Where is the pain? Spatial patterns of pain co-occurrence in a population-based study of 4833 pain drawings incorporating network analysis

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Abstract

Spatial pain patterns are widely used as diagnostic tools, yet population-level estimates, such as the prevalence of pain in specific body regions and likelihood of their co-occurrence, are lacking. Despite this, bilateral limb pain is considered relatively uncommon. Baseline data from a population-based Danish cohort were analysed. Twenty-one pain drawing regions, coded as binary “pain”/“no-pain” variables, were entered into an Ising model. Conditional dependencies between pairs of painful regions were quantified, while accounting for the pain state of other regions. Four-week prevalence of pain was also calculated for body regions. Of 4833 analysed pain drawings, 34.7% (1676) reported bilateral (upper or lower) limb pain and 32.3% (1561) reported symmetrical (mirrored) bilateral limb pain. Strongest positive edge weights of the Ising model were between mirrored contralateral regions; the strongest being between left and right hips (mean: 3.86, 95% confidence interval: 3.84-3.87). Next strongest edge weights were between spatially adjacent ipsilateral regions; the strongest being between the right hip and right buttock (mean: 2.72, 95% confidence interval: 2.71-2.74). Negative edge weights, indicating inhibitory relationships, were consistently seen between nonmirrored contralateral regions, the strongest being between regions adjacent to their mirrored contralateral counterparts. In conclusion, bilateral limb pain, particularly in mirrored regions, is more prevalent than previously thought. Pain co-occurrence is facilitated between mirrored contralateral regions and, to a lesser degree, between adjacent ipsilateral regions. An inhibitory effect occurs between nonmirrored contralateral regions, diminishing with increasing distance from the mirrored region. Potential inhibition between mirrored contralateral regions is likely overshadowed by the more dominant facilitation.

Keywords

Pain location, Pain drawing, Spatial data, Network analysis, Ising model

Introduction

With the exception of phantom sensations, pain is usually experienced within the physical boundaries of the body. The spatial characteristics of pain, which form an integral part of its sensory-discriminative dimension [39], are deeply connected to the experience itself. This connection to specific body parts is reflected in how people describe their pain; for example, "*my foot hurts*" or "*I have pain in my shoulder*."

From angina [43] to zygapophysial joint pain [1], clinicians have long used topographical patterns of pain as a diagnostic tool. This practice stems from the observation that similar pathologies tend to produce relatively consistent and recognisable pain distributions across different individuals. Spatial pain patterns are therefore highly relevant and valuable for clinical practice. Despite their importance, population-level estimates of spatial pain patterns – such as the relative prevalence of pain in different anatomical regions and the co-occurrence of pain across these regions – remain scarce in the research literature.

Several known neurophysiological mechanisms suggest that the presence of pain in one body region increases the likelihood of pain being present in spatially proximate body regions. These mechanisms include somatic referred pain, peripheral and central neuropathic pain, expanded receptive fields due to central sensitization, and local inflammatory processes [35; 60; 63], all of which patients typically report as pain in nearby, usually unilateral, body regions. This notion is supported by a general principle of spatial data known as Tobler's First Law of Geography [56], originating in the geosciences and since applied to many fields including the biological sciences, which states that "everything is related to everything else, but near things are more related than distant things." While

some empirical evidence suggests this principle holds with regard to the location of pain [3; 11; 61], it remains largely untested.

Pain co-occurrence may depend on more than just spatial proximity in peripheral body tissues, however. Neural proximity may also play a significant role. Pain in one region may increase the likelihood of pain being present in regions that are 'nearby' within the nervous system. Indeed, the manifestation of pain – including its spatial characteristics – is considered part of a protective output of the central nervous system [18; 38-40] that results from several interacting processes, including the transduction and encoding of threatening inputs such as noxious stimuli, relaying of nociceptive information through the spinal cord and thalamus, the activation of cortical representations of the body [15; 27], and multiple levels of facilitatory and inhibitory modulation [52; 57]. These processes incorporate both predictions and errors [26; 53]. Because of this complexity and potential uncertainty, researchers have sought to identify patterns of spatial pain co-occurrence. So far, these efforts have largely relied upon a latent variable approach [5; 20; 21; 29; 50], in which patterns are based on underlying but unobserved variables. However, identified patterns may therefore not always align with the actual distributions of pain reported by patients, potentially limiting the value of this approach for making direct diagnostic or mechanistic deductions.

To date, network analysis has not been applied to spatial pain data. This approach, rooted in graph theory, would provide a more direct representation of relationships between the pain states of body regions, either facilitatory or inhibitory, while accounting for the pain state of all other body regions. Network analysis therefore has the potential to reveal previously unseen interactions between painful regions and highlight patterns indicative of underlying mechanisms. Moreover, it enables the creation of population-level

summaries that are more directly applicable to individual patients, offering potentially valuable insights for personalised diagnosis and treatment planning.

Methods

Aims

The aims of this study were (1) to describe the relative prevalence of pain in anatomical regions and (2) to describe topographic pain patterns using correlations and a network analysis approach in a large, general population sample. We will primarily test the hypothesis that nearby body regions are more likely to be in the same pain state than distant regions.

Study design

This paper reports an analysis of the baseline data from the Odder cohort [25; 41], a population-based longitudinal cohort administered by the Department of Occupational Medicine, Goedstrup Regional Hospital, Denmark. The study conforms to the ethical guidelines of the World Medical Association's 'Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects' [64] and written informed consent for the use of data was obtained from all patients. As per Danish law [13], approval for the study was granted by the Danish Data Protection Agency (project number 1-16-02-141-18). Briefly, the Odder cohort was established in 2008 and the baseline data comprises adults aged 17 to 64 years who were registered with one of eight general practitioners (GPs) at a shared primary care healthcare centre in the town of Odder, Denmark. Odder is a medium-sized town in eastern Jutland with a demographic and geographic profile representative of the Danish general population.

Data collection

In February 2008, baseline questionnaires were sent (via either email or postal address, as available) to 8,517 adults registered with the healthcare centre. A total of 5,097 individuals (59.8%) responded, with 5,068 (59.5%) being identifiable and providing useable data. The questionnaire captured a range of demographic (including sex and age), individual, work-related, psychosocial, and health-related details using validated scales. Information regarding topographical pain location was gained using a pain drawing – a pair of line drawings representing the front and back outlines of the body, in which participants can mark the area(s) where they have experienced pain (Figure 1) – within the Standard Evaluation Questionnaire (SEQ), a validated questionnaire for assessing pain in population-based studies [42]. Participants were asked to mark on this pain drawing the location(s) of any pain experienced during the prior 4 weeks. The original (Danish) wording for the pain drawing question was: "Hvis du har haft smerter indenfor de sidste 4 uger, angiv da den/de mest

nøjagtige områder for smerten/smerterne. (Skraver området)", which can be translated to: "If you have experienced any pain during the last 4 weeks, please indicate the exact location(s) of your pain. (Shade the area)." This pain drawing data was then coded as 21 binary ('pain' or 'no pain') variables, each representing an anatomical region of the body (Figure 1). Each body region had been coded as a unique variable, except for the thigh and lower leg regions adjacent to each knee, which were combined into a single variable despite being non-contiguous. Additionally, most body regions were represented on both front and back manikins (i.e., no distinction could be made between anterior and posterior aspects of these regions). Original questionnaires were unavailable to recode these as unique regions.

[Insert Figure 1 here]

Statistical analysis

The dataset was analysed using R statistical software (version 4.2.2) in the RStudio environment. Alpha was set at 0.05 and 95% confidence intervals (95% CIs) were calculated where possible. We deemed pain drawing data to be missing if a participant declared non-zero pain intensity in an earlier survey question whilst also returning an empty pain drawing; these participants were removed from the analyses reported here.

To gain a topographical overview of the sample, four-week prevalence of pain was calculated for combinations of the following regions from the SEQ pain drawing: head or facial pain; axial (torso and neck) pain; right-sided and left-sided pain; upper limb pain (incorporating shoulder, arm, and hand regions) ; lower limb pain (incorporating buttock, hip, thigh, knee, lower leg and feet regions); right/left limb pain; unilateral/bilateral limb pain; hemilateral limb pain (both limbs of the right or left side of the body); symmetrical (mirrored) bilateral limb pain; and contiguous limb pain (i.e., pain in two or more adjacent regions).

Phi correlation coefficients were calculated, using the *phi()* function from the 'psych' R package [47], to assess pairwise associations between the presence or absence of pain across the 21 body regions, without controlling for any other variables or incorporating spatial distances between regions. The Phi coefficient quantifies the association between two binary variables, providing a measure ranging from -1 to +1 that indicates the strength and direction of the relationship. A positive value of Phi would indicate that the presence of pain in one region is independently associated with the presence of pain in another region, while a negative value would indicate that the presence of pain in one region is independently associated with the absence of pain in another region. We hypothesised that

neighbouring regions would be most strongly correlated; in other words, pain in one region (e.g., left shoulder) would be most likely to co-occur with pain in an adjacent region (e.g., left arm). *P*-values of Phi correlations were calculated using Fisher's Exact Test. To adjust for multiple comparisons, a Bonferroni correction was applied by multiplying each *p*-value by the number of comparisons (n=210), which was the total number of unique pairs among the 21 regions.

Next, each of the 21 body regions depicted within the manikins of the pain drawing was represented as an individual node in a graph to leverage network analysis techniques. By corollary, relationships between painful regions were represented as edges in this network. For the binary data provided by a standard pain drawing (i.e., 'pain' or 'no pain'), a potentially useful network analysis approach is the Ising model. Originally developed to study spin states in ferromagnetism, the Ising model is designed to represent and analyse interactions between binary states. Ising models have been utilised in many fields, including the neurosciences [10; 54], psychosocial sciences [7; 34], image analysis [6; 37], and geospatial data analysis [66] making them very suitable for pain drawing data. In this context, the data-driven Ising model represents the joint probability distribution of binary variables (pain presence or absence in each body region) using pairwise interactions and individual thresholds. Mathematically, this can be expressed as:

$$P(x) = \frac{1}{Z} \exp\left(\sum_{i<j} J_{ij} x_i x_j + \sum_i h_i x_i \right)$$

where $x = (x_1, x_2, \dots, x_p)$ denotes the pain states of p body regions (nodes), each of which can take a value of 0 or 1; J_{ij} are the interaction parameters (edge weights) between regions i and j; h_i are the threshold parameters for each region; and Z is the partition function for normalization. In an Ising model, edge weights can be positive (i.e., $J_{ij} > 0$) or

negative (i.e., $J_{ij} < 0$). A positive weight indicates that the two variables (body regions) are directly related; that is, when one region is in a given state (e.g., pain), the other region is more likely to be in the same state (e.g., also pain), analogous to a facilitatory interaction. Conversely, a negative weight indicates that the two regions are inversely related; that is, when one region is in a particular state (e.g., pain), the other region is more likely to be in the opposite state (e.g., no pain), analogous to an inhibitory interaction.

We created a data-driven Ising model, using the 'IsingFit' model parameter in the *bootnet()* function of the 'bootnet' R package [12], to produce an undirected network representing the mutual (i.e., reciprocal) conditional dependencies between pairs of regions being painful, while accounting for the influence of all other regions, regardless of their spatial distances. To estimate the parameters J_{ij} and h_i, this model employed a pseudolikelihood approach with least absolute shrinkage and selection operator (LASSO) penalty [55] to encourage sparsity in the network. Specifically, for each region i, the conditional probability of pain presence was modelled using logistic regression, given the states of all other regions except i (denoted by x_{-i}):

$$P(x_i = 1 \mid x_{-i}) = \frac{\exp\left(h_i + \sum_{j \neq i} J_{ij} x_j\right)}{1 + \exp\left(h_i + \sum_{j \neq i} J_{ij} x_j\right)}$$

The LASSO penalty shrinks smaller J_{ij} coefficients (edge weights) toward zero, resulting in a sparse network that retains only the most significant associations between regions [55; 58]. This method captures both direct and indirect associations within the network without requiring any information about the spatial relationships between nodes.

Bootstrapping (1,000 iterations [33]) was used to calculate means and 95% CIs of estimated edge weights and other network indices. Importantly, these edge weights were calculated without the inclusion of any prior information about the relative size of each

region, spatial distances between regions, or which regions neighbour one another. From the estimated network, we extracted the adjacency matrix and excluded self-loops (i.e., edges that connect a node to itself). We hypothesised that edges between adjacent neighbouring regions would be positive and exhibit the strongest magnitudes; in other words, pain in one region would most likely be associated with pain in an adjacent region (e.g., left shoulder and left arm).

Finally, using the 'igraph' R package [9], the following measures of centrality were calculated for each node (i.e., body region) of the bootstrapped Ising network: *Strength* (sum of the absolute values of weights of edges connecting to a node); *Betweenness* (how often a painful node lies on the shortest path between other painful nodes); and *Closeness* (inverse of the average shortest path length from a painful node to all other painful nodes). Table 1 lists our interpretation of each centrality measure in the context of a cross-sectional network analysis of painful regions within a pain drawing.

[Insert Table 1 here]

To facilitate the visualisation of patterns between painful regions, we developed a plotting method intended to be intuitive. By superimposing each node upon its corresponding body region on the pain drawing manikin (Figure 1), edges would illustrate the relationship between the connected regions. Front and back images of the pain drawing were also vertically offset to ensure plots of bilateral network edges would not overlap or obscure any anterior-posterior edges. In the SEQ pain drawing, since most nodes represented both anterior and posterior body regions, all nodes except for that representing the abdomen were placed onto the image depicting the back view of the body. We then

mapped the coordinates for each node onto its corresponding body region, using the *locator()* function in base R, which produced a list of x-y coordinates, enabling us to overlay the final network diagram (exported in PNG format with transparent background) upon the image of the offset pain drawing.

Results

We removed 235 participants from the analysis because they were deemed to have missing pain drawing data, having declared non-zero pain intensity in an earlier question whilst also returning an empty pain drawing. Hence, 4,833 pain drawings were retained for analysis. Participant characteristics of those analysed are displayed in Table 2. The mean age of these participants was 45.6 (SD: 12.8) years and the majority (55.4%) were female, which is typical of health surveys in Denmark [49] and other northern European countries [16; 19; 24; 44; 48; 51]. Most of the sample (81.4%) were either employed, a student or an apprentice, and almost two-thirds (64.4%) reported having experienced pain for longer than three months.

[Insert Table 2 here]

Figure 2 displays the number of painful body regions reported by participants during the previous 4 weeks. The modal number of painful regions was two (832/4833, 17.2%). Beyond this, there was a general pattern of decreasing participant numbers reporting increasing numbers of painful regions. Notably, only 11.7% (565/4833) of participants reported no pain in *any* body region (indicating a four-week pain prevalence of 88.3%) and just 0.1% (5/4833) of participants reported pain in *all* 21 body regions.

[Insert Figure 2 here]

Figure 3 displays the four-week prevalence of pain reported in each region of the pain drawing for all participants. This shows that pain was most prevalent in the head/face, neck, thorax, and lower back regions, with a slightly higher prevalence in right-sided limb regions than their left-sided counterparts. Table 3 presents the four-week prevalence of pain in combinations of regions. Approximately two-thirds of participants (3177/4833, 65.7%) reported some axial (torso and neck) pain in the preceding 4 weeks. During the same period, approximately half (2404/4833, 49.7%) of all participants reported an experience of lower limb pain, while slightly fewer (2110/4833, 43.7%) reported upper limb pain. By comparison, approximately one-third (32.5%, 1571/4833) reported head or facial pain during this period.

[Insert Figure 3 here]

[Insert Table 3 here]

Notably, 34.7% (1676/4833) of participants reported bilateral pain in either their upper or lower limbs. Of these, the vast majority (93.1%, 1561/1676) reported pain in one or more pair of bilaterally symmetrical (i.e., mirrored around the sagittal plane) limb regions. Of the 2,404 participants reporting lower limb pain, 1,231 (51.2%) were bilateral and 1,173 (48.8%) were unilateral. Of the 1,231 participants reporting bilateral lower limb pain, 1,125 (91.4%) reported pain in one or more mirrored pairs of lower limb regions. By

contrast, of the 2,110 participants reporting upper limb pain, fewer reported this to be bilateral (886, 42.0%) than unilateral (1224, 58.0%). Of the 886 participants reporting bilateral upper limb pain, 833 (94.0%) selected one or more mirrored pairs of upper limb regions.

Of the 2404 participants reporting lower limb pain, 655 (27.2%) reported pain in two or more adjacent regions of their lower limbs (i.e., contiguous lower limb pain). A similar proportion (28.8%, 608/2110) reported contiguous upper limb pain. Contiguous limb pain in one lower limb (5.9%, 284/4833) was more frequently reported than contiguous limb pain in both lower limbs (4.6%, 222/4833), with similar proportions reported for the upper limbs.

Of the 4,833 participants, 3,479 (72.0%) reported pain in two or more regions and therefore contributed to pairwise estimates of co-occurrence. Correlations between painful body regions revealed that the strongest relationships were between mirrored regions (Figure 4). The strongest of these mirrored correlations was between left and right buttock regions (ϕ = 0.56, Bonferroni-adjusted p = 2.06E-244), followed by that between left and right hands (ϕ = 0.55, Bonferroni-adjusted p = 3.57E-214). This contrasts with our hypothesis that adjacent regions would be the most strongly correlated. However, in partial support of this hypothesis, the next strongest correlations were between ipsilateral adjacent (i.e., contiguous) regions; the strongest of which was between the left arm and left hand (ϕ = 0.40, Bonferroni-adjusted p = 2.74E-109).

[Insert Figure 4 here]

Figure 5 displays the strength of conditional dependencies between body regions, being the edge weights from the Ising model. In contrast to our hypothesis that the

strongest positive edge weights would be between adjacent regions, these were instead seen between mirrored contralateral regions: for example, the strongest positive edge weight was between the left hip and right hip (mean: 3.86, 95%CI: 3.84, 3.87). In partial support of our hypothesis, the next strongest positive edge weights were seen between ipsilateral adjacent regions: for example, the strongest of these was between the right buttock and the right hip (mean: 2.72, 95%CI: 2.71, 2.74).

[Insert Figure 5 here]

Notably, no contralateral regions other than those that were symmetrical (mirrored) were connected by a strong positive edge weight. Indeed, negative edge weights – potentially representing inhibitory relationships – were consistently seen between contralateral non-mirrored regions, the strongest of which being between regions adjacent to their mirrored contralateral counterparts. For example, the strongest negative edge weight was between the left buttock and the right hip (mean: -1.78, 95%CI: -1.79, -1.76). Figure 6 displays significant mean positive and negative edge weights superimposed over their associated body regions, illustrating their highly symmetrical distribution around the sagittal plane. A complete table of edge weights is provided in the Supplementary Material for inspection.

[Insert Figure 6 here]

Centrality indices, based on edge weights from the Ising model, are illustrated in Figure 7. Strength centrality was highest in the legs, hips, buttocks, and hands, which

approached anatomical symmetry. Eigenvector centrality also approached anatomical symmetry, being strong in bilateral buttocks, hips, and legs and in no other nodes. By contrast, both closeness and betweenness centrality were anatomically right-side dominant. Closeness was strongest in the lower back, followed by the right upper limb and then right lower limb. Betweenness was strongest in the right upper and lower limbs, followed by the lower back. Full details of centrality indices for each node are provided within the Supplementary Material for inspection.

[Insert Figure 7 here]

Discussion

This paper reports spatial patterns of pain in a large general population sample, including a description of the four-week prevalence of pain in different body regions, and an implementation of network analysis techniques. To the authors' knowledge, this is the first analysis of its kind to be used with spatial pain data.

Four-week pain prevalence was most common in the axial regions (65.7%), followed by pain in one or more lower limbs (49.7%), then pain in one or more upper limbs (43.7%), while head or facial pain was found to be 32.5%. These regional figures resonate with those reported in previous studies [4; 11; 45; 46]. However, our overall four-week prevalence of pain reported in any body region (88.3%) is markedly higher than prevalence estimates from other general population studies; global pain prevalence has previously been estimated to be 27.5% (ranging from 9.9% to 50.3% depending on the country) [65], while another Danish population-based sample reported pain prevalence to be ~40% [20]. We suspect that our

higher prevalence figure is in part due to disproportionately more missing survey data in pain-free individuals.

When limb pain was present, this was bilateral approximately half of the time (34.7% of total) and the vast majority of bilateral limb pain was reported in symmetrical (mirrored) regions (32.3% of total). Although this finding must at this point be limited to the anatomical regions defined within the SEQ pain drawing, which cover relatively large areas of the body compared to region definitions of other pain drawings [2; 36; 59], this is an important result that should stimulate verification elsewhere.

We did not include any information relating to clinical diagnoses in our analyses. Nevertheless, the spatial distribution of pain invites consideration of underlying mechanisms. Bilateral limb pain, particularly when symmetrical, is suggestive of systemic inflammatory conditions such as rheumatoid arthritis [28], or nociplastic pain such as fibromyalgia [14; 62]. Current population estimates – up to 8% for inflammatory conditions [8; 17] and up to 15% for nociplastic pain [14; 23] – indicate that the prevalence of symmetrical bilateral limb pain observed here is too high to be accounted for by these conditions. Accordingly, either current population estimates of these conditions require revision, or some other mechanisms are generating bilateral limb pain.

When using both Phi correlation coefficients (independent pairwise associations) and an Ising model (which incorporate the influence of all other regions in the network) to evaluate spatial co-occurrence of pain, we saw a striking pattern of the strongest associations being between symmetrical (mirrored) contralateral regions. This was unexpected and in contrast to our prior hypothesis, based on clinical experience, known neurophysiological mechanisms, and Tobler's First Law of Geography [56], that spatially adjacent regions would display the strongest associations. Although, the next strongest

associations were indeed seen in adjacent ipsilateral regions, providing some support for our hypothesis and its underlying rationale.

Most surprising of all, in the Ising model, significant negative edge weights – which suggest a mutual inhibitory effect – were not only uniquely observed between contralateral regions but were also consistently strongest between regions that were adjacent to their mirrored contralateral counterparts (Figure 6). Based on edge weights observed between increasingly distant regions (see Supplementary Material for full details), this contralateral inhibitory effect appears to diminish with distance from the mirrored contralateral region. This pattern of contralateral inhibition has not previously been described and may be our most important finding. With potential clinical and mechanistic implications, not least that it could be exploited by pain interventions, this pattern of inhibition deserves some explanation. Nociception-activated inhibitory mechanisms, such as diffuse noxious inhibitory controls [30-32], have long been demonstrated in laboratory studies. However, our consistent finding of a contralateral pattern to this inhibition has not previously been described and may represent the first identification of nociception-activated inhibitory mechanisms at play in self-reported population data.

Taken together, our interpretation of these findings is that three mechanisms – two facilitatory and one inhibitory – predominantly shape the topographical pain patterns that we have described within our results. Firstly, pain in a particular body region facilitates pain in its mirrored contralateral counterpart, increasing the likelihood of symmetrical bilateral pain; a phenomenon previously considered unusual [22], yet the most dominant spatial pattern seen here. Secondly, neighbouring ipsilateral regions are also mutually facilitatory, though to a lesser extent than mirrored contralateral regions; a finding that partially supports our original hypothesis. Thirdly, contralateral regions of the body inhibit the

manifestation of pain in one another, with the strength of this contralateral inhibition appearing to decrease with distance from the mirrored region. This may seem paradoxical given the observed mirrored facilitation; however, if this interpretation is accurate, any inhibitory effect that exists between mirrored regions must be obscured by the more dominant mirrored facilitation, at least when both mechanisms are active. The alternative explanation is that contralateral inhibition only operates beyond some as-yet undetermined distance from the mirrored counterpart region, which seems less likely to us. Further investigation is needed to explore these possibilities.

Notably, negative Phi correlations were not observed between the contralateral regions that demonstrated negative edges in the Ising model. Instead, weak positive correlations were found between these contralateral regions. This apparent discrepancy likely arises from the differences in how these measures are calculated. Phi correlations reflect independent pairwise linear associations, which do not account for the influence of any other variables. In contrast, Ising model edge weights are derived from probabilistic interactions that consider the state of all variables in the network [58]. The negative edges seen in the Ising model indicate that, within the full network context, the presence of pain in one region is likely to be associated with the absence of pain in non-mirrored contralateral regions, even if this is not captured by simpler pairwise correlations. The weak positive Phi correlations between these regions imply that this inhibitory relationship may be subtle in real-world conditions and not easily detectable through pairwise associations alone. This also indicates that the underlying inhibitory interaction between these contralateral regions is context-dependent and influenced by the broader network of painful body regions. This important finding highlights the value of utilising whole-network techniques to analyse spatial pain data and warrants further investigation in future population studies.

Another virtue of utilising network analysis techniques, such as an Ising model, is the calculation of several established metrics, such as indices of centrality. We found that strength centrality was highest in the legs, hips, buttocks, and hands, which approached anatomical symmetry; this suggests that these regions exhibit a higher likelihood of pain co-occurrence (or inhibition) with other regions. This is supported by eigenvector centrality, which was high in bilateral buttocks, hips, and legs, but not in other nodes. Interestingly, both closeness and betweenness centrality were also strong in limbs. However, like limb pain prevalence, closeness and betweenness were highest on the right-side of the body, suggesting that limb-dominance might play a role in the prevalence and interactions of painful regions. In the context of our analysis, while these centrality indices are not calculated using spatial anatomical relationships, they may still have neurophysiological relevance. For example, high betweenness might indicate a predisposition for a particular body region to become painful when other regions are painful. This could be due to mechanisms such as neural convergence, a greater somatotopic representation of that region in the central nervous system, or increased tendency for involvement in central sensitization processes such as receptive field expansion. Similarly, closeness centrality may represent a predisposition for pain in one body region to propagate to others. The full meaning and potential utility of these metrics for investigating the dynamics of the spatial spread of pain need to be further explored. Indeed, utilising network analysis metrics could usefully inform the classification of pain conditions beyond the current reliance upon temporal characteristics such as ‘acute’ or ‘chronic’.

An inherent limitation of the study is that painful regions were coded as binary variables, which do not contain any information about the relative intensities of pain in different anatomical regions. Accordingly, in our analyses, a region with an intensity of 1/10

held equal value to a region coded 9/10. Using intensity-based thresholds, perhaps including only regions with high pain intensity in a network analysis, could provide very different topographical patterns. Hence, the current results are likely to form only part of the full pain topography story, and the potential influence of pain intensity should be explored in future studies.

When combined with the four-week recall period used within the SEQ, the binary nature of the pain drawing data introduces some temporal ambiguity. Pain reported in multiple regions of the pain drawing may reflect asynchronous painful events occurring within a four-week period of time, rather than reflecting simultaneous pain in multiple body locations. As such, we must interpret these associations with some caution. Future studies with finer temporal resolution – such as utilising *current* pain intensity, daily diaries, or event-based reporting – should be used to explore instantaneous and dynamic spatial pain patterns more precisely.

There were several limitations imposed by the anatomical regions predefined in the dataset analysed here. Firstly, the regions of the SEQ pain drawing did not distinguish between anterior and posterior aspects of most body regions, particularly within limbs. It is quite possible that contiguous anterior and posterior regions would have provided the strongest associations, but this hypothesis could not be tested in the current dataset. This should be explored in future studies where pain region boundary definitions separate anterior and posterior regions. Secondly, because axial, head and facial regions combined both left and right sides into single regions, we could only evaluate unilateral, bilateral, and symmetrical patterns in limbs. Aggregating bilateral regions should preferably be avoided in future studies to allow for a comprehensive exploration of laterality across the body, including the torso, neck and head. A further limitation, peculiar to the current dataset, is

that the originally defined thigh and lower leg regions were not contiguous, being separated by the knee, yet were coded as a single 'leg' region. This is problematic for a network analysis as edge weights connected to these leg regions may be over- or under-estimated. Unfortunately, original questionnaires were no longer available to recode these as separate regions. In future studies, all non-contiguous regions should be uniquely coded to avoid such issues.

Conclusions

Bilateral limb pain appears to be more prevalent than previously thought, particularly in regions that are symmetrical (mirrored) around the sagittal plane. Pain co-occurrence seems to be most strongly facilitated between these mirrored contralateral regions and, to a lesser degree, between adjacent ipsilateral regions. An inhibitory effect was consistently observed between non-mirrored contralateral regions, which appears to diminish with increasing distance. Any potential inhibition occurring between mirrored contralateral regions is likely being obscured by the more dominant facilitation.

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Conflicts of Interest.
The authors have no conflicts of interest to declare.

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Figure titles and legends

Figure 1. Pain drawing divided into body regions
A list of body region variables is provided in the Supplement

Figure 2. Number and proportions of painful body regions

Figure 3. Four-week prevalence of pain in body regions
Percentages based on entire sample (n=4,833). The intensity of colour within nodes represents the relative four-week prevalence of pain (brighter red = higher value).

Figure 4. Correlations between painful body regions
Each edge in the graph represents either a positive (blue) or negative (red) correlation. The thickness and colour intensity of an edge denotes the magnitude of the Phi correlation coefficient ϕ between two nodes (body regions). **A.** All correlations are displayed. **B.** Correlation coefficients $\phi < 0.3$ are removed.

Figure 5. Bootstrapped means and 95% confidence intervals of estimated edge weights from the network (Ising model)
Only significant edges (for which bootstrapped estimated weight values did not include zero) with a value above 10% of the largest absolute weight value were retained for plotting. The vertical reference line (x=0) separates negative and positive edge weight values.

Figure 6. Network (Ising model) of painful body regions
Each edge in the network represents either a positive (blue) or negative (red) relationship between the connected nodes. The thickness and colour intensity of an edge denotes the magnitude of its weight. **B.** Edge weights < 10% of the largest absolute edge weight are removed.

Figure 7. Centrality indices for the network (Ising model)
The intensity of colour within nodes represents the strength of the index (brighter red = higher value).

Tables

Table 1. Interpretation of network indices (derived from the Ising model) in the context of a pain drawing with binary regional data

Index	Nodes	Edges
Network graph (Ising model)	Each node represents an anatomical body region in which pain can be reported. The value for each node is binary, indicating either the presence (1) or absence (0) of pain in that region.	Edge values are those derived from an Ising model and therefore represent the strength of mutual conditional dependencies between pairs of nodes, while accounting for all nodes in the network. In a pain drawing, a positive edge between a pair of regions indicates that pain in one region is associated with an increased likelihood of pain in the other. Conversely, a negative edge indicates that pain in one region is associated with a decreased likelihood of pain in the other.
Strength	The sum of the absolute weight values of all edges connected to that anatomical region (node), reflecting the total magnitude of connectivity. A high strength value indicates that the node has strong associations with multiple other nodes. In a pain drawing, high strength suggests significant interaction and influence of pain in this region with other regions.	Edge values are those derived from the Ising model
Eigenvector centrality	A node's influence in the network by considering the influence of its neighbours, calculated as the principal eigenvector of the network's adjacency matrix. Nodes with high eigenvector centrality are connected to other nodes that are themselves highly connected.	Edge values are those derived from the Ising model.
Betweenness centrality	How often a node lies on the shortest paths between all other nodes in the network. Calculated by summing the proportion of shortest paths for each pair of nodes that pass through the node, it indicates the role of a node as a connector or bridge in the network. In a pain drawing, high betweenness will reflect the importance of an anatomical region in facilitating indirect connections between other regions.	Edge values are those derived from the Ising model
Closeness centrality	How close a painful anatomical region (node) is to all other painful nodes in the network, calculated as the reciprocal of the average shortest path length from that node to all other nodes. In a pain drawing, high closeness will reflect the region's	Edge values are those derived from the Ising model

	centrality and accessibility within the network, indicating that pain in this region is highly influential or can easily be influenced by pain in other regions.	

Table 2. Demographic characteristics (n=4,833)

Characteristic	Value
Age in years, mean (SD)	45.6 (12.8) Missing: 0 (0%)
Sex, n (%)	Female: 2678 (55.4%) Male: 2155 (44.6%) Missing: 0 (0%)
Body mass index, mean (SD)	25.5 (4.4) Missing: 199 (4.1%)
Country of origin, n (%)	Denmark: 4595 (95.1%) Other: 208 (4.3%) Missing: 30 (0.6%)
Education, n (%)	No education beyond primary school 816 (16.9%) Less than 3 years of education beyond high school): 2142 (44.3%) More than 3 years of education beyond high school): 1608 (33.3%) Missing: 265 (5.5%)
Work status, n (%)	Employed, student or apprentice: 3936 (81.4%) Temporary sick leave or job activation: 203 (4.2%) Pension or early retirement: 552 (11.4%) Unemployed or social benefit recipient: 69 (1.4%) Missing: 73 (1.5%)
Marital status, n (%)	Married or cohabiting: 3777 (78.2%) Living with parents: 263 (5.4%) Widowed, divorced or single: 587 (12.1%) Other: 8 (0.2%) Missing: 198 (4.1%)
Smoking status, n (%)	Daily: 1054 (21.8%) No, but used to: 1623 (33.5) Never: 1984 (41.1%) Missing: 172 (3.6%)
Duration of pain, n (%)	3 months or less: 1121 (23.2%) More than 3 months: 3111 (64.4%) Missing: 601 (12.4%)
Physical Component Score from SF-12, mean (SD)	51.2 (9.3) Missing: 327 (6.8%)
Mental Component Score from SF-12, mean (SD)	48.8 (9.6) Missing: 327 (6.8%)

Table 3. Four-week prevalence of pain in combinations of body regions

Percentages based on entire sample (n=4,833)

Anatomical regions	**n (%)**
Head or facial pain	1571 (32.5%)
Axial pain (torso and neck)	3177 (65.7%)
Left side pain (any)	2442 (50.5%)
Right side pain (any)	2614 (54.1%)
Left upper limb pain	1386 (28.7%)
Right upper limb pain	1610 (33.3%)
Upper (left or right) limb pain	2110 (43.7%)
Left lower limb pain	1797 (37.2%)
Right lower limb pain	1838 (38.0%)
Lower (left or right) limb pain	2404 (49.7%)
Left unilateral (upper or lower) limb pain	618 (12.7%)
Right unilateral (upper or lower) limb pain	790 (16.3%)
Unilateral (left or right) upper limb pain	1224 (25.3%)
Unilateral (left or right) lower limb pain	1173 (24.3%)
Unilateral (left or right, upper or lower) limb pain	2023 (41.9%)
Hemilateral (left or right, upper and lower) limb pain	1556 (32.2%)
Bilateral (left and right, upper or lower) limb pain	1676 (34.7%)
Bilateral (left and right) upper limb pain	886 (18.3%)
Bilateral (left and right) lower limb pain	1231 (25.5%)
Bilateral (left and right, upper or lower) and symmetrical limb pain	1561 (32.3%)
Bilateral (left and right) and symmetrical upper limb pain	833 (17.2%)
Bilateral (left and right) and symmetrical lower limb pain	1125 (23.3%)
Contiguous (≥2 adjacent regions, left or right, upper or lower) limb pain	1092 (22.6%)
Contiguous (≥2 adjacent regions, left or right) upper limb pain	608 (12.6%)
Contiguous (≥2 adjacent regions, left or right) lower limb pain	655 (13.6%)
Contiguous (≥2 adjacent regions) and bilateral (left and right, upper or lower) limb pain	382 (7.9%)
Contiguous (≥2 adjacent regions) and bilateral (left and right) upper limb pain	206 (4.3%)
Contiguous (≥2 adjacent regions) and bilateral (left and right) lower limb pain	222 (4.6%)
Contiguous (≥2 adjacent regions) and unilateral (left or right, upper or lower) limb pain	523 (10.8%)
Contiguous (≥2 adjacent regions) and unilateral (left or right) upper limb pain	278 (5.8%)
Contiguous (≥2 adjacent regions) and unilateral (left or right) lower limb pain	284 (5.9%)