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Spatiotemporal patterns of pain distribution and recall accuracy

a dose-response study

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SPATIOTEMPORAL PATTERNS OF PAIN DISTRIBUTION AND RECALL ACCURACY: A DOSE-RESPONSE STUDY

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ABSTRACT

Background and aims: Clinical decisions rely on a patient's ability to recall and report their pain experience. Monitoring pain in real-time (momentary pain) may reduce recall errors and optimize the clinical decision-making process. Tracking momentary pain can provide insights into detailed changes in pain intensity and distribution (area and location) over time. The primary aims of this study were i) to measure the temporal changes of pain intensity, area, and location in a dose-response fashion and ii) to assess recall accuracy of the peak pain intensity and distribution seven days later, using a digital pain mapping application. The secondary aims were to i) evaluate the influence of repeated momentary pain drawings on pain recall accuracy and ii) explore the associations among momentary and recall pain with psychological variables (pain catastrophizing and perceived stress).

Methods: Healthy participants (N=57) received a low (0.5ml) or a high (1.0ml) dose of hypertonic saline (5.8%) injection into the right gluteus medius muscle and, subsequently, were randomized into a non-drawing or a drawing group. The non-drawing groups reported momentary pain intensity every 30-seconds. Whereas the drawing groups reported momentary pain intensity and distribution on a digital body chart every 30-seconds. The pain intensity, area (pixels), and distribution metrics (compound area, location, radiating extent) were compared at peak pain and over time to explore dose-response differences and spatiotemporal patterns. All participants recalled the peak pain intensity and the peak (most extensive) distribution seven days later. The peak pain intensity and area recall error was calculated. Pain distribution similarity was determined using a Jaccard index which compares pain drawings representing peak distribution at baseline and recall. The relationships were explored among peak intensity and area at baseline and recall, catastrophizing, and perceived stress.

Results: The pain intensity, area, distribution metrics, and the duration of pain were lower for the 0.5ml than the 1.0ml dose over time ($p<0.05$). However, the pain intensity and area were similar between doses at peak pain ($p>0.05$). The pain area and distribution between momentary and recall pain drawings were similar ($p>0.05$), as reflected in the Jaccard index. Additionally, peak pain intensity did not correlate with the peak pain area. Further, peak pain intensity, but not area, was correlated with catastrophizing ($p<0.01$).

Conclusions: This study showed differences in spatiotemporal patterns of pain intensity and distribution in a dose-response fashion to experimental acute low back pain. Unlike pain intensity, pain distribution and area may be less susceptible in an experimental setting. Higher intensities of momentary pain do not appear to influence the ability to recall the pain intensity or distribution in healthy participants.

Implications: The recall of pain distribution in experimental settings does not appear to be influenced by the intensity despite differences in the pain experience. Pain distribution may add additional value to mechanism-based studies as the distribution reports do not vary with pain catastrophizing.

REC# N-20150052

Keywords (3-6)

Hypertonic solutions, saline; digital technology; surveys and questionnaires; mental recall; pain measurement; ecological momentary assessment.

1 Introduction

To date, our understanding of pain distribution patterns in patient populations stems from cross-sectional studies (1–7,7–10). Such studies provide evidence that pain distribution can

assist with the prognosis of low back pain (11), the process of differential diagnosis of low back (1) and sacroiliac pain (2), as well as to differentiate between somatic referred and radicular back pain (12–14).

Traditionally, pain distribution can be acquired using pen-to-paper pain drawings (15,16) and provide information about pain extent (area) and location (17). However, there is no gold standard and there exist few metrics for accurately assessing and quantifying changes in pain distribution (18). Indeed changes in pain distribution may reflect an alteration in the location, the size of the total area of pain, or both. Furthermore, we lack the knowledge or appreciation of the dynamic changes in pain distribution from daily, weekly and monthly timescales (19). Only a handful of studies attempted to track pain over time and may be a result of practical, technical and implementation barriers (19–21).

Another consideration for tracking pain distribution over time is that clinical assessments are based on the patients' recall of their pain, which may be especially problematic as the onset of pain can occur well before an initial consultation (1,22–26). Pain recall can be influenced by pain experiences and psychological variables, such as catastrophizing and stress (27–37). Errors in the pain recall accuracy may obscure the clinical decision-making process (26). Therefore, amongst other foreseeable benefits of tracking pain distribution over time, assessing pain in a more continuous fashion and in real-time (momentary) could mitigate recall errors and optimize the clinical decision-making process and improve knowledge stemming from pain mechanism-based studies.

As a starting point, experimental pain studies in health individuals can help clarify the spatiotemporal patterns of pain distribution in response to noxious stimulation and algesic

substances. Such studies provide a stepping stone for teasing out differences between healthy and clinical populations. In short, experimental pain studies utilize a number of algesic substances, such as hypertonic saline (HS), mustard oil, and nerve growth factor, to model and characterize various interactions with evoked pain intensity and distribution (38–40). Some of these prior studies furthered our understanding of referred pain mechanisms and hyperalgesia (41,42). Of particular interest, HS is known to evoke transient, local, and referred pain resembling clinical musculoskeletal pain (41,43,44). Thus, the HS experimental model is an ideal starting point for exploring and quantifying changes in spatiotemporal patterns of pain distribution and recall accuracy.

To track pain distribution over time, the digitalization of the pain drawings overcomes some practical, technical, and implementation barriers encountered by pen-to-paper methods. Further, digital pain drawings enable the testing and establishment of new metrics for assessing and quantifying the momentary pain experience over time. Moreover, they enable the exploration of spatiotemporal patterns of pain distribution in experimental and clinical settings.

The primary aims of this study were i) to measure the temporal changes of pain intensity, location, and area in a dose-response fashion using digital pain mapping, and ii) to assess recall accuracy of the peak pain intensity and distribution. The secondary aims were to i) evaluate the influence of repeated momentary pain drawings on pain recall accuracy and ii) explore the associations of momentary and recall pain experience with psychological variables (pain catastrophizing and perceived stress).

2 Materials And Methods

2.1 Participants

Participants were recruited through social media groups, the university research recruitment website, and posters displayed on the university campus. Inclusion criteria included healthy adults age 18-65 years. Exclusion criteria included cognitive limitations, current or past history of chronic or recurrent pain or any other known medical condition that might affect pain perception and processing, such as neuropathy, epilepsy, or diabetes. A total of 57 participants were recruited and randomized using a simple randomization method.

2.2 Study design overview

Healthy participants (N=57) participated in a baseline and recall session. Participants were randomized into four groups. Firstly, participants were blinded to receive either a 0.5ml (low-dose) or a 1.0ml (high-dose) bolus injection of HS (NaCl 5.8%) to the right gluteus medius muscle (GMM). A second randomization divided participants from the low and high-dose groups into a drawing or a non-drawing group to assess the influence of repeating pain drawings every 30 seconds post-injection on recall accuracy. This means that we explored whether recall accuracy is influenced by reporting multiple drawings post-injection to those who did not. Thus, there are four groups: low-dose drawing (N=13), low-dose non-drawing (N=15), high-dose drawing (N=14), and high-dose non-drawing (N=15). Participants from the drawing groups reported the intensity of the HS evoked pain in addition to completing a pain drawing every 30 seconds. Whereas participants from the non-drawing groups verbally reported the HS evoked pain intensity every 30 seconds. Additionally, all participants completed a Perceived Stress Scale (PSS) and the Pain Catastrophizing Scale (PCS) at

147 baseline to determine the influence of these psychological factors on the four groups'
148 momentary and recall pain. These questionnaires were reproduced in Danish and English with
149 permission.
150
151 All pain drawings were completed using a digital body mapping android application
152 (*Navigate Pain, Version 0.1.9.9.3, Aalborg University, Denmark*). A hand-held tablet
153 (*Samsung Galaxy Note 10.1 2014 Edition*) displayed a high-resolution 2D male body chart in
154 a posterior view. Drawings were completed using the tablet's s-pen (45,46). Females drawing
155 pain patterns onto a male body chart have not been shown to affect the ability to capture the
156 perceived pain area (47).
157
158 Seven days later, all participants were asked to recall their peak pain intensity rating and the
159 most extensive evoked area and location on a digital body chart. Participants were not
160 informed they would be asked to recall the pain intensity and distribution during their second
161 session, prior to the study, to reduce possible expectation and attention biases. Therefore, both
162 groups actively concentrated on the pain every 30 seconds to capture the information
163 requested.
164
165 The ethics committee in the North Denmark Region (N-20150052) approved the protocol. All
166 participants gave written informed consent in accordance with the Declaration of Helsinki.
167
168 **2.3 Experimental Saline-Induced Low Back Pain**
169 HS injections were used as a model of nonspecific, acute, soft tissue, referred low back pain.
170 The belly of the GMM was selected due to its accessibility, lack of large neural tissues that
171 could be injured, and the expected area of pain distribution (48). The injection site in the right

GMM belly was located by palpating above an imaginary line between the right greater trochanter and the right posterior superior iliac crest while the participant lay in a prone position. Participants were asked to abduct the hip to confirm the location of the muscle (49). The injection site was marked, the skin was disinfected and let air-dry.

Pilot studies were performed to gain training experience. A total of six pilots using real-time ultrasonography confirmed the location and injection technique reached the muscle belly of the GMM in individuals within normal and overweight Body Mass Index (BMI). Therefore, the use of ultrasound was deemed unnecessary during the main experiment.

2.4 Assessment of the Momentary Pain Experience

Participants remained in a prone position for the duration of the experiment and were asked by the examiner (MGV) to report their pain experience every 30 seconds.

2.4.1 Pain Intensity

All participants were asked to rate their pain intensity every 30 seconds on a Numerical Rating Scale (NRS, 0=no pain, 10=worst pain imaginable) immediately following the HS injection until the cessation of pain. Cessation of pain was defined as *no pain* (NRS=0). Participants from the non-drawing groups rated their pain intensity verbally. In contrast, participants from the drawing groups rated their pain intensity directly on the digital pain drawing application (app) using the tablet's S-pen. The examiner (MGV) immediately transcribed all the NRS scores on a separate document for future analyses. The participants' highest pain intensity was defined as the peak pain (PP) intensity and used for analyses. The time (in minutes) to reach PP intensity from post-injection was also calculated for statistical analyses.

PP intensity ratings were compared to assess dose-response differences among the four groups. The area under the pain intensity-time curve ($Intensity_{AUC}$) was obtained for each of the four groups to measure the overall temporal changes of pain intensity. The area under the curve (AUC) over time for each participant from each group was calculated for the time all participants reported pain.

2.4.2 Pain Area

HS injection evoked pain is characterized by localized and referred soft-tissue pain on and around the injection site (41,42,50). In this study, localized and referred pain are combined when referring to pain area and distribution. Thus, the term pain area only accounts for the drawn areas of pain without any regard to the location, whereas the term pain distribution is defined as the area and location of pain drawn on the digital body chart. Participants from the low- and high-dose pain drawing groups reported their pain on the digital body chart every 30 seconds from the time of injection until pain cessation. Participants from the drawing groups were instructed to save the time-stamped drawing and, automatically, reveal a new body chart.

To quantify changes in pain area, two measures were used. As a first and simple measure, the most extensive pain area evoked immediately following the injection of HS was identified and defined as the PP area for each participant. The digital body mapping app automatically extracted and quantified the total area in pixels. The maximum total drawable area in the body chart was 204,410 pixels. The time (in minutes) to reach the PP area from the injection time was also identified and used for analyses.

The second measure utilized the area under the pain area-time curve ($Area_{AUC}$) as an overall measure of the spatiotemporal changes in pain area for the low- and high-dose drawing groups. The AUC for each participant was calculated for the time all participants reported pain.

2.4.3 Pain Distribution

Pain drawing overlays were created for the low- and high-dose drawing groups for each 30-second interval immediately following the HS injection, as well as for the drawing and non-drawing groups during the recall session. These overlays facilitated the visualization of similarities and differences in pain distribution between pain drawings.

Novel approaches were applied, in an exploratory fashion, to quantify similarities and differences in the spatiotemporal patterns of pain distribution over time. Digital image analyses were used to extract and provide quantitative descriptors of the pain distribution over time and between doses. Three descriptors or pain distribution metrics were determined to detail the radiating extent (vector length), compound area (bounding box area), and location (centroid). The AUC assessing vector length ($Vector_{AUC}$), bounding box area (BBA_{AUC}) and centroid ($Centroid_{AUC}$) were obtained to assess changes in pain distribution over time and between doses. The AUC for each participant was calculated until pain cessation, that is, until the pain rating was zero (NRS=0).

Radiating Extent (vector length)

Referred pain following experimental stimuli has previously been shown (51,52). The distance reached by the expansion of evoked pain area can be expressed as a vector length. Measuring the vector length provides insight into how far the pain spreads vertically or refers

beyond the injection site. The vector length was defined as the maximum distance, measured in pixels, from the injection site to the farthest located pixel on the pain drawing. Considering that the pain drawing might contain two or more areas in a discontinuous manner (53–55), the total vector length added the distance from the injection site to the periphery of each individual pain area, e.g. buttock and leg.

Compound area (Bounding Box Area)

The bounding box area describes the overall shape or spread of pain, regardless of the total number or shape of the drawn areas. The bounding box area is calculated by identifying the most distal pain locations on the body chart in the vertical and horizontal directions. These locations are then used to determine the maximum horizontal and vertical distances, enclosing the area or areas of pain in a box. The bounding box area is calculated by multiplying these two distances or lengths.

Location (centroid)

The centroid provides information about the general location or shift in the overall location of the pain area. The centroid is the weighted average point (geometric center) of all the points in a drawn area or areas. Shifts in the general location of the pain may result from changes in location, and the shape of the pain pattern. The centroid is expressed as X and Y coordinates.

2.4.4 Pain Duration

Dose-response differences in pain duration have been shown with a continuous infusion of HS (56). Thus, pain duration was calculated as the time immediately following the removal of the injection needle (time=0) until the cessation of pain. Additionally, the time-to-peak intensity and time-to-peak area (in minutes) were determined.

2.5 Assessment of Pain Recall Accuracy

2.5.1 Recall Accuracy of Pain Intensity

The accuracy of the pain intensity recall was assessed by subtracting the recalled PP intensity (RPP intensity) from the baseline PP intensity of each participant. The difference between the RPP and PP intensity was compared to the null hypothesis for each of the four groups to determine the pain intensity's recall error.

2.5.2 Recall Accuracy of Pain Area

The pain area recall accuracy was assessed by subtracting the recalled PP area (RPP area) from the baseline PP area. The 0.5ml and the 1.0ml non-drawing groups do not have a baseline PP area. Therefore, their RPP area was contrasted to the drawing groups (0.5ml and 1.0ml, respectively). The difference between the RPP and the PP area, measured in pixels, was compared to the null hypothesis to measure the pain area recall error.

2.5.3 Recall Accuracy of Pain Distribution

To quantify the pain distribution recall accuracy, the following measures were calculated: similarity index, homogeneity of variance, and pain distribution metrics (compound area, location, radiating extent). The pain distribution recall accuracy reflects the similarity between the PP area and the RPP area, as assessed in the drawing groups only.

The similarity is calculated and expressed using the Jaccard similarity coefficient or Jaccard index (7). A high Jaccard index (range 0 -1) represents a greater pixel overlap and is a proxy measure for assessing the accuracy of pain location (7,10,57). A Jaccard index of 1, for example, would represent a 100% overlap between two pain drawing areas and location.

Levene's tests assessing the pain area recall homogeneity of variance were explored among the four groups to assess the spread around the mean and data variability (homogeneity or equality of variances).

Lastly, the differences in compound area, location, and radiating extent for the four groups were determined by subtracting the recall metrics from the baseline metrics. Similar to the recall error, the baseline drawing groups were used as a reference to compare the recall non-drawing groups.

2.6 Assessment of Pain Catastrophizing and Perceived Stress

Psychological variables, such as pain catastrophizing, are known to positively bias the pain intensity recall (58–61). Furthermore, stress can influence the quantity and quality of memory formation (62–67).

Pain catastrophizing and perceived stress were registered at baseline using the Pain Catastrophizing Scale (PCS) and the Perceived Stress Scale (PSS). Both of these questionnaires have been validated and previously used in a healthy population receiving experimental models of pain (30,68). The PCS (69) is a standard tool to measure catastrophizing thoughts based on anticipated or actual pain (70,71). The PCS has three sub-scales: rumination, magnification, and helplessness (72). All 13-items are rated on a 5-point scale with the anchors "0" not at all and "4" all the time. Total scores equal to or greater than 30 suggest clinically relevant levels of catastrophizing (72). We hypothesized greater PCS scores will be associated with greater pain momentary peak pain intensity and area and with an exaggeration in pain recall.

The PSS measures the degree of perceived stress levels by rating feelings and thoughts that may have been experienced during the last month (73). Each of the 10-item self-reported questions rated on a 5-point scale with the anchors "0" never, and "4" very often. Total scores ranging from 0-13, 14-25, or 25-40 are considered to represent low, moderate, or high perceived stress levels, respectively (73). We hypothesized greater PSS scores will be associated with greater pain momentary peak pain intensity and area, as well as with a decrease in pain recall.

2.7 Statistical analyses

Histograms and Q-Q plots revealed parametric and non-parametric data distribution for the PP intensity and area, as well as the Jaccard indexes for the low-dose and high-dose groups. When no differences were identified between the drawing and non-drawing groups within the same dose at baseline, the data were pooled into the respective low-dose and high-dose groups for dose-response comparisons.

The $Intensity_{AUC}$ and $Area_{AUC}$ from the different groups were compared using a Kruskal-Wallis H test. Changes in the pain distribution metrics over time were assessed with repeated measures ANOVA, with bins of 0.5, 1.0, 2.0 and 3.0 minutes. The vector length, bounding box area and centroid (X and Y coordinates) AUC values for the drawing groups were compared using a Mann-Whitney U test.

One-sample T-tests were used to calculate the pain recall intensity and area error by comparing the difference between the RPP and the PP to the null hypothesis. Cronbach's alpha correlation coefficients were used to calculated the PP intensity and area recall accuracy. Repeated measures ANOVA were used to assess the pain intensity and area recall

accuracy among drawing and non-drawing groups. Furthermore, parametric and non-parametric Levene's tests for homogeneity of variance on the pain area were used to test for equal variance. Baseline and recall pain distribution metrics were compared using the Mann-Whitney U test to assess the influence of repeating pain drawings post-injection on the recall accuracy.

The PSS and the PCS scores were calculated and used for the correlation analyses. Spearman's correlations were run to determine dose-response associations related to the pain area, intensity ratings, duration, PSS, and PCS at baseline and recall. These correlations were also carried out for a dose-independent, pooled dataset.

Statistical analyses were performed using SPSS 25 (*SPSS Statistics, 2018*). The pain mapping metrics, as well as the Jaccard indexes and pain drawings' overlays, were obtained with MATLAB R2017b (*The MathWorks, Inc., Natick, Massachusetts, US*). Correlation coefficients, means, and standard error of the mean (Mean ± SEM) are reported where relevant. P-values of less than 0.05 were considered statistically significant. A Bonferroni adjustment was used for all multiple analyses.

3 Results

3.1 Participants

The study recruited 57 healthy participants. However, one participant from the low-dose non-drawing and one participant from the high-dose non-drawing groups were excluded as they did not report pain within the first 3 minutes following the injection (n=2). In contrast, two participants from the high-dose non-drawing group were unable to remain in prone position due to the high intensity of pain evoked and thusly were also excluded. Therefore, a total of

53 participants were included (age range 19-45 years) with a BMI within the normal range (18.5-24.9 kg/m^2). Twenty-five females (47%) were included in the study.

3.2 Assessment of the Momentary Pain

3.2.1 Pain Intensity

There were no differences in PP intensity among the four groups ($p>0.05$) (Table 1). Additionally, the PP intensity ratings were similar between the low-dose (3.8±0.3) and the high-dose (5.3±0.6; $p>0.05$) groups.

(please, insert table 1 here)

Differences in pain intensity ratings over time were shown between the four groups ($\chi2(3) = 20.35$, $p<0.01$), with a mean rank $Intensity_{AUC}$ of 5.9 for the low-dose drawing and 11.6 for the low-dose non-drawing groups; 16.0 for the high-dose non-drawing and 25.5 for the high-dose drawing groups (Figure 1). Pairwise comparisons showed that the $Intensity_{AUC}$ for the low-dose drawing group was significantly lower than the high-dose drawing group ($p<0.001$, figure 1).

(please, insert figure 1 here)

3.2.2 Pain Area

Similar to the PP intensity, there was no difference in the PP area between the low-dose and the high-dose drawing groups, as expressed in pixels ($p>0.05$) (Table 1). The $Area_{AUC}$ differed between the low-dose and the high-dose drawing groups ($\chi2(1) = 6.545$, $p<0.01$). The

mean rank $Area_{AUC}$ was 2.5 for the low-dose drawing and 8.0 for the high-dose drawing groups (Figure 2).

(please, insert figure 2 here)

3.2.3 Pain Distribution

The $Centroid_{AUC}$ location differed between the low- and the high-dose (X coordinate U=3.0, $p<0.05$, with a Greenhouse-Geisser correction). The BBA_{AUC} was smaller for the low- than for the high-dose (U=0.001, $p<0.05$, with a Greenhouse-Geisser correction). There was no dose-response difference for the $Vector_{AUC}$ ($p>0.05$) or intra-dose pain distribution metrics differences for the low- and high-dose drawing groups. ($p>0.05$) (Figure 3).

(please, insert figure 3 here)

3.2.4 Pain Duration

Participants in the high-dose groups reported pain over a longer duration (11.3±1.2 min), as compared to the low-dose groups (6.6±0.5 min) (U=3.20, $p<0.05$) (Figures 1 and 3). The time-to-peak intensity was similar among the four groups ($p>0.05$, Table 1). The low dose drawing and non-drawing groups reached PP intensity at 0.8±0.2min and 1.6±0.4min, respectively. The high dose drawing and non-drawing groups reached PP intensity at 1.8±0.5min and 1.8±0.4min, respectively. There was also a similar time-to-peak area of pain for the low and high-dose drawing groups (2.0±0.4min and 2.9±0.5min, $p> 0.05$, respectively).

3.2.5 Assessment of Pain Catastrophizing and Perceived Stress

There were no differences in the PCS and PSS scores between the four groups at baseline ($p>0.05$, Table 1).

3.3 Assessment of the Pain Recall Accuracy

3.3.1 Pain intensity

The RPP intensity was similar between the drawing and non-drawing groups in the low-dose ($p> 0.05$) and the high-dose groups ($p> 0.05$). The pain intensity recall error for the low-dose (0.30 ± 0.16) and the high-dose (0.04 ± 0.09) groups did not significantly differ from zero ($p>0.05$). The pain intensity recall error was similar between the low- and the high-dose groups ($p>0.05$). The Cronbach's alpha for the peak pain intensity recall for the four groups ranged between 0.75 and 0.99.

3.3.2 Pain Area

The RPP area was similar between the drawing and non-drawing groups in the low-dose ($p> 0.05$) and the high-dose groups ($p> 0.05$). The pain area recall error for the low-dose (160 ± 1600) and the high-dose (10193 ± 6612) groups did not significantly differ from zero ($p>0.05$). The pain area recall error was similar between the low- and the high-dose groups ($p>0.05$). The Cronbach's alpha for the peak pain area recall was 0.66 for the high-dose drawing and 0.74 for the low-dose drawing group.

3.3.3 Pain Distribution

One subject from the high-dose non-drawing group recalled the pain on the non-painful side of the body map. Therefore, this wrong-sided data point was removed for the location recall accuracy statistical analysis.

There were no differences in the Jaccard indexes for the pain drawings representing the PP and the RPP areas for the low- (0.27 ± 0.07) and the high-dose drawing groups (0.43 ± 0.04) ($p>0.05$). Levene's tests showed equality of variance between the PP area and RPP area for the low- and high-dose drawing groups ($p>0.05$). Subsequent Levene's tests also showed equality of variance between the drawing and non-drawing pain area recall in the low- and high-dose ($p>0.05$). Additionally**,** the four groups did not differ in their ability to recall the pain distribution in terms of pain distribution metrics (vector length, bounding box area, centroid) ($p>0.05$) (Figure 4).

(please, insert figure 4 here)

3.4 Associations among pain intensity, area, duration, catastrophizing, and perceived stress at baseline and recall.

The low-dose (drawing and non-drawing) groups showed correlations between the PP intensity with the RPP intensity, the PP area and the RPP area. A correlation between the PP intensity and the RPP area ($p<0.01$) was also shown (Table 2).

(please, insert table 2 here)

The high-dose (drawing and non-drawing) groups showed correlations between the PP intensity with the RPP intensity, the PP area with the RPP area, and the RPP intensity with the RPP intensity. Additionally, a correlation was shown between the PCS and the PSS ($p<0.01$) (Table 3).

(please, insert table 3 here)

There was no dose-response difference in peak pain intensity and area at baseline and recall, as well as PCS and PSS. Therefore, data were pooled to explore dose-independent correlations.

Pooled data showed a correlation (Table 4) between the RPP area, the PP intensity, and the RPP intensity ($p<0.01$). The PCS also correlated with the PP intensity and RPP intensity ($p<0.01$). Additionally, PCS was correlated with the PSS.

(please, insert table 4 here)

4 Discussion

This is the first study to assess dose-response spatiotemporal patterns of pain intensity and distribution and the recall accuracy in response to experimentally evoked pain using digital pain mapping. The results show dose-response differences in pain intensity and distribution over time. However, no dose-response differences were identified at peak pain (PP) intensity and area. The results show that all participants had a similar recall accuracy for PP intensity and distribution seven days later, independently of the dose and drawing group. Lastly, results did not show a dose-response association among PCS and PSS with momentary and recall PP area and intensity. Additionally, the results show that more intense pain ratings did not associate with more extensive pain distributions.

4.1 Momentary pain

Repeated momentary pain assessments every 30 seconds revealed that a dose of 1.0ml of HS evoked a more prolonged, intense and extensive pain distribution over time, as captured by the area under the time-curve (AUC) than a dose of 0.5ml. Participants from the high dose

groups reported pain of longer duration; however, participants from the 0.5ml and the 1.0ml groups reached their PP intensity and area at a similar time following the injection of HS. Dose-response differences in the evoked pain intensity and area have been previously shown for HS (56) and for other experimental models, such as mustard oil (38). However, not all experimental models of pain show dose-response differences, as is the case of experimental pain induced by capsaicin injections (39).

A relatively surprising finding is that the intensity ratings were not associated with the size of the area in the 1.0ml group when assessed at PP and overall (pooled, dose-independent data). However, the PP intensity ratings were strongly associated with the size of the PP area in the 0.5ml group. These results suggest that more intense pain ratings are not clearly associated with more extensive pain distributions.

The results showed that a 1.0ml HS dose evoked a greater overall pain spread, as expressed by the size of the bounding box area, and a greater overall shift laterally towards the hip, as expressed by the centroid X coordinate, than the 0.5ml dose. These results suggest that larger doses of HS evoke a larger pain spread. The results were could not identify any significant patterns in pain distribution within the 0.5ml or the 1.0 ml doses in a systematic fashion. The lack of pain distribution pattern identification for the 0.5ml or the 1.0ml may be explained by large variability in pain extent among participants and the moderate pain intensity evoked.

In contrast to our study, Lei and colleagues (56) showed dose-response differences for the PP intensity and the PP area and for the time-to-PP intensity and area. These contradictory results may be explained by different HS doses and administration methods (56), evoking more or less intense pain ratings (42). Lei's study administered much larger doses of HS (2.0ml and

4.8ml) by infusion (141,142) than our bolus injected 0.5ml and 1.0ml. Interestingly, Lei's 2.0ml dose and our 0.5ml dose evoked similar mean peak pain intensities (56). However, Lei's pain duration was considerably longer (56). These findings suggest that longer pain duration may be associated with larger volumes of HS (50) rather than with the intensity of the pain evoked. Therefore, the individual's HS reabsorption ability may be a factor influencing the duration of HS-evoked pain.

Overall, these results suggest that there is evidence of the variability of spatiotemporal patterns of pain distribution following an acute low-back experimental model of pain, likely missed with traditional pen-and-paper approaches and that repeated momentary digital pain drawings can be used as a tool to explore further and deepen our understanding of the mechanisms of referred pain.

4.2 Pain Recall

Results show that the pain drawings representing the PP area and RPP (recalled peak pain) area were similar seven days later among the four groups. Participants accurately recalled the pain intensity and distribution independently of the dose received or the repeated pain drawing task, suggesting a low pain recall error. Therefore, repeated pain reports of pain intensity and drawings of pain distribution did not influence the pain recall accuracy in healthy participants following a single pain event. These results may differ in cases of multiple events of pain throughout the day or week and, most likely, under acute and persistent pain conditions.

4.3 Associations among psychological variables with momentary and recall pain.

The size of the PP area and the RPP area were not associated with pain catastrophizing or perceived stress scores overall, as opposed to the PP intensity and RPP intensity ratings, suggesting that the pain area may be less susceptible to catastrophizing. These results suggest that pain distribution may add additional information during pain assessment, not captured by the pain intensity, as the area and intensity are not always correlated. The relationship between pain experience and catastrophizing in the clinical population has been widely described (74–76). However, none of the healthy participants in our study reported high catastrophizing scores (PCS<30); thus, these results may not apply to clinical pain populations where catastrophizing may play a role in the patient's pain mediation (74–77).

These findings can have implications in studies exploring experimental pain models including HS evoked pain. Future studies should consider the capture of momentary pain distribution to obtain a complete assessment of the experience of pain and modulation. Prospective studies could benefit from the use of digital pain drawings to explore spatiotemporal patterns of evoked pain following high doses of HS and other models.

4.4 Limitations

The assessment of momentary pain in this study had methodological limitations known prior to the start of the study. Firstly, the participants' perceived body image may influence the ability to accurately represent the HS evoked pain distribution onto the body chart (78). Secondly, a discrepancy between the real pain distribution and the drawable area on the body chart cannot be rule out, although in this study, each group would be equally influenced by this limitation. A visual review of the drawings does not show any pain areas extending to the edge the body chart; although this cannot rule out whether participants experienced pain on

570 the posterior aspect of the body. Future studies should include both front and back views of
571 the body. Lastly, the number of participants in each of the four groups may not have been
572 large enough to identify spatiotemporal differences in momentary pain due to the large
573 variability of pain intensity ratings and distribution among participants. A post-hoc effect size
574 calculation (partial ETA squared) for the PP area showed that 10% of the size of the PP area
575 was attributable to the group, suggesting that the group size may be underpowered.
576
577 The assessment of the pain recall accuracy also had a methodological limitation as the non-
578 drawing groups did not complete momentary pain drawings to quantify the size of the PP
579 area. Therefore, the size of the PP area from the drawing groups was used as a reference for
580 the non-drawing groups during the pain recall assessment. Using G*Power (79) it is estimated
581 that a minimal sample size of 37 participants receiving a 1.0ml injection of hypertonic saline
582 is necessary when exploring PP area recall accuracy This study design limitation may also
583 have affected the results showing a lack of influence in the pain recall from the continuous
584 pain drawing task.
585
586 **4.5 Conclusions and implications**
587 This study showed differences in spatiotemporal patterns of pain intensity and distribution in
588 a dose-response fashion to experimental acute low back pain. Unlike pain intensity, pain
589 distribution and area may be less susceptible in an experimental setting. Higher intensities of
590 momentary pain do not appear to influence the ability to recall the pain intensity or
591 distribution in healthy participants.
592
593 The recall of pain distribution in experimental settings does not appear to be influenced by the
594 intensity despite differences in the pain experience. Pain distribution may add additional value

to mechanism-based studies as the distribution reports do not vary with pain catastrophizing.

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Informed consent: Informed consent has been obtained from all individuals included in this study.
Ethical approval: The research related to human use complies with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

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