physiological systems. Network analysis has only been recently used to better understand the psychological complexity of chronic pain disorders (15, 16); but this approach has already been routinely used to disentangle complex molecular pathways (17), general psycho-pathologies, e.g., post-traumatic stress disorder (18), personality disorders (19), and bipolar or major depressive disorder (20), to name a few.

This study applied network analysis to better understand the relationships between the clinical and psychophysical variables in women with CTS. The main aims of the current study were to 1) describe the network including pain intensity, related-function, symptom's severity, depressive levels, and pressure pain threshold (PPTs) in women with CTS; and 2) illustrate the potential of a network analysis perspective for understanding potential mechanisms of CTS, generating research questions, and improving treatment strategies.

Methods

Participants

Patients included in this study were derived from a previously published randomized clinical trial (21, 22). Briefly, adult women, aged 18 or older, with symptoms compatible with CTS attending a regional Hospital in Madrid (Spain) were screened for eligibility criteria. To be included, they had to: 1) exhibit symptoms (unilateral or bilateral) compatible with CTS (i.e. pain and/or paresthesia in the median nerve distribution); 2) positive findings on clinical examination (i.e., positive Tinel or Phalen signs), and, 3) deficits of sensory/motor median nerve conduction on electro-diagnostic examination according to the American Association of Electrodiagnosis, American Academy of Neurology, and the American Physical Medicine and Rehabilitation Academy guideline (23). Exclusion criteria included: 1, motor and/or sensory deficits in the ulnar/radial nerves; 2, previous surgery; 3, previous steroid injections; 4, multiple diagnoses on the upper extremity (e.g., cervical radiculopathy); 5, previous cervical, shoulder, or upper extremity trauma; 6, systemic diseases causing CTS such as diabetes mellitus, thyroid disease; 7, any systemic medical condition, e.g., rheumatoid arthritis or fibromyalgia; or, 8, pregnancy. The study was approved by Ethic Human Research Committee of the regional Hospital in Madrid (PI14/00364-HUFA12/14). All participants signed the written informed consent form before their inclusion in the study.

Outcomes

Data included in this network analysis included pain intensity, related-disability as the clinical variables, pressure pain threshold as psycho-pshycial variable, and depressive levels as psychological variable (24). We also assessed the history (years) with pain symptoms.

Pain intensity: A 10-point (0: no pain, 10: maximum pain) Numerical Pain Rate Scale (NPRS) was used to assess the mean level of hand pain, and the worst and lowest level of hand pain

experienced in the preceding week. The mean of the three scores was calculated and used in the analyses (25).

Related-Disability: The Spanish version of the Boston Carpal Tunnel Questionnaire (BCTQ) was used for assessing pain-related disability (26) since this questionnaire is valid and reliable for being used in individuals with CTS (27). The BCTQ includes a functional status scale that assesses the ability to perform eight common hand-related tasks, and a symptoms' severity scale including 11-items evaluating pain severity, numbness, and weakness at night and during the day. Each question is answered with a 5-point score (1: no complaint; 5: severe complaint) with higher scores indicating greater disability. Each scale was entered independently in the network analysis.

Depressive levels: The Beck Depression Inventory (BDI-II) was used for assessing depressive symptoms. The BDI-II is a 21-item self-reported questionnaire assessing affective, cognitive, and somatic symptoms of depression (28). The total score ranges from 0 to 21 which higher scores suggestive of higher depressive levels.

Pressure pain thresholds (PPT): the amount of pressure where a sense of pressure first changes to pain, were bilaterally determined in kPa with an electronic algometer (Somedic AB©, Farsta, Sweden) over the median, ulnar and radial nerves, the cervical spine, the carpal tunnel, and tibialis anterior as previously described (4). The order of assessment was randomized between participants. The mean of 3 trials at each site was calculated and used in the analyses. It has been previously found no side-to-side differences in widespread pressure pain sensitivity in women with CTS (4). We analyzed side-to-side differences in our sample with pairwise student t-tests and no significant differences were found (all, $P>0.80$). Therefore, the mean of both sides was used in the network analysis. The reliability of PPTs assessed over the upper extremity has been shown to be excellent (29).

Approach to Network Analysis

Software and Packages

Data were analyzed with R software (version 3.6.0) (30). Packages used to carry out the analysis include qgraph (version 1.6.5) (31) and glasso (version 1.11) (32) for network estimation, huge (version 1.3.4.1) (33) for variable transformation, and bootnet (version 1.4.6). All codes to reproduce the findings of the present study can be found on public github repository (https://bernard-liew.github.io/2020_cts_bn/3-network.html)

Network Estimation

A network is made up of nodes and edges. Presently, the nodes were made up of the 10 variables (i.e., pain intensity, function, symptoms' severity, depressive levels, PPT median nerve, PPT radial nerve, PPT ulnar nerve, PPT cervical spine, PPT carpal tunnel, PPT tibialis anterior) included as continuous variables. Edges represent connections between two nodes and are interpreted as the existence of an association between two nodes, controlling for all other nodes. Each edge in the network represents either positive regularised partial correlations (visualized as blue edges) or negative regularised partial correlations (visualized as red edges). The thickness and color saturation of an edge denotes its weight (the strength of the association between two nodes).

A nonparanormal transformation to ensure that the 10 variables ($\boldsymbol{y}$) were multivariate normally distributed was applied (33), a requirement to estimate a Gaussian Graphical Model (GGM) (34). Since $\boldsymbol{y}$ is multivariate normal, the following relationship can be described:

$$\boldsymbol{y} \sim N(\mathbf{0}, \boldsymbol{\Sigma})$$

where $\boldsymbol{\Sigma}$ (sigma) is the variance-covriance matrix. Next, the inverse of $\boldsymbol{\Sigma}$, $\boldsymbol{K}$ (kappa), was calculated and is termed the precision matrix

$$K \sim \Sigma^{-1}$$

Finally, the element κ_{ij} (row i, column j of $\boldsymbol{K}$) was standardized to obtain the partial correlation coefficient between variable y_i and variable y_j, after conditioning on all other variables in $\boldsymbol{y}$, $\boldsymbol{y}_{-(i,j)}$:

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

When estimating the network the graphical least absolute shrinkage and selection operator (LASSO) regularization LASSO (32) was used to elicit a sparse model. If $\boldsymbol{S}$ represents the sample variance– covariance matrix, LASSO aims to estimate $\boldsymbol{K}$ by maximizing the penalized likelihood function:

$$log\det(K) - trace\,(SK) - \lambda \sum_{<i,j>} |\kappa_{ij}|$$

Compared to a saturated model, a sparse model is one with a comparatively fewer number of edges to explain the covariation structure of the data - with the benefit that the ensuing model becomes more interpretable (12). The LASSO uses a tuning parameter to control the sparsity of the network, which we chose by minimizing the Extended Bayesian Information Criterion (EBIC) (35). The graphical LASSO was ran for 100 values of the λ logarithmically spaced between the maximal value of the tuning parameter at which all edges are zero (λ_{max} = 0.695), and λ_{max}/100. For each of these graphs the EBIC is computed and the graph with the lowest EBIC is selected ($\lambda_{EBIC=867.44} = 0.098$). This methodology is explained in more detail in previous tutorial papers (12, 36).

Node Centrality

Not all nodes in a network are equally important in determining the network's structure (36). Centrality indices provide a measure of a node's importance, which are based on the pattern of connections of a node of interest with its surrounding nodes. In network analysis, centrality indices are used 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

(37), and can constitute a guide for network interventions (14). In the current study, we calculated three centrality indices:

1) Strength centrality, defined as the sum of the weights of the edges (in absolute value) incident to the node of interest (38, 39). Clinically, a high strength node represents potentially good therapeutic targets, because a change in the value of this node has a strong direct, and quick (because of its strong direct connections) influence on the nodes within the network.

2) Closeness centrality (38), defined as the reciprocal of the sum of the length (inverse of the absolute value of edge's weight) of the shortest paths between a node of interest and all other nodes in the network. Clinically, a high Closeness node represents potentially good therapeutic targets, because the effects of a change in the value of this node will spread more quickly throughout the network, via direct and indirect connections to other nodes.

3) Betweenness centrality, defined as the number of times a node acts as a bridge along the shortest path between two other nodes. (37, 38). Clinically, a high betweenness node suggests that the node represents a potential mediator since it acts as a bridge for "information flow" connecting different nodes or even different clusters of nodes.

Network Edge and Node Centrality Variability

We assessed the variability of the edge weights and three centrality indices using bootstrapping (40). This step is essential given that networks were built using real-world clinical data with intrinsic sources of variation, with the consequence that the results may not necessarily translate to an independent dataset. We bootstrapped using 2000 iterations, 95% confidence intervals (CI) of all edge weights.

Given that LASSO regularization was used to retain only edges with non-zero weights, the edge-weight bootstrapped CIs should not be interpreted as significance tests of a null relationship hypothesis. Instead, these edge-weight CIs reflect the accuracy of the estimated edge-weights. With wide CIs, it becomes challenging to interpret the strength of an edge.

Interpreting the presence of an edge, however, is not affected by large CIs as the LASSO already performed a model selection. Also, the sign of an edge (positive or negative) can be interpreted regardless of the width of a CI as the LASSO rarely retains an edge in the model that can either be positive or negative.

To gain an estimate on the variability of the found centrality indices (CS-coefficient) - meaning if the order of centrality indices remains the same after re-estimating the network with fewer participants, we applied the participant-dropping subset bootstrap (40). This procedure drops a percentage of participants, re-estimates the network, and re-calculates the three centrality indices. The CS-coefficient reflects the maximum proportion of participants that can be dropped, such that with 95% probability the correlation (of the centrality value of the bootstrapped sample vs. that of the original) would reach a certain value (0.7 in current study, $CS_{cor=0.7}$). It is suggested that $CS_{cor=0.7}$ should be >0.25 and better if it is >0.5 (40).

Results

Descriptive characteristics of the cohort and scores of the variables used in the network analysis can be found in **Table 1**. **Figure 1** shows the network in our sample of women with CTS. From Figure 1, it can be readily observed that the correlations within clinical self-reported variables, and within the psychophysical variables, were stronger than the correlations between them. For example, the correlation between PPTs over the median and radial nerves (V2-V4) was 0.34, and that over the carpal tunnel and tibialis anterior (V6-V7) was 0.29 (Figure 1). Also, the correlation between function and depressive levels (V8-V10) was 0.30, and between function and symptoms' severity was 0.25 (Fig. 1). In contrast, the correlation between PPT over the median nerve and symptoms' severity was only -0.07 (Figure 1). The variability associated with the strength of each edge can be observed in **Figure 2.** As an illustration of the utility of Figure 2, the non-overlap of the 95%CI of the PPT over the median and radial nerves

(V2-V4) edge, with the 95%CI of PPT over the carpal tunnel and tibialis anterior (V6-V7) edge indicates that the strength of the former edge is significantly greater than the strength of the latter.

The top two nodes with the highest Strength centrality measure are PPT over the tibialis anterior and median nerve (Fig 3). The top two nodes with the highest Closeness centrality measure are PPT over the carpal tunnel and tibialis anterior, whilst the top two nodes with the highest Betweenness centrality measure are PPT over the carpal tunnel and symptom severity (**Fig. 3**). The Betweenness and Closeness measures of the network were extremely unstable at $CS_{cor=0.7} = 0$ and $CS_{cor=0.7} = 0.05$, respectively (**Fig. 4**). The Strength centrality measured were relatively stable ($CS_{cor=0.7} = 0.36$) (Fig. 4).

Discussion

This is the first study to apply network analysis to understand the mechanisms of women with CTS. Consistent with current research on CTS mechanisms, the current network supports a model where pain and function, depressive levels and widespread pressure pain sensitivity are associated. However, the modeled associations tended to be grouped into two clusters - a neurophysiological cluster including PPTs and a symptom cluster including clinical features. These separate clusters reflect two different, but associated, spectrums of a neuropathic pain condition such as CTS, wherea clinical and neurophysiological outcomes are associated.

The identified neurophysiological cluster was represented by PPTs, a psychophysical outcome commonly used for assessing widespread pressure hyperalgesia (a manifestation of central sensitization), whereas the symptomatic cluster was represented by pain intensity, function, symptoms' severity, and depressive levels. Interestingly, both clusters do not exhibit strong associations in the network supporting the finding that clinical and neurophysiological variables represent two different dimensions of the CTS disorder spectrum. Given the small

associations between the clusters, our findings support the need to collect both clinical and neurophysiological outcomes in individuals with CTS to obtain a holistic understanding of the disease process. The small association between the two network clusters could explain the common finding of a lack of association between clinical symptoms (e.g., pain symptoms) and electrodiagnostic findings (9). In fact, it has been previously observed that electrodiagnostic findings are not either associated with widespread pressure pain hyperalgesia in women with CTS (41). The results of a randomized clinical trial showing that clinical outcomes (i.e., pain), but not psychophysical outcomes (i.e., PPTs) improved after the application of a physical therapy program would support the present study's findings (42). Nevertheless, the network identified that the strongest link between neurophysiology and symptoms clusters was between PPT at the carpal tunnel and symptoms' severity (V6-V9 pathway) supporting the relevance of peripheral nociception (as expressed by lower PPTs over the carpal tunnel) and symptoms' severity. It is also possible that neurophysiological and symptomatic clusters have a link or mediator not identified in this study. Future studies using network analyses would benefit from including a greater number of psychophysical (i.e., wind-up, conditioned pain modulation) and psychological (i.e., anxiety, kinesiophobia, sleep quality) variables to understand the complex relationships between clinical, psychological, and neurophysiological outcomes in CTS.

The network also revealed that those edges with the strongest weights were PPTs over median nerve with PPT over radial nerve (V2-V4), PPT over the carpal tunnel with PPT over tibialis anterior (V6-V7) and function with depressive levels (V8-V10). The strong associations between the affected (PPT over the median nerve) and non-affected (PPT over the radial nerve and tibialis anterior) region, potentially reflect the duel presence of both peripheral and central sensitization processes in oru sample of women with CTS. The presence of altered nociceptive pain processing is typically manifested by widespread pressure pain hypersensitivity (4).

PPT over the median nerve and tibialis anterior showed the highest centrality strength measures, meaning that these nodes can directly influence other nodes, such as PPT over the radial nerve, or be directly influenced by them. In such a scenario, the network suggests that if clinicians want to influence other variables, e.g., clinical symptoms, the best variable to focus treatment on would be to influence peripheral (PPT median nerve) and central sensitization (PPT tibialis anterior) mechanisms. In agreement with the current findings, Roh et al found that centrally-mediated symptoms were associated with poorer clinical short-term outcomes after surgery in CTS (43). This finding may be related to the fact that surgery mainly targets peripheral, but not central, mechanisms. Similarly, preliminary evidence suggests that central sensitization is associated with poorer outcomes in response to surgical or conservative treatment in people with musculoskeletal pain (44). However, the role of central sensitization as a prognostic factor for CTS management is controversial. An old cohort study reported that the presence of central sensitization was not associated to positive short-term effects of physical therapy treatment in women with CTS (45). In fact, the posterior validation of this cohort study was not supported in a further randomized controlled trial (46). The prognosis role of both peripheral and central sensitization mechanisms in individuals with CTS needs further studies.

The network also revealed that depressive levels (V10) were associated with symptoms' severity (V9), but largely through the effects of function (V8). The mediating role of function on the relationship between depression and symptoms' severity with pain intensity in women with CTS has been previously reported (47). The presence of complex interactions between clinical, psychophysical, and psychological outcomes would suggest that management of CTS should include multimodal therapeutic interventions targeting pain and function (i.e., physical therapy, surgery), psychological aspects (i.e., cognitive behavior approaches), and underlying psychophysical mechanisms (i.e., neuro-modulatory pain approaches). These assumptions are also supported by a long-term clinical trial where conservative treatment targeting peripheral

and central mechanisms was effective for the management of individuals with CTS (21, 22). Hence, the importance of the PPT findings over the median nerve or carpal tunnel and tibialis anterior identified in the network agree with recent theories emphasizing the importance of targeting both peripheral and central sensitization mechanisms in patients with CTS (3). This aspect is clinically relevant since most interventions recommended by Clinical Guidelines, e.g., orthoses, wrist exercises, wrist manual therapy, are mainly focused on the wrist/carpal tunnel (48). These interventions are able to manage peripheral, but not central, sensitization since they target the potentially injured area. A recent meta-analysis has found small differences between peripherally physical therapy and surgical procedures for the management of CTS (49). The presence of central mechanisms in individuals with CTS supports that clinical management of this condition needs to extend beyond local pathology (i.e., the median nerve entrapped at the carpal tunnel), to incorporate strategies directed at normalizing the central nervous system. These strategies could include management of segmentally-related areas (such as the cervical spine, the shoulder and the elbow), the inclusion of global exercises and pain neuroscience education sessions (3).

Despite the positive aspects of the use of network analysis, potential limitations must be also acknowledged. Given that only women with CTS were included in the present analysis, findings should not be extrapolated to men with this neuropathic pain condition. Conditional independence relationships, as encoded by the edge weights in the networks, cannot be a source of confirmatory causal inference, but may provide indicative potential causal pathways (12, 50). For example, if all relevant variables are modelled in a network, an observed adjusted association between variables X and Y would only be possible if, either X causes Y, Y causes X, X and Y exhibits a bidirectional relationship, or X and Y have a common effect (12, 50). Hence, network analysis may be conceptualized as a highly exploratory hypothesis-generating technique, indicative of potential causal effects. Further replication studies testing the proposed

model on independent cohorts of patients and considering the limitations exposed here would help to elucidate better the clinical application of network analysis. Despite the limitations, our findings provide candidate therapeutic targets for future clinical intervention trials.

Conclusions

The application of network analysis in women with CTS revealed the presence of two different clusters, one neurophysiological, including widespread PPTs, and one symptomatic (clinical), with poor direct associations between them. The network also showed that PPTs over the affected (median nerve or carpal tunnel) and PPTs over non-affected remote areas (tibialis anterior) were the nodes with the highest centrality strength. Current findings support a model where pain, function, depression, and widespread pressure pain sensitivity are connected, albeit in separate clusters. Clinical implications of current findings, such as developing treatments targeting these mechanisms, are also discussed.

Figure Legends

Figure 1: Network analysis of the association between clinical, psychological, and psycho-physical clinical 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 (blue 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).

Figure 2: Bootstrapped 95% quantile confidence interval of the estimated edge weights of the network. "Bootstrap mean" reflects the average magnitude of edge weights across the bootstrapped samples. "Sample" reflects the magnitude of edge weights of the original network built on the entire input dataset. Abbreviation: V1-Mean pain intensity; V2-PPT median nerve; V3-PPT ulnar nerve; V4-PPT radial nerve; V5-PPT neck region; V6-PPT carpal tunnel; V7-PPT tibialis anterior region; V8-function; V9-Symptom severity; V10-Depressive levels.

Figure 3: Centrality measures of Closeness, Strength, and Betweenness of each node in the network. Centrality value of 1 indicates maximal importance, and 0 indicates no importance.

Figure 4: 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.

Figures

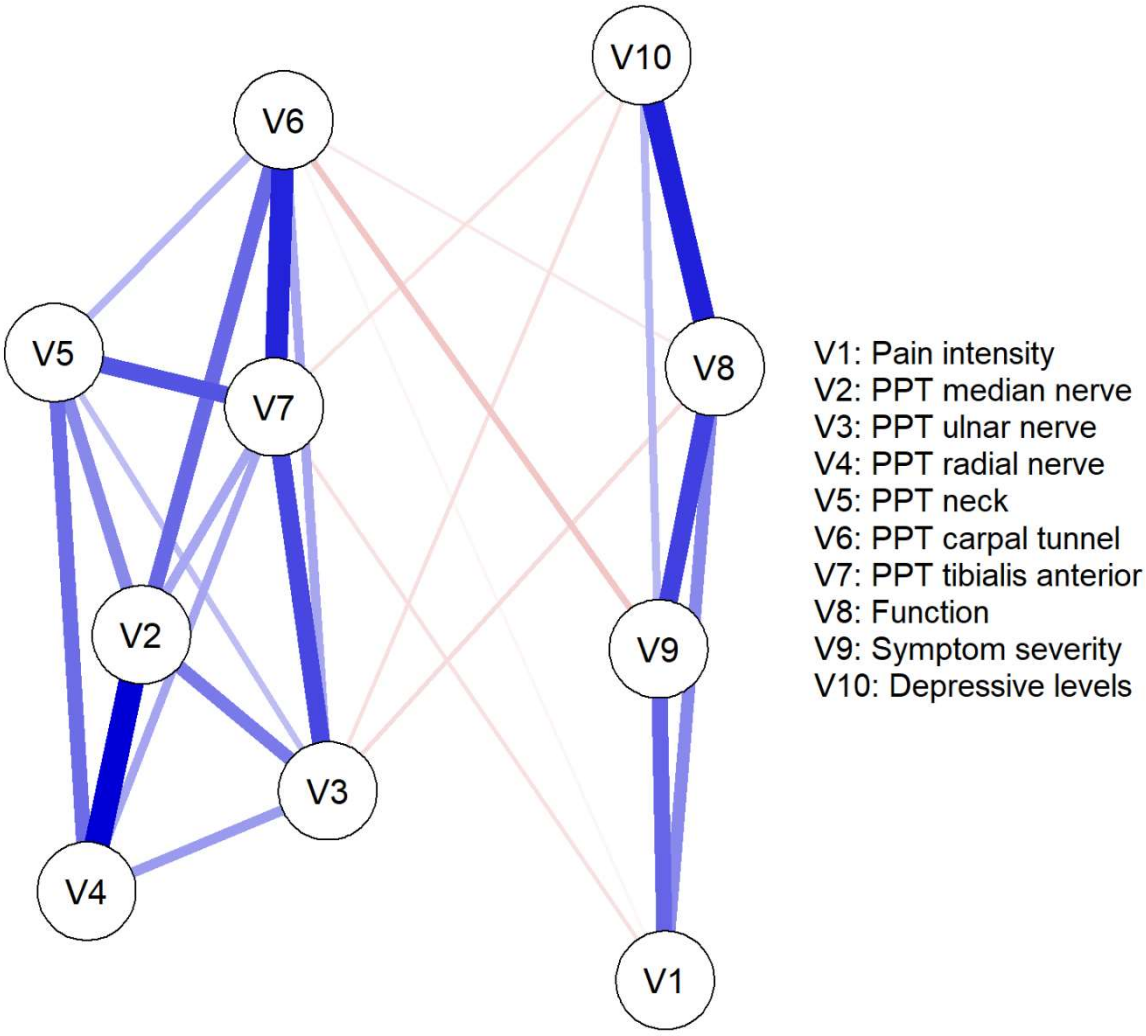
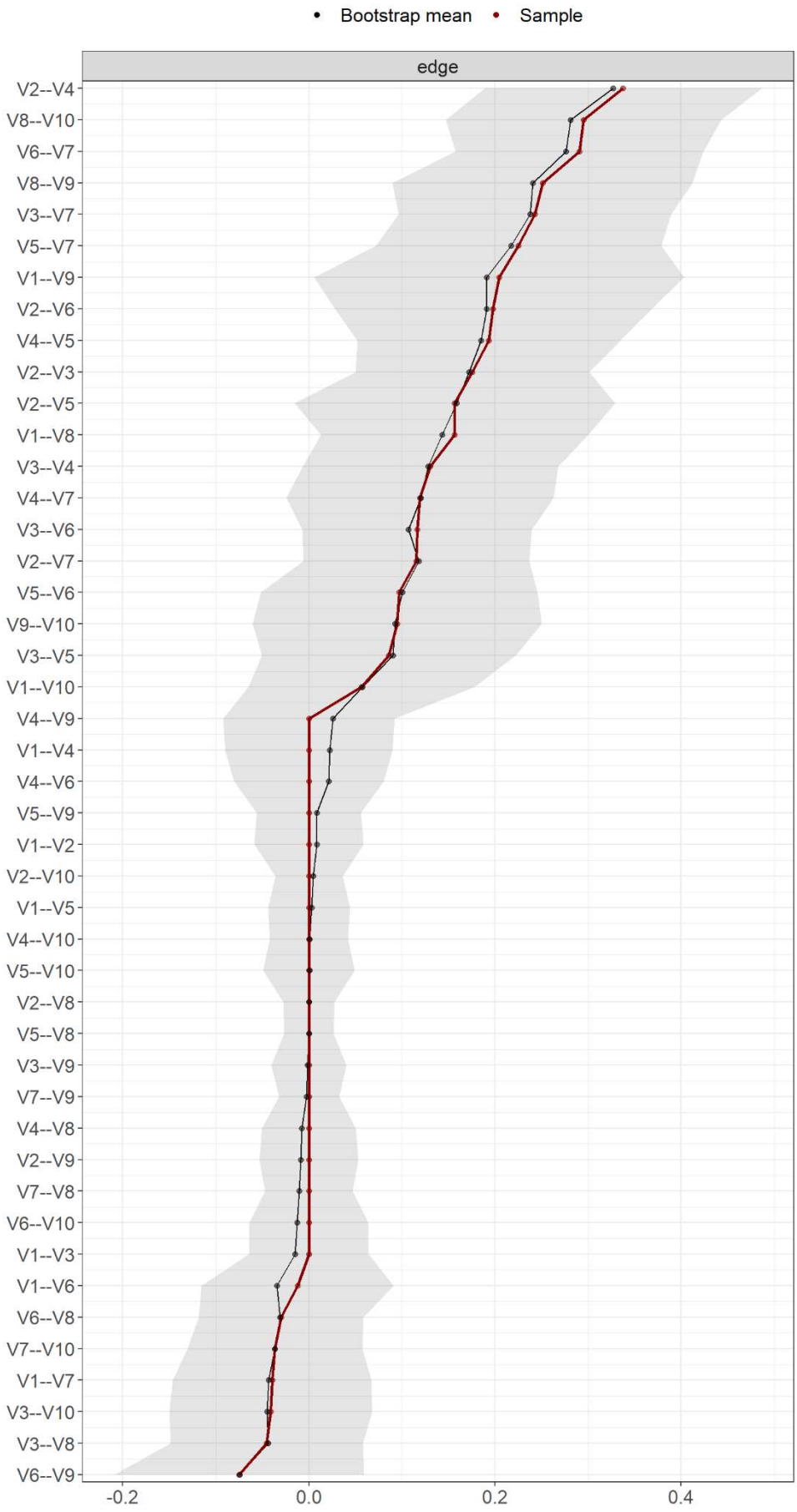


Figure 1


Bootstrap mean
Sample
edge
V2--V4
V8--V10
V6--V7
V8--V9
V3--V7
V5--V7
V1--V9
V2--V6
V4--V5
V2--V3
V2--V5
V1--V8
V3--V4
V4--V7
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V6--V10
V1--V3
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V7--V10
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V6--V9
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0.2
0.4

Figure 2

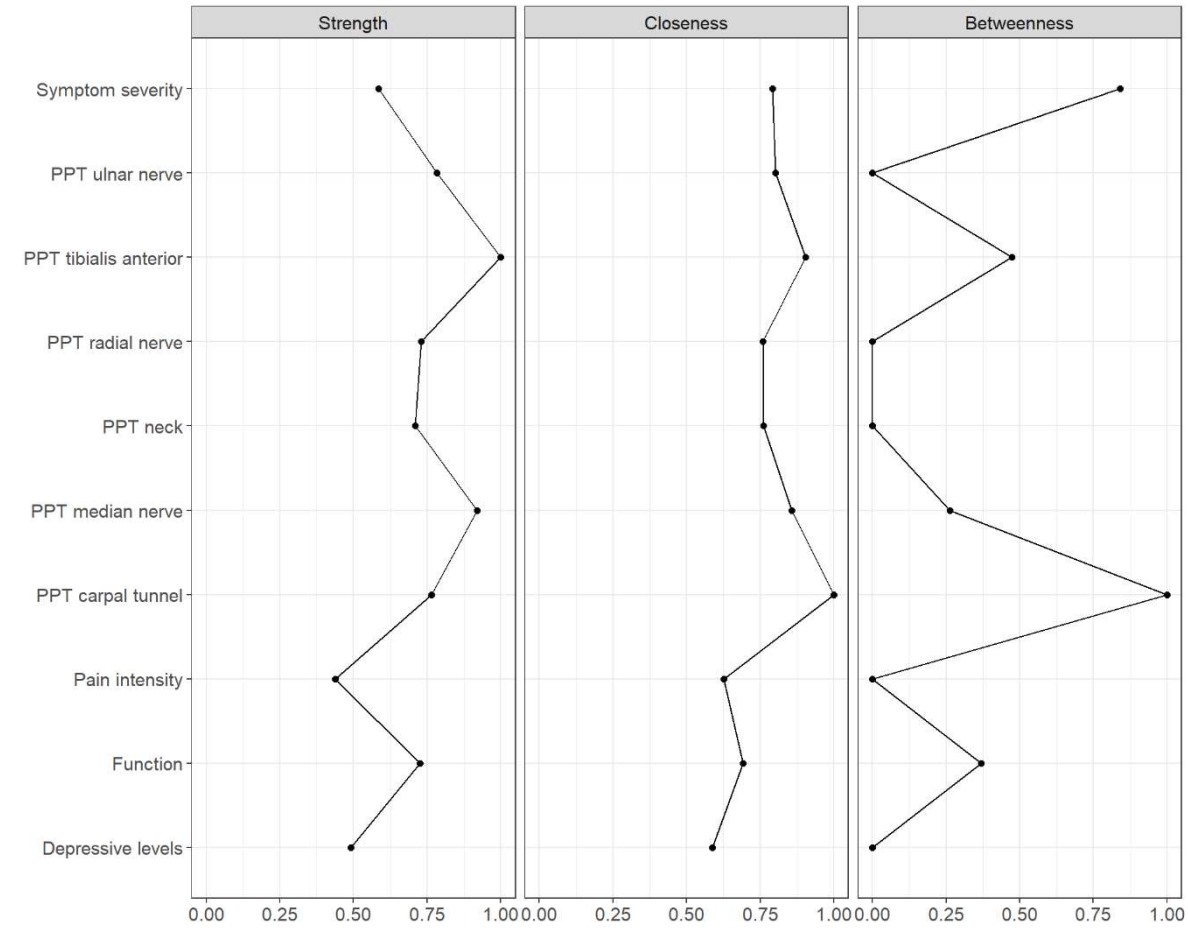

Figure 3

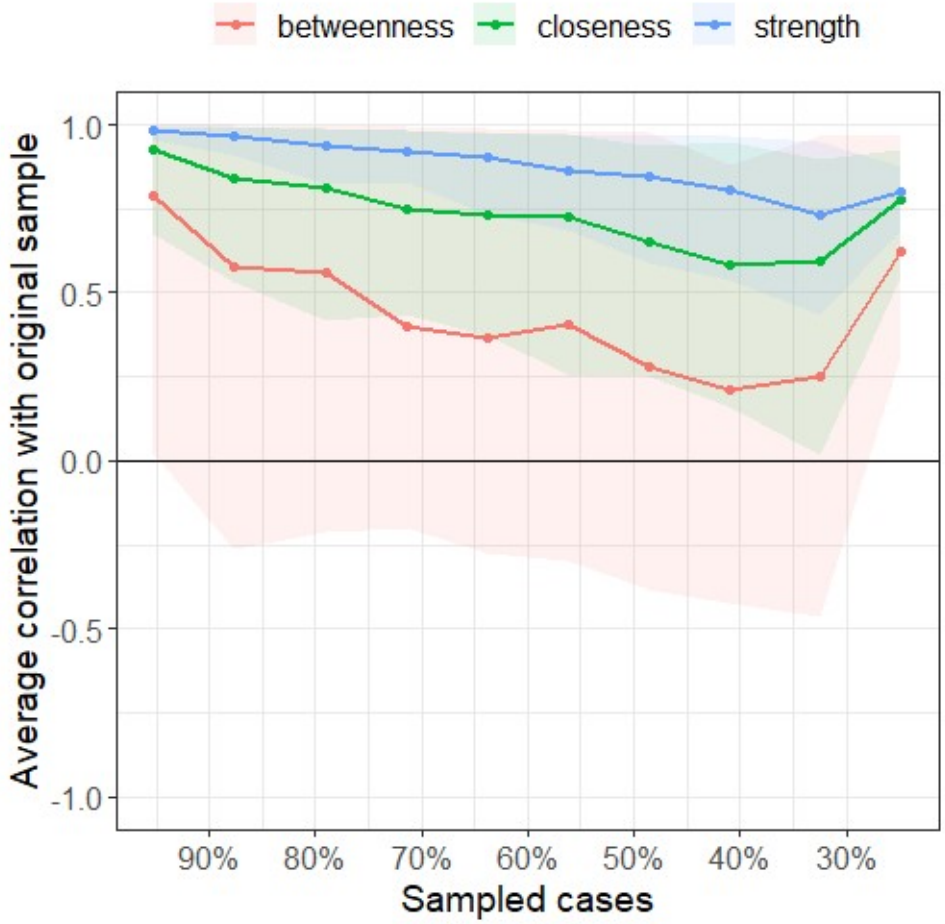

Figure 4

Table

Baseline variable	Mean (SD)
age	46.82(9.17)
pain_years	3.24(2.91)
pain	5.02(1.75)
ppt_medn	194.32(54.39)
ppt_uln	299.3(80.82)
ppt_radn	226.43(64.02)
ppt_neck	172.2(48.47)
ppt_cts	352.77(113.98)
ppt_ta	325.2(88.15)
cts_func	2.35(0.57)
cts_severe	2.63(0.66)
dep	3.84(2.37)

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