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Spectral Clustering Reveals Different Profiles of Central Sensitization in Women with Carpal Tunnel Syndrome

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Abstract: Identification of subgroups of patients with chronic pain provides meaningful insights into the characteristics of a specific population, helping to identify individuals at risk of chronification and to determine appropriate therapeutic strategies. This paper proposes the use of spectral clustering (SC) to distinguish subgroups (clusters) of individuals with carpal tunnel syndrome (CTS), making use of the obtained patient profiling to argue about potential management implications. SC is a powerful algorithm that builds a similarity graph among the data points (the patients), and tries to find the subsets of points that are strongly connected among themselves, but weakly connected to others. It was chosen due to its advantages with respect to other simpler clustering techniques, such as k-means, and the fact that it has been successfully applied to similar problems. Clinical (age, duration of symptoms, pain intensity, function, and symptom severity), psycho-physical (pressure pain thresholds—PPTs—over the three main nerve trunks of the upper extremity, cervical spine, carpal tunnel, and tibialis anterior), psychological (depressive levels), and motor (pinch tip grip force) variables were collected in 208 women with clinical/electromyographic diagnosis of CTS, whose symptoms usually started unilaterally but eventually evolved into bilateral symmetry. SC was used to identify clusters of patients without any previous assumptions, yielding three clusters. Patients in cluster 1 exhibited worse clinical features, higher widespread pressure pain hyperalgesia, higher depressive levels, and lower pinch tip grip force than the other two. Patients in cluster 2 showed higher generalized thermal pain hyperalgesia than the other two. Cluster 0 showed less hypersensitivity to pressure and thermal pain, less severe clinical features, and more normal motor output (tip grip force). The presence of subgroups of individuals with different altered nociceptive processing (one group being more sensitive to pressure pain and another group more sensitive to thermal pain) could lead to different therapeutic programs.

Keywords: carpal tunnel syndrome; spectral clustering; pain; groups; sensitization

1. Introduction

Carpal tunnel syndrome (CTS) is considered the most prevalent entrapment neuropathy of the upper extremity. Although prevalence data may vary depending on the definition used for CTS [1], it is estimated that CTS has a lifetime prevalence of 3.1% and an incidence rate of 1.73 per 1000 person-year in the general population [2]. The prevalence can reach 10% in middle-age workers [3,4]. This condition creates substantial health care costs and economic burden, particularly in relation to loss of work [5].

Sensory disturbances, e.g., pain, numbness, tingling, and/or paresthesia in those areas innervated by the median nerve are the symptoms most commonly experienced by patients with CTS, although fine motor deficits are also frequently present [6]. Whereas CTS has been traditionally considered a localized peripheral neuropathy associated to the entrapment of the median nerve at the carpal tunnel, recent theories support the presence of an alteration of central nociceptive processing [7]. This is based on the observation of generalized pressure [8] and thermal [9] pain hyperalgesia and enhanced wind-up [10] in extra-median nerve territories, all signs associated to impaired central mechanisms. Additionally, the appearance of bilateral deficits in pinch tip grip force and motor control in women with strictly unilateral sensory symptoms also support brain mechanisms underlying CTS [11].

The interaction between peripheral and central sensitization mechanism can explain the heterogeneity in the clinical presentation observed in these patients. Identification of subgroups of patients with different pain mechanisms can help provide a better classification of this condition and the development of more adequate therapeutic strategies. There is a lack of studies investigating different profiles and subgrouping in individuals with CTS. The only study investigating different profiles in women with CTS identified two groups of individuals with CTS, one hypersensitive (higher pressure and thermal pain sensitivity) and the other less sensitive (with lower pressure and thermal pain sensitivity) by using a “predetermined” clinical classification originally developed for identifying individuals with CTS who were likely to respond positively to a physical therapy intervention [12]. This subgrouping was based on “a priori” determination of different variables, which may account for potential biases.

Spectral clustering (SC) is a technique that is extensively studied in image processing, data mining, and machine learning. It is an unsupervised learning model, meaning that no “a priori” hypotheses need to be injected by the expert (clinician); therefore, it provided results are data-driven and unbiased from previously proposed groupings [13]. The results obtained by SC usually outperform other traditional approaches (such as k-means) and can be solved efficiently by standard linear algebra methods. The objective of the current study was to investigate if the application of SC is able to identify subgroups (clusters) of women with CTS differing in clinical, psycho-physical, psychological, and motor variables to propose different profiles of patients. Secondary, this subclassification could also be related to potential specific therapeutic interventions.

2. Methods

2.1. Participants

Participants included in this study were the same as in a previous study using Bayesian Linear Regression as the method of analysis [14]. In summary, patients with clinical symptoms (i.e., pain and/or paresthesia in the hand associated to median nerve distribution increasing during the night), positive physical examination (i.e., positive Tinel or Phalen signs), and electrodiagnostic findings (e.g., deficits of sensory and/or motor median nerve conduction) [15] attending a local urban hospital in Madrid (Spain) from January 2017 to June 2019 were recruited. Exclusion criteria included: (1) motor or sensory deficits in ulnar or radial nerves; (2) previous surgery or steroid injections in the upper extremity; (3) other painful diagnoses on the upper extremity (e.g., cervical radiculopathy); (4) previous trauma; (5) any systemic underlying medical disease that causes CTS (e.g., diabetes mellitus) or influencing perception (e.g., fibromyalgia); and (6) pregnancy. Written informed consent was obtained from all participants. The Ethic Human Research Local Committee (PI14/00364-HUFA12/14) approved the study design.

2.2. Self-Reported Outcomes

Age, years with symptoms, side of symptoms, intensity of hand pain, pain-related disability, and depressive symptoms were self-reported and collected. An 11-point (0: no pain, 10: maximum pain) Numerical Pain Rate Scale [16] (NPRS) was used to evaluate mean pain symptoms, as well as the worst and the lowest levels of pain symptoms experienced

in the preceding week. The mean was calculated and used in the primary analyses. Pain-related disability was assessed with the Spanish version [17] of the Boston Carpal Tunnel Questionnaire (BCTQ), consisting of a functional status and a symptom severity scale [18]; higher scores are indicative of a worse function or higher symptom severity. This questionnaire has been shown to be valid, reliable, and responsive for use in people with CTS [19]. The Beck Depression Inventory (BDI-II) was used for assessing symptoms potentially compatible with depression [20].

2.3. Quantitative Sensory Testing

Pressure and thermal pain thresholds were calculated to assess sensitivity to pressure and thermal stimuli. Pressure pain threshold (PPT), defined as the minimal pressure to be applied for eliciting a first sensation of pain with an algometer (Somedic AB©, Farsta, Sweden), was bilaterally measured over the main three nerve trunks of the upper extremity (i.e., median, ulnar and radial), cervical spine, carpal tunnel, and tibialis anterior, as previously described [8,14]. Heat (HPT) and cold (CPT) pain thresholds were also bilaterally calculated with a Thermotest System (Somedic AB© Farsta, Sweden) on the carpal tunnel and the thenar eminence, as previously described [9,14]. Three consecutive measurements on each point were obtained and the mean was calculated. Since no side-to-side differences were found, the mean of left and right sides for each measure was used in the analysis. Quantitative sensory testing has shown excellent reliability for assessing PPTs [21] and fair to excellent for HPT and CPT assessment [22].

2.4. Motor Output

Pinch tip grip force (pounds) was calculated with a pinch grip dynamometer (Psymptec©, Spain) as previously described [11]. All pinch tip grips (i.e., between the thumb and the second, third, fourth, and fifth fingers) were calculated. Again, the mean of three trials was used in the analysis; the reliability for tip grip assessment has been found to be excellent [23].

2.5. Data Preprocessing

Before applying the spectral clustering (SC) algorithm, the dataset was prepared as described in a previous work [14]. Summing up, out of 220 initial patients, 12 were removed due to missing or erroneous samples. Then, for the remaining 208, categorical features of electromyography (EMG) affection (minimal, moderate, severe) and affected side (left, right, bilateral) were one-hot encoded. For instance, two new indicator features were created for EMG affection: minimal affection and severe affection. Hence, a patient with severe affection would have a value of zero in the “minimal affection” indicator feature and one in the “severe affection” indicator, while a patient with moderate affection would have a zero in both. Finally, all variables were standardized to a null mean value and unitary standard deviation, by applying $\tilde{x} = \frac{x - \mu_x}{\sigma_x}$, where x is the original feature, σ_x represents its sample standard deviation, μ_x its sample mean, and \tilde{x} is the resulting standardized feature. Table 1 summarizes the statistics for the complete dataset.

2.6. Clustering Algorithms

Clustering techniques seek to automatically detect sets of points that are similar among them, but different from the rest, thus forming a cluster [24]. Among the many different clustering algorithms that have been proposed, k -means is perhaps the simplest and the most commonly employed. It starts by randomly positioning k centroids among all the data points (k is chosen beforehand and represents the number of clusters to find). Then, it iteratively assigns each data point (each patient) to the closest centroid (in terms of Euclidean distance) and recalculates the position of each centroid as the mean of all the points assigned to it. This process repeats until convergence.

Table 1. Clinical and neurophysiological data of the sample ($n = 208$).

	Mean	SD	Min.	Max.
Age (years)	45.5	9.1	21.0	64.00
Years with Pain	3.5	3.0	0.5	17.00
Right Side Affected *	0.9	0.3	0.00	1.00
Left Side Affected *	0.75	0.45	0.00	1.00
EMG Minimal affectation #	0.3	0.45	0.00	1.00
EMG Severe affectation #	0.4	0.5	0.00	1.00
Pain Intensity (NPRS, 0–10)	5.8	2.1	0.00	10.00
Symptom Severity (BCTQ, 1–5)	2.75	0.7	1.25	5.00
Function (BCTQ, 1–5)	2.4	0.75	1.0	4.62
Depression (BDI-II, 0–21)	4.6	2.9	0.0	15.0
CPT carpal tunnel (°C)	19.4	6.7	5.00	30.2
CPT thenar eminence (°C)	19.2	6.45	5.00	29.75
HPT carpal tunnel (°C)	39.9	2.6	35.2	48.45
HPT thenar eminence (°C)	40.1	2.85	32.1	48.2
PPT median nerve (kPa)	192.55	50.7	57.65	365.5
PPT ulnar nerve (kPa)	293.7	73.6	115.5	465.5
PPT radial nerve (kPa)	225.25	61.9	109.5	433.5
PPT cervical spine (kPa)	171.1	53.75	57.0	499.5
PPT carpal tunnel (kPa)	346.05	95.4	130.5	731.0
PPT tibialis anterior (kPa)	322.85	85.5	110.5	652.5
Thumb-index finger pinch tip (pounds)	4.15	1.7	0.5	8.5
Thumb-little finger pinch tip (pounds)	1.1	0.8	0.0	5.5
Thumb-middle finger pinch tip (pounds)	4.0	1.9	0.0	9.5
Thumb-ring finger pinch tip (pounds)	2.45	1.4	0.0	6.35

EMG: Electromyography data; NPRS: Numerical Pain Rating Scale; BCTQ: Boston Carpal Tunnel Questionnaire; BDI-II: Beck Depression Inventory; CPT: Cold Pain Thresholds; HPT: Heat Pain Thresholds; PPT: Pressure pain Thresholds. # 1: patient has minimal or severe affectation, respectively; 0: patient has moderate affectation. * 1: patient has right or left symptoms, respectively; 0: patient has no left or right symptoms (bilateral).

Gaussian Mixture clustering can be seen as a generalization of k-means, where points are no longer assigned to a single cluster, but rather to all of them with a degree of probability. Furthermore, the resulting clusters must not be spherical, and can instead be ellipsoidal in shape. The SC algorithm, which will be described in Section 2.7, builds a similarity graph between any two data points, and tries to find the sets of points that are strongly connected among themselves, but weakly connected to others, hence allowing clusters with arbitrary shape. Finally, (agglomerative) hierarchical clustering begins assigning each point to its own cluster and works by successively combining any two clusters which are most similar, until a given number of clusters k remains. Similarly to SC, this technique allows to find arbitrarily shaped clusters.

For clustering problems where most features are in \mathbb{R} , any of these clustering techniques could be used. However, algorithms such as SC or hierarchical clustering are often preferred for their extended clustering capabilities (e.g., clusters can have arbitrary shapes and considerably different sizes).

2.7. Spectral Clustering

SC is a clustering algorithm that considers all the data points (the patients) as an undirected graph $G = \{V, E\}$, where each vertex $v \in V$ represents one data point, and each edge $e \in E$ weights ($w_{i,j}$) the similarity between any two vertices (e.g.: $w_{i,j}$ will be high for two very vertices i and j). The objective of the SC algorithm will be to find k partitions (also known as cuts or clusters) in the graph such that: (1) among partitions, the edges have small weights (in different clusters, patients are dissimilar); (2) within a partition, the edges have high weights (within a cluster, patients are similar), and (3) the partitions are of similar sizes.

All three previous goals are combined in the Normalized Cut cost function, theoretically allowing to solve the problem via its optimization [25]. However, since this has been

proven to be an NP-complete problem, normalized SC was proposed as an approximation [24]. The pseudocode for normalized SC is shown in Algorithm 1. Pairwise Gaussian similarity was chosen as the similarity function, as is typical for \mathbb{R}^n input data.

Algorithm 1: Normalized Spectral Clustering using pairwise Gaussian similarity

Input: Standardized data points x_1, x_2, \dots, x_N , Number of clusters $k = 3$, Gaussian variance $\sigma = 10$

Output: Label of the cluster $C_{i \in V} \in \{1, 2, \dots, k - 1\}$ to which each point x_i has been assigned.

- Compute the similarity matrix $W = (w_{i,j})$, where $w_{i,j}$ is the pairwise Gaussian similarity between any two points x_i and x_j : $w_{i,j} = \exp\left(-\frac{\|x_i - x_j\|^2}{2\sigma^2}\right)$
 - Build the normalized graph Laplacian matrix: $L_{rw} = I - D^{-1}W$, where I is the identity matrix and $D = (d_{i,i})$ is a diagonal matrix with $d_{i,i} = \sum_{j \in V} w_{i,j}$
 - Obtain the k eigenvectors u_1, u_2, \dots, u_k associated with the k smallest eigenvalues of L_{rw} .
Note: $u_i \in \mathbb{R}^N$
 - Apply k -means clustering over the transformed data points defined as $y_i = (u_{i,1}, u_{i,2}, \dots, u_{i,k})' \in \mathbb{R}^k$.
 - The cluster label C_i assigned to each y_i by k -means is the same label that is finally returned for each original data point x_i
-

2.8. Statistical Analysis of the Clusters

After applying the SC algorithm to the data, the mean and standard deviation was computed for each continuous feature within each cluster, and a one-way ANOVA test was employed to find which variables had a statistically different mean value between (at least two) clusters as previously done in patients with tension type headache [26]. Similarly, a Chi-square test was employed for binary features. ANOVA and Chi-square tests were performed using Python library Scipy (ver. 1.6.2) [27] and the p-values were corrected with Python library statsmodels (ver. 0.12.1) [28] with Holm–Bonferroni correction for multiple comparisons.

3. Results

As previously reported, 208 women with CTS were finally included in the current analysis [14]. As expected according to symmetry, 83 (40%) had strictly unilateral symptoms (58 right side, 25 left side), whereas the remaining 125 (60%) had bilateral symptoms. A total of 61 (29%) had minimal CTS, 69 (33%) had moderate CTS, and 78 (38%) had severe CTS according to EMG data. SC reveals three different clusters with different distributions in the variables, as visualized in Figure 1.

Table 2 summarizes the mean values and standard deviations of all the variables for every cluster. By analyzing Table 2, one cluster (number 1) grouped those patients exhibiting the highest pain intensity, worst function and highest symptom severity, highest depressive levels, lowest widespread PPTs, and lowest pinch tip grip force with all the fingers when compared with the other two clusters (numbers 0 and 2). Cluster 1 also included older women than the other two clusters and grouped the greatest proportion of individuals with minimal EMG affection. No differences in the side of the symptoms were observed among the three clusters.

Similar to cluster 1, patients in cluster 2 also showed high pain intensity, symptom severity, and depressive level, but lower widespread PPTs and higher pinch tip grip force than those in cluster 1. Interestingly, patients in cluster 2 exhibited the most impaired heat pain thresholds, i.e., the lowest HPTs and highest CPTs, hence constituting the group with the worst generalized thermal pain hyperalgesia. Cluster 0 showed the least pressure and thermal pain hyperalgesia, the most favorable clinical features, and the highest tip grip pinch force.

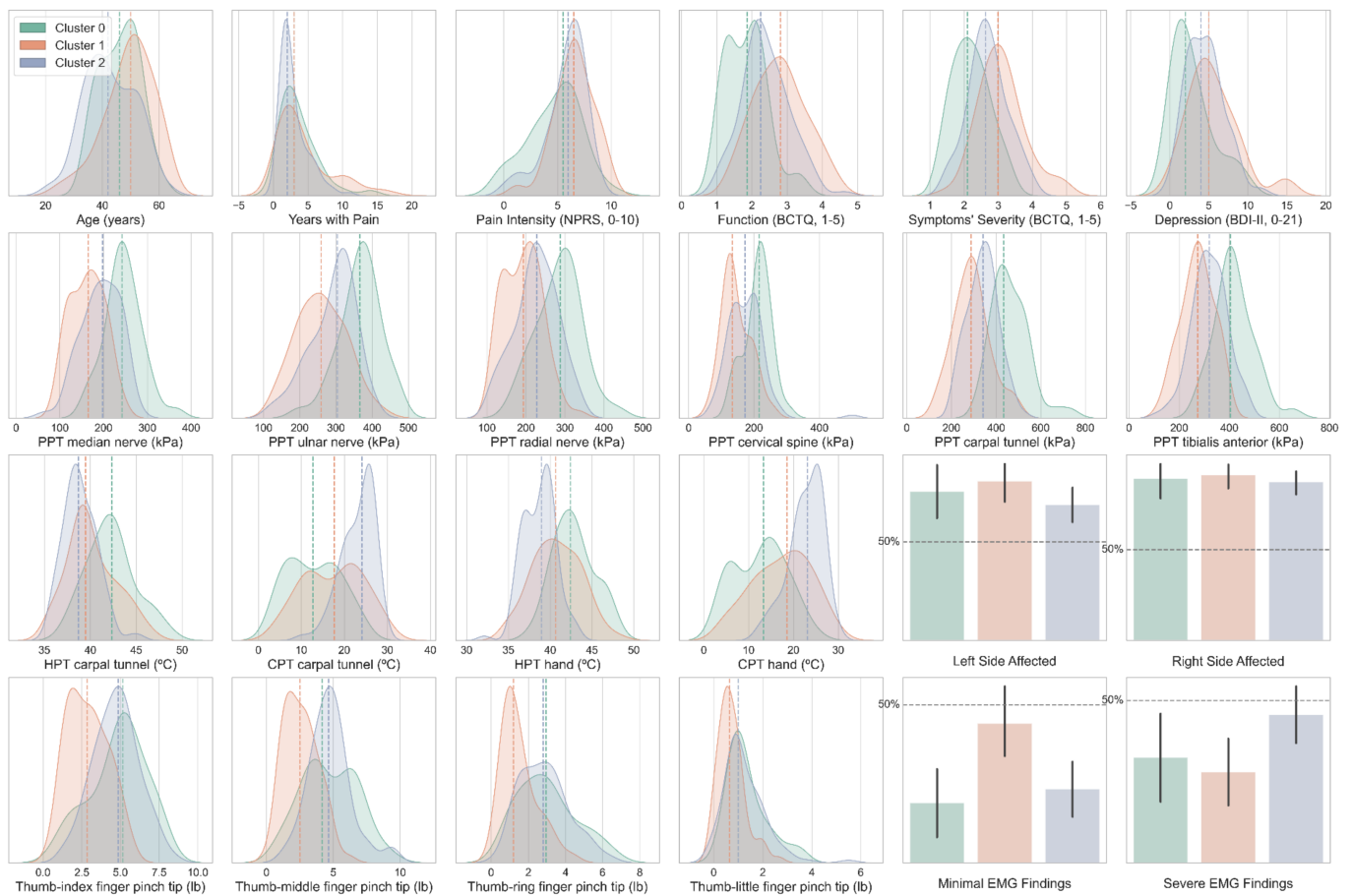


Figure 1. Plots of the distribution of the outcomes for each of the identified clusters. Categorical outcomes have been represented as bar plots.

Table 2. Mean and standard deviation of the outcomes according to each cluster.

	Cluster 0 (<i>n</i> = 37)	Cluster 1 (<i>n</i> = 68)	Cluster 2 (<i>n</i> = 103)	<i>p</i> -Value
Age (years)	46.19 ± 6.84	49.37 ± 8.81	42.71 ± 9.02	<0.001
Years with Pain	3.68 ± 2.79	4.43 ± 3.94	2.88 ± 2.01	0.0162
Pain Intensity (NPRS, 0–10)	4.68 ± 2.46	6.54 ± 1.84	5.77 ± 1.91	<0.001
Function (BCTQ, 1–5)	1.84 ± 0.58	2.8 ± 0.74	2.39 ± 0.67	<0.001
Symptom Severity (BCTQ, 1–5)	2.2 ± 0.54	3.1 ± 0.69	2.69 ± 0.57	<0.001
Depression (BDI-II, 0–21)	2.92 ± 2.71	5.57 ± 3.36	4.52 ± 2.38	<0.001
PPT median nerve (kPa)	245.24 ± 41.99	162.85 ± 39.22	193.22 ± 44.62	<0.001
PPT ulnar nerve (kPa)	366.25 ± 57.53	259.3 ± 68.51	290.37 ± 63.45	<0.001
PPT radial nerve (kPa)	284.88 ± 57.71	191.8 ± 48.69	225.9 ± 54.9	<0.001
PPT cervical spine (kPa)	211.01 ± 40.47	145.44 ± 43.66	173.75 ± 54.85	<0.001
PPT carpal tunnel (kPa)	463.34 ± 83.18	291.31 ± 81.54	340.06 ± 68.16	<0.001
PPT tibialis anterior (kPa)	419.01 ± 76.96	273.34 ± 65.82	321.0 ± 70.06	<0.001
HPT carpal tunnel (°C)	42.25 ± 2.61	40.14 ± 2.65	38.91 ± 1.84	<0.001
CPT carpal tunnel (°C)	12.83 ± 6.01	17.34 ± 6.89	23.11 ± 3.89	<0.001
HPT hand (°C)	42.83 ± 2.45	40.76 ± 2.91	38.67 ± 1.91	<0.001
CPT hand (°C)	12.57 ± 5.71	17.37 ± 6.48	22.72 ± 3.85	<0.001
Left Side Affected *	0.76 ± 0.43	0.81 ± 0.4	0.69 ± 0.47	1
Right Side Affected *	0.89 ± 0.31	0.91 ± 0.29	0.87 ± 0.33	1
Thumb-index finger pinch tip (pounds)	4.84 ± 1.8	2.87 ± 1.29	4.72 ± 1.47	<0.001
Thumb-middle finger pinch tip (pounds)	4.72 ± 2.03	2.56 ± 1.27	4.75 ± 1.58	<0.001
Thumb-ring finger pinch tip (pounds)	2.99 ± 1.54	1.49 ± 0.96	2.84 ± 1.31	<0.001
Thumb-little finger pinch tip (pounds)	1.37 ± 0.81	0.72 ± 0.55	1.25 ± 0.86	<0.001

Table 2. Cont.

	Cluster 0 (n = 37)	Cluster 1 (n = 68)	Cluster 2 (n = 103)	p-Value
Minimal EMG Findings #	0.19 ± 0.4	0.44 ± 0.5	0.23 ± 0.42	0.0845
Severe EMG Findings #	0.32 ± 0.47	0.28 ± 0.45	0.46 ± 0.5	0.4656

NPRS: Numerical Pain Rating Scale; BCTQ: Boston Carpal Tunnel Questionnaire; BDI-II: Beck Depression Inventory; PPT: Pressure pain Thresholds; HPT: Heat Pain Thresholds; CPT: Cold Pain Thresholds; EMG: Electromyography data. # 1: patient with minimal or severe affection, respectively; 0: patient has moderate affection. * 1: patient has right or left symptoms, respectively; 0: patient has no left/right symptoms (bilateral).

4. Discussion

The current study has identified three subgroups of women with CTS by using, for the first time, the SC algorithm. In particular, one of the clusters (number 1) mainly profiled patients with the worst clinical features, the highest widespread pressure pain hyperalgesia, and the lowest pinch tip grip force. It also included the oldest women, as well as the most patients with minimal CTS according to EMG features. Another cluster (number 2) contained patients with widespread hyperalgesia to pressure pain, and the worst thermal pain hyperalgesia when compared with the other two clusters. The third cluster (cluster 0) grouped patients with the least mechanical and thermal pain hyperalgesia, the lowest clinical pain features, and the best motor output.

There is evidence supporting that clinical manifestation of central sensitization, such as widespread pressure and thermal pain hyperalgesia, is not associated with electrodiagnostic findings in CTS [29]. The SC analysis identified two groups of women with CTS based on pain hyperalgesia, one with higher sensitivity to pressure pain (cluster 1) and another with higher sensitivity to thermal pain (cluster 2). Hypersensitivity to pressure pain is more related to nociceptive pain, whereas thermal pain hypersensitivity is usually more associated with neuropathic pain [30]. Interestingly, more individuals with minimal EMG affection were located in cluster 1, whereas more patients with severe EMG affection were in cluster 2. Current results would support that minimal CTS could be more strongly associated to nociceptive pain, whereas the features of severe CTS (where the median nerve exhibits more damage) resemble more those of neuropathic pain. In fact, SC also found that patients in cluster 1 had higher levels of pain intensity, higher symptom severity, and worse function. This hypothesis agrees with the theory proposing that long-lasting peripheral nociception (local pain) is a key factor for triggering central sensitization [31]. Therefore, this subclassification could potentially help to identify specific underlying mechanisms in CTS and individuals at a higher risk for developing more severe or more widespread symptomatology, e.g., fibromyalgia [32].

The identification of central sensitization could also play an important role as a prognostic factor for treatment outcomes. In fact, preliminary evidence suggests that sensitization of the central nervous system is associated with poorer treatment outcomes in individuals suffering from musculoskeletal pain [33]. Similarly, the presence of central sensitization provides a pathophysiological explanation for patients with CTS who experience persistent symptoms despite successful surgery. Centrally-mediated symptoms have been associated with poorer outcomes after carpal tunnel surgery, supporting this hypothesis [34]. However, peripheral sensitization has been also found to be associated with poorer clinical outcomes after conservative treatment [35]. Clusters identified in the current study could explain discrepancies in previous findings, since dominant nociceptive pain (cluster 1) may respond better to peripheral treatments, whereas dominant neuropathic pain (cluster 2) may need different approaches, such as pharmacological approaches.

Our results showed that patients in cluster 1 also exhibited lower pinch tip grip force, whereas no differences in motor output between the other two clusters were found. The association between sensory and motor variables in CTS is conflicting in the literature. For instance, Tamburini et al. did not find a correlation between pain and function [36], whereas Yoshida et al. recently observed that pain and grip strength were associated with function [37]. As has been identified in the current study with SC, different subgroups

of patients with CTS exist, where sensory and motor outcomes are affected and more associated in one group (cluster 1), but not in the other two (clusters 0 and 2).

The identification of subgroups of patients has potential implications for clinicians. First, therapeutic interventions should be adapted to the underlying mechanisms of each particular patient. According to SC, one group (cluster 1) seems to be more nociceptive dominant, whereas the other (cluster 2) seems to be more neuropathic dominant. This potential difference should be considered by the clinicians when designing treatment protocols for individuals with CTS. For instance, physical therapy interventions are more appropriate for nociceptive pain, whereas pharmacological treatments are usually required in neuropathic pain conditions. It is possible that the subgroup of patients identified in cluster 1 are those responding more positively to physical therapy approaches [38]. Second, the SC identified that patients in cluster 1, showing higher pain intensity, widespread pressure sensitivity, and lower tip pinch grip force, also exhibited higher depressive levels. The association between pain intensity, depression, and function has been described [39]. It is possible that this group of women with CTS would be more susceptible to stressful events and, hence, more widespread hyperalgesia. Consequently, psychological approaches targeting mood disorders such as depression should also be included when managing this group of patients. Therefore, the SC algorithm supports the clinical reasoning that treatment of CTS should include multimodal therapeutic interventions targeting pain and related mechanisms—function (i.e., physiotherapy, surgery), mood disorders (i.e., cognitive behavior), and psycho-physical (i.e., neuro-modulatory pain approaches).

Although, to the best of the authors' knowledge, this is the first study investigating a classification system in CTS by using SC analysis, some limitations are present. First, we recruited just a sample of women and from a tertiary hospital; therefore, the identified groups should be considered under this particular situation. Second, we only tested the static outcomes of altered nociceptive processing (i.e., PPT, CPT, HPT); it would be interesting to include dynamic outcomes, e.g., conditioning pain modulation or wind-up, to determine differences between the identified clusters. Third, the levels of depression of our sample were generally low; therefore, the role of this mood disorder should be considered with caution at this stage. Similarly, the role of other psychological factors in CTS has not yet been clarified.

5. Conclusions

The application of SC analysis has identified one cluster of women with CTS with worse clinical features, higher widespread pressure pain hyperalgesia, and lower pinch tip grip force; the second cluster also displayed widespread hyperalgesia to pressure pain, but mainly featured by thermal pain hyperalgesia. This subgrouping may reflect different underlying mechanisms, nociceptive versus more neuropathic, which should be considered in therapeutic interventions of this population since physical therapy interventions are more appropriate for nociceptive pain (cluster 1), whereas pharmacological treatments are usually required in neuropathic pain conditions (cluster 2).

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