Distress is positively associated with induced secondary hyperalgesia in people with suppressed HIV

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Abstract:

Pain and distress are frequently reported by people with HIV. Although pain is widely acknowledged to contribute to distress, distress may also contribute to pain and its persistence. Given the evidence supporting a relationship between distress and clinical pain, the current study investigated the relationships between distress, secondary hyperalgesia (SH), and persistent pain. We anticipated that SH is an important link between distress and persistent pain, with distress potentially exacerbating pain by increasing the responsiveness of neurons in the central nervous system to nociceptive signalling. Our primary hypothesis was that self-reported distress would be positively associated with the induced surface area (primary measure) and magnitude (secondary measure) of SH. The secondary hypothesis was that individuals with persistent pain would display greater induced SH compared to those who reported being pain-free. The results showed that distress was positively associated with the surface area and the magnitude of induced SH. However, participants with persistent pain showed no difference in the surface area of SH compared to pain-free participants, and those with pain displayed a marginally lower magnitude of SH. These findings suggest that distress may be a worthy target of interventions in people exposed to acutely painful events. While this relationship may not be specific to people with HIV, further research is needed to establish its relevance to people without HIV.

Introduction

Pain is frequently reported by people with HIV, and is closely linked to distress. Pain prevalence in people with HIV (25% to 85%) exceeds that in the general population (11% to 50%) [60,97,103]. Even without pain, people with HIV report distress more commonly than their HIV-negative peers [1,79], and living with pain exacerbates these mood problems. People with HIV *and* pain report more mood problems and are twice as likely as their pain-free peers to consider suicide [24,27,56,62,70,82,121].

Several psychosocial factors can cause distress for people with HIV and pain. HIV-related factors include diagnosis, changes in sexual behaviour, lack of support, and challenges of chronic illness [4,28,102,128]. Each can contribute to emotional distress. Similarly, pain factors include constant pain [93] and uncertainty about its cause, both linked to increased emotional distress, depression, and fear [35,41,93,104,109].

Distress can also worsen pain. Many people with HIV and pain find that depression exacerbates their discomfort [108]. Distress may increase neuronal responsiveness to nociceptive signals in the central nervous system [29,87,116,134], positioning neuronal responsiveness as a possible link between distress and pain persistence [17,19,33,100,138]. Indeed, clinical tests for hyperalgesia, allodynia, or temporal summation can detect this increased responsiveness.

Observational studies show that distress coexists with increased central nervous system responsiveness in pain-free and clinical groups [47,111,119,136,137]. Investigating this relationship can use experimental inductions of neuronal hyperresponsiveness to determine if distress temporally predicts hyperresponsiveness, thereby providing evidence for a causal link. This approach has shown that lifelong exposure to adversity correlates with greater temporal summation, induced secondary allodynia, and the area of secondary hyperalgesia in healthy adults [111,119,136,137].

As evidence links distress to neuronal hyperresponsiveness, precision is needed. First, a person's response to stressors likely determines outcomes more than the events themselves [122]; which highlights the importance of assessing individual response. The current study uses distress to represent this response, through self-reported symptoms indicative of depression and anxiety. Second, we clarify how distress affects neuronal responsiveness. Known connections exist between the brain's corticolimbic regions, particularly the amygdala and anterior cingulate cortex which are pivotal to distress [5,39,53,126], and areas involved in modulating nociceptive signalling [11,94]. This study tests if distress facilitates afferent nociception after a neural challenge that simulates tissue injury: high-frequency electrical stimulation. Third, given that most work on induced SH has been done in healthy controls, we test whether neuronal hyperresponsiveness differs between people with and without persistent pain.

This study aimed to clarify the relationship of induced secondary hyperalgesia (SH) to distress and persistent pain status, in people with HIV. It tested two hypotheses: (i) that the magnitude of self-reported distress would be positively associated with induced SH (*primary hypothesis*), and (ii) that people with HIV reporting persistent pain would display greater induced SH than people with HIV reporting no pain (*secondary hypothesis*).

Methods

Overview

The cross-sectional data for this study were collected as part of a larger study focused on psychological distress, inflammatory reactivity, induced SH, and persistent pain in people with HIV (protocol published at [78]). In brief, participants with well controlled HIV, who reported either no pain or persistent pain, who had completed the distress self-report questionnaire, and who were eligible to undergo electrical stimulation, were invited to attend a separate session where SH was induced and assessed.

Ethical approval was granted by the Faculty of Health Sciences Human Research Ethics Committee of the University of Cape Town (764/2019) and the local health authority (ref: 24699). The larger study was registered at ClinicalTrials.gov (NCT04757987). The current study was preregistered along with a preliminary version of the analysis script developed using pilot data, at Open Science Framework (posted on 30 March 2022). An updated analysis plan was locked on 7 April 2022 before data were processed, and a record of blinded analysis and interpretation was locked on 16 November 2022, before unblinding of the analyst (LM). [link to pre-registration: https://osf.io/2hdpy/?view_only=c26d1a3e4e0a4506a836972262a9468f].

Participants

We enrolled people with HIV who were virally suppressed (< 50 copies/ml) and reported either persistent pain or no pain. Participants who reported persistent pain had to report pain on most days for more than three months [13]. Participants were eligible if they were aged 18 to 65 years, fluent in English or isiXhosa, and living with HIV, with recent evidence of viral suppression (viral load < 50 copies/ml within the preceding three months). Exclusion criteria included pregnancy or suspected pregnancy; electrical or metal implants in the forearm to be tested; known neurological, cardiovascular, or acute psychiatric conditions; sensation problems or tattoos on the forearm to be tested; or advice from a medical practitioner to avoid stressful situations. The community from which participants were recruited has high rates of unemployment (38%) and informal housing (55%) [115]. Unemployment and informal housing have been linked to distress, which aligns with the focus of this study [32,42,46,139].

Participant pain status was determined using questions adapted from the Brief Pain Inventory (BPI) self-report measure [25], which has been translated and validated in isiXhosa and used in people with HIV in South Africa [96]. The opening statement to the screening questions was: "*Throughout our lives, most of us have had pain from time to time*

(such as minor headaches, sprains, and toothaches). This statement was followed by three screening questions on pain frequency and duration: (i) *"Do you have pain other than these kinds of pain today?"* (ii) "*Other than those day-to-day kinds of pain, do you have pain in part of your body on most days?"* (iii) *"Have you had that pain on most days for more than 3 months?"* Participants who answered 'yes' to all three questions were included in the 'pain' group, whereas those who answered 'no' to all the questions were included in the 'pain-free' group. Participants who answered 'yes' to questions (i) and (ii), but 'no' to question (iii) were excluded because they were deemed to have acute pain. Participants who completed the SH procedure were compensated ZAR 150 (~USD 9.72) for their time in addition to the larger study compensation, whereas those who withdrew during the procedure received *pro rata* compensation.

Outcomes

Independent variable: psychological distress

Psychological distress was self-reported using the Hopkins Symptom Checklist-25 (HSCL-25) [127], which consists of 25 items that estimate symptoms of depression (15 items) and anxiety (10 items). Participants rate how much each symptom (e.g., 'poor appetite', 'feeling lonely', 'trembling', 'feeling fearful', etc.) applied to them in the past month on a four-point scale (1 = 'not at all' to 4 = 'extremely'). The final score (and the study measure of distress) was the arithmetic mean of all the item scores and lies between 1.00 and 4.00. The HSCL-25 has been used in South Africa [57], including with people with HIV [58]. The HSCL-25 was translated into isiXhosa using a forward-and-back-translation process to ensure the language was locally relevant [16].

Dependent variable: secondary hyperalgesia

To capture the increase in central nervous system facilitation after a barrage of afferent nociception, we chose a human surrogate model of SH for direct *in vivo* characterisation of the aspects of the response that are thought to rely on central (rather than peripheral)

changes [64,65]. In short, the induction protocol involved the delivery of controlled electrical stimulation to the skin of the forearm (Figure 1). Hyperalgesia to pinprick stimulation of the skin develops in the area surrounding the induction stimulus within 20-30 minutes after the induction. We quantified SH using two measures: surface area (primary measure) and magnitude (secondary measure).

Primary measure of SH: surface area

The surface area of SH was estimated using the 8-radial-lines method [3,68], which identifies the boundary between hypersensitive and normosensitive skin by using repeated stimuli along 8 radial lines that transect the site of stimulation at 45° angles. We used the method previously reported in [10], except that we used a 128mN Von Frey filament (Marstock nervtest, Germany), as in [23]. The surface area was assessed 30, 45, and 60 minutes after the induction.

Secondary outcome: magnitude of SH

Participants gave Visual Analogue Scale (VAS) ratings of pain to two punctate mechanical stimuli (128 mN and 256 mN; PINPRICK, MRC systems, Heidelberg, Germany) applied for ~1 s, at three different points within 1 cm of the electrode. The scale was a touch-based, electronic, vertical VAS, anchored with 0 for “no pain” at the bottom and 100 for “pain as bad as you can imagine” at the top (anchors translated for isiXhosa-speaking participants). Participants selected their rating by swiping a stylus pen across the vertical scale on the screen, prompting the bar to fill up with red to the level of the rating. This rating was recorded electronically as a number between 0 and 100. The vertical VAS is a valid and reliable measure that is easy to use, requires less reliance on numeracy concepts and is suitable for different adult populations [15,55,77,86]. This assessment was performed three times immediately before the induction and at 35, 50, and 65 minutes after the induction.

Exploratory variables

Recognising that high frequency electrical stimulation (HFS) is commonly reported to be painful and that the relationship between HFS painfulness and SH is controversial [101], we assessed the painfulness of the induction trains. Participants rated each train of HFS using the electronic VAS. The results of this assessment were reported descriptively, and we planned to include this variable as a covariate.

Given accumulating, but conflicting data, on the relationship between social support and reduced responsiveness to nociceptive signalling [21,34,36,54,69,83,91,92,105], we made a *post hoc* decision to test whether social support moderated the relationship between distress and SH outcomes, using data from the Medical Outcomes Study Social Support Survey (MOS-SSS) [110]. Due to a technical error, MOS-SSS items 17 (from the subscale for positive social interaction), 18 (subscale for emotional support), and 19 (subscale for affectionate support) had not been presented to participants. Therefore, the overall survey score was a mean of 16 items rather than 19.

** Figure 1 approximately here**

Procedure

Informed consent and participant orientation

Participants had the option to communicate in English or isiXhosa. An assessor screened participants for eligibility and facilitated the written informed consent process, during which participants were informed that their participation was voluntary, with no impact on their clinical care. Participants were free to withdraw without negative consequences. The assessor then administered the battery of self-report questionnaires (including the Hopkins Symptom Checklist-25 and BPI), drew two blood samples (results not reported here), and scheduled the participant's SH induction session.

A second assessor (LM), who was blinded to the results of the first assessor, conducted the SH induction and related assessments. The assessor settled the participant on a seat facing her across a table, with the designated pain-free arm resting on the table and a touch monitor facing the participant, to one side. Following a standardised script for consistency, the assessor orientated the participant to the study equipment and procedures. Participants were allowed to ask questions, and then verbally confirmed their previously written consent. The assessor marked the participant's forearm for the electrode location and the radial lines and calibrated the electrical current for each participant (see Calibration of electrical current). The assessor then demonstrated how to use the electronic touch-based VAS, and participants received an opportunity to practice rating each sensory modality. All practice ratings were recorded but excluded from the analysis.

Calibration of electrical current

The individual detection threshold for a single electrical stimulus was used to determine the current for HFS and subsequent assessment of primary hyperalgesia (not reported here). We used an adaptive staircase procedure to calibrate the electrical current [120]. First, the current was gradually increased from 0 mA in 0.10 mA increments until the participant reported feeling the stimulus. Second, the current was reduced in 0.5 mA increments until the participant no longer felt the stimulus. Third, the current was increased in 0.2 mA increments until the participant could once again perceive the stimulus. The final current detected in the last step represented the participant's threshold for detecting a single electrical stimulus and was multiplied by 10 and used for the stimulation intensity for both inducing SH and administering single electrical stimuli during sensory testing, as seen in other studies [64].

Baseline tests

Three rounds of baseline tests each used five sensory modalities: 128mN, 256mN, single electrical stimulus, brush and VFF (last three not reported here). The three rounds of

baseline tests were completed in approximately six minutes. Next, temporal summation was assessed (results not reported here).

SH induction

Secondary hyperalgesia was induced by applying HFS to a pain-free area of the forearm, using a circular cathode with 10 blunt steel pins against the anterior forearm and an anode around the upper arm. We chose the forearm that had not undergone venepuncture for blood collection in the primary study because venepuncture can cause local sensitivity, which could interfere with SH assessment. If both arms had undergone venepuncture or the venepuncture-spared arm had a contraindication to HFS (e.g., metal implant), SH induction and assessment were conducted on the forearm used for venepuncture seven days after venepuncture. The HFS consisted of five one-second trains, separated by 9-second breaks, at a current of 10 times the individual's detection threshold for a single electrical stimulus [66]. The study assessments were programmed in Affect5 [114]. A constant current electrical stimulator (DS7A; Digitimer Limited, Hertfordshire, UK) was used to deliver the electrical stimulation. The settings for the electrical stimulation were a voltage of 400V, a pulse width of 2000μs, and a square pulse shape. The effect of HFS is typically centred around the cathode. The participant received five trains of HFS and rated each one on the VAS. Thus, the induction yielded one VAS rating for each of the five HFS trains from each participant.

Follow-up tests

A 30-minute waiting time allowed for the development of SH [12,20], which typically becomes apparent within 20-30 minutes after induction using HFS [99,101]. Therefore, we started testing 30 minutes after the first HFS train to capture the peak effect of SH. During the waiting time, participants were provided with popular reading materials with content unrelated to the study. The surface area of SH was assessed 30, 45, and 60 minutes after the induction (Figure 1). The 5 sensory tests were re-administered 35, 50, and 65 minutes after the induction (Figure 1).

Blinding

Two assessors collected study data. The first assessor collected self-reported distress and pain status. The second assessor induced SH using HFS and assessed its surface area and magnitude. Participants were blinded to the study hypotheses; the first assessor was blinded to the study aims and hypotheses; the second assessor was blinded to participant distress self-report and study group (pain or pain-free); the data analyst for hypothesis 2 (people with HIV reporting persistent pain would display greater induced SH than people with HIV reporting no pain) was blinded to the study group.

To support the blinding of participants to the study aims and hypotheses, we withheld information on the study aims and hypotheses, including that participants were being grouped by pain status. Participants completed a blinding assessment after the procedure: they were asked to guess the purpose of the study, and their response was recorded. We applied conservative criteria to assess whether participants remained blinded to the study's aims and hypotheses.

After the SH assessments, the blinding assessments were completed, first by the assessor, and then by the participant. The assessor had to guess each participant's study group and rate her confidence in her guess on a five-point Likert scale of "not at all confident", "not confident", "confident", and "extremely confident" (the planned 'neutral option was omitted by technical error – protocol deviation 1 of 4). Finally, the assessor asked the participant for feedback on her communication and the general experience of the procedure. The second assessor also conducted the preliminary data analysis; therefore, to maintain blinding to the study group, the study data were assigned a second study ID for each participant and the study groups were recoded as 'a' and 'b' by VJM. The second assessor then conducted the preliminary data analysis and interpretation with this recoding in place, after which the assessor was unblinded to complete the interpretation and write the manuscript.

Data handling and analysis

Participant demographic information, distress and pain status data were recorded using the University of Cape Town's RedCap database [48,49]. The data on SH outcomes were directly recorded into Affect5, and additional procedural notes were manually recorded and later transcribed into an Excel sheet. All data from RedCap, Affect5, and Excel were imported into R for analysis, using R version 4.2.0 (The R Foundation for Statistical Computing) and RStudio (Integrated Development Environment for R 2023 version 12.1.402) [118]. The packages used were: tidyverse [129], readxl [130], gridExtra [6], here [90], kableExtra [141], ggstatsplot [76], pracma [14], dplyr [131], readr [132], arsenal [52], bayestestR [80], DescTools [112], rcompanion [81], performance [76], ggrepel [113], formatR [133], magrittr [7], ggeffects [75], lme4 [9], and rlmer [67].

The target sample size was determined pragmatically: given the sourcing of participants from the pool of ~100 participants in the larger study, the more restrictive inclusion criteria for the SH induction, and the likelihood of some attrition. We planned to recruit 60 participants (30/group) to the SH induction. Previous studies of experimentally induced SH using HFS without between-group comparisons had used samples of 7-20 [20,64], and we deemed the 85% power to detect a correlation of r=0.40 (when alpha is 0.05) offered by a sample size of n=53 to be sufficient. To contextualise the statistical power provided by our final sample, a sample size of n=45 would be expected to provide 80% power to detect a correlation of r=0.41 when alpha is 0.05.

Demographic data were presented in tables and reported descriptively. Frequencies and proportions are reported for categorical variables and median (IQR) for numerical variables. In all box-and-whisker plots, individual participant scores are represented by dots, while horizontal lines show the 25th, 50th (median), and 75th percentiles. The whiskers of the boxplots indicate the spread of the data beyond the IQR: the upper whisker extends from Q3

to reach the maximum data point that falls within 1.5 times the IQR, whereas the lower whisker extends from Q1 to reach the minimum data point that falls within 1.5 times the IQR.

Primary and secondary measures

Both hypotheses were tested together, using one model for each measure of SH. The dependent variable was the surface area (primary measure) or magnitude (secondary measure) of SH.

For surface area, the within-participant area was the sum of the areas of the 8 triangles formed by the transition points on the radial lines, resulting in one estimate of surface area for each of the three post-induction time points. In the protocol, we planned to sum the area across the three time points for each participant, using the 'area under the line' for both surface area and magnitude of SH. However, given that the area under the line can yield unreliable estimates when few replicates are available, we opted to include all three assessments, clustered as repeated measurements within each participant, in a linear mixed model in R (protocol deviation 2 of 4).

For magnitude, the mean ratings for the two punctate mechanical weights were calculated for each time point, and the mean rating before induction was subtracted from the mean rating at each post-induction time point. This was protocol deviation 3 of 4: in the protocol, we had planned to express follow-up ratings as a percentage of baseline mean ratings, but we opted for the difference calculation to avoid artificially inflated statistical estimates of effect.

The independent variables were distress and group. A random factor allowed a different intercept for each individual; the three repeated measures were nested within each individual. Unadjusted models were specified, followed by models adjusted by three covariates: the current used for SH induction (calibrated to individual), the within-participant median of the ratings of the HFS induction trains, and the number of days between distress self-report and SH induction. The last covariate was relevant to only a few participants (n=8)

but was included in case the delay led to the distress score poorly representing the participant's state at the time of SH induction and assessment. For only the magnitude models, the within-participant mean of all pinprick ratings (128 mN and 256 mN) for the baseline timepoint was also included as a covariate, to control for baseline differences in sensitivity to pinprick stimulation.

We visualised model assumptions by generating plots to check the following model assumptions: normality of residuals, linearity, homogeneity of variance, influential observations, and collinearity, where applicable. Given that the conventional linear mixed models violated model assumptions, we conducted robust linear regression to account for influential observations. Next, we computed bootstrapped 95% confidence intervals for the robust regression estimates to account for the violations of the normality assumption. Bootstrapping provides a way to assess the stability of the findings by resampling the data and evaluating the variability of the regression estimates across multiple samples to offer a more reliable estimate of model uncertainty [38]. We report effects as estimates bootstrapped from covariate-adjusted robust models including model parameters without bootstrapping. We opted against transforming the data given the nature of the violations of distributional assumptions and to retain interpretability

Blinding analysis

We report the percentage of participants who correctly guessed the aim of the study. We also report the percentage of participants for whom the second assessor correctly guessed group membership. Given that no single method perfectly captures blinding effectiveness, we assessed the blinding of the second assessor using three methods.

First, we used Cohen's Kappa statistic (protocol deviation 4 of 4). Whereas James's Blinding Index, which was planned in the protocol, prioritises a "do not know" response that was not offered in our design [8], Cohen's Kappa is suitable for a two-category forced-choice design like ours ("pain" or "pain-free") [26]. Second, we used Chi-square goodness-of-fit tests to

assess whether the observed distribution of guesses about group membership differed from the expected distribution based on a 50% chance of guessing correctly (which would reflect random guessing and retained blinding) [30]. Third, we also considered the match between correct guesses about group membership and assessor-reported confidence. The availability of confidence ratings allowed us to look more closely at potential unblinding for a subgroup of participants about whose group status the assessor reported feeling confident. Therefore, we drew the data on only those participants for whom the assessor reported confidence of 4 or 5 and conducted a separate chi-square test on the group guess data, comparing the actual frequency of accurate group guesses to the 50% frequency expected under chance conditions (i.e. random guessing; blinding retained). Finally, we repeated the main analyses without participants for whom the second assessor had accurately and confidently guessed group membership, as identified above, to assess the sensitivity of the main findings to potentially broken blinding.

Planned exploratory analyses

We plotted the VAS ratings for the five HFS trains and reported data descriptively. We imputed missing values (which appeared to be missing at random), with the median group rating within the HFS train (1-5) and grouped from the available data. This approach considered potential variations in painfulness between trains and study groups. Medians, being robust to outliers and less reliant on data distribution shape, are well-suited for imputation as they help preserve underlying patterns within groups and across HFS trains [50]. This approach was taken to avoid losing participants in the main regression analyses for whom ratings for the HFS trains were missing.

Post-hoc exploratory analyses

We visually investigated whether withdrawal from the procedure was predicted by distress severity, and planned to follow up any visual indication of a relationship using logistic regression. In addition, we tested whether social support moderated the relationship between distress and SH outcomes by including a term for an interaction between distress

and social support in each model and computed bootstrapped 95% confidence intervals for the effect of this interaction term on SH outcomes. Further, we planned to follow up on any significant result with interaction plots [74].

Results

Data were collected from 9 February 2021 to 24 November 2021.

** Figure 2 approximately here**

Participants

Sixty-three participants, 17 identifying as males and 46 as females, were deemed eligible and enrolled in the study. Seven participants withdrew during the procedure; data from another eleven were excluded from the analysis due to incompleteness or subsequently identified ineligibility (details in Figure 2). Complete datasets were available for 45 participants (pain: n=19; pain-free: n=26). None of the participants reported taking analgesic medication within 24 hours before the induction. For pain *in the past week*, low back pain was the most reported site (n=11) and the most common site of worst pain (n=10). For pain *for the past 3 months*, upper back pain was the most reported site (n=11), whereas the upper back (n=9) was reported as frequently as the low back (n=9) as the site of the worst pain. Data on pain severity (for *pain in the past week* and *pain for the past 3 months*) and interference for all *pain in the past week*, presented only to participants reporting persistent pain are shown in Table 2. The baseline ratings to pinprick stimulation were higher in the pain group (7.50(0.67-22.67)) than in the pain-free group (1.00(0.33-3.38), p=0.05).

Results of HFS induction

The median (IQR) current used for HFS was 0.14 mA (0.09-0.18 mA) and there was no difference in current between groups (Table 2, p=0.9). Nearly half (126 of 255, 49%; pain:

50; pain-free: 73) of the VAS ratings of the HFS trains were missing due to a technical problem. We used the available data to calculate the median (IQR) ratings of the HFS trains for the sample and found 48 (10-82) on a VAS expressed from 0-100. There was no difference in the ratings of HFS trains between the pain (61(13-90)) and pain-free (44(8-73)) groups (p=0.13), but the group-level ratings differed between trains and were non-parametrically distributed. Therefore, for the adjusted models in the main analyses, we imputed the missing ratings for HFS trains by using the group-specific median rating for each train.

The median (IQR) surface area of SH for the sample was 22.27cm^2 (5.66-49.85). Of the 135 surface area data points (three per participant), 12 participants had no SH at T30, eight had no SH at T45, and 10 had no SH at T60. Five (of 45) participants showed hyposensitivity at all post-induction time points. The median (IQR) magnitude of SH for the sample was 1.17 (0-7.67). Of the 135 post-induction data points, hyposensitivity was observed at 21 data points at T35, 22 at T50, and 23 at T65. Eight (of 45) participants showed hyposensitivity at all time points. Both the surface area (p=0.15) and magnitude (p=0.61) of SH were no different between groups.

** Table 1 approximately here**

Participants with persistent pain reported more distress

The median (IQR) distress severity for the sample was 1.48 (1.12-2.24). The pain group reported significantly higher distress severity (2.24 (1.68-2.58)) than the pain-free group (1.38 (1.08-1.60)) (p<0.001, Table 2).

Distress positively predicted induced SH area and magnitude

Figure 3A-D shows the relationship between distress and SH without accounting for the clustered nature of the data. Formal analysis showed that distress severity was positively associated with the surface area of SH in both unadjusted and covariate-adjusted models

across conventional (Table S1, model diagnostics Figures S1 and S2) and robust models (Table S2). On average, a 1-unit increase in distress was associated with an average 19.10 cm^2 (Table 2, 95% CI: 2.85-35.34; p=0.02) increase in the surface area of SH, with all other variables held constant.

For the magnitude of SH, distress severity was positively associated with the magnitude of SH in all models except the unadjusted conventional model (Table S1-S2, model diagnostics Figures S3 and S4). On average, a 1-unit increase in distress was associated with an average increase in the magnitude of SH of 6.24 (Table 2, 95% CI: 1.28-11.21; p=0.01) (change in rating on a 0-100 scale).

** Figure 3 approximately here**

** Table 2 approximately here**

Only induced SH magnitude was related to pain status

Figure 4 shows the SH over time between groups. For the surface area of SH, the main effect of group was not statistically significant (p=0.87). For the magnitude of SH, the main effect of group was statistically significant: on average, magnitude was marginally *lower* in participants with pain than in pain-free participants, by 6.92 units (95% CI: -13.70 to -0.13, p = 0.05).

** Figure 4 approximately here**

The distress-SH relationship was stronger for people with pain, on one measure

Given that Figures 3C and 3D suggested that the strength of the associations between distress and the two SH measures might differ between groups, we included an exploratory analysis of the interaction between distress and group in each covariate-adjusted robust

regression model (Table S3). For the surface area of SH, there was no interaction between distress and group and surface area (Table S3, bootstrapped coefficient: 17.63; 95% CI: -14.48-49.75; p=0.28). For the magnitude of SH, there was a significant interaction between magnitude and group (Table S3, bootstrapped coefficient: 13.13; 95% CI: 4.04-22.21; p<0.01): the relationship between distress and magnitude was greater in the group with pain than in the pain-free group.

Blinding check

None of the participants correctly guessed the aim of the study. The assessor correctly guessed the group membership of 20 out of 45 participants (44%). Cohen's Kappa estimate was -0.13 (95% CI: -0.42-0.16), indicating no meaningful agreement between the assessor's guesses and the actual group memberships. The Chi-square goodness-of-fit tests confirmed no relationship between the actual group and the assessor's guess of the group (pain: X^2=1.3; p=0.3; pain-free: X^2=0.03, p=0.8). There were 4 instances of correct group guesses with confidence rated 4 or 5 (pain: n=2; pain-free: n=2), and 11 instances of incorrect group guesses with confidence rated 4 or 5 (pain: n=6; pain-free: n=5). The Chi-square goodness-of-fit tests on these data confirmed no relationship between the actual group and the assessor's guess of the group (pain: X^2=2; p=0.2; pain-free: X^2=0.5, p=0.5). Together, these assessments suggest that participant and assessor blinding was maintained throughout the procedure. Nevertheless, as planned, we excluded instances where blinding might have been compromised (n=4) and reran the main analyses. The main effects of distress on the surface area (p=0.03) and magnitude (p=0.04) of SH remained significant. However, the between-group difference in magnitude of SH was no longer statistically significant (p=0.30).

Post-hoc exploratory analyses

There was no significant difference in distress between participants who withdrew (n=7, median HSCL-25 score: 1.44; IQR: 1.20-1.92) and those who completed the study

procedure (n=45, median: 1.48; IQR: 1.12-2.24; p=0.7). Social support did not moderate the relationships between distress and either measure of SH (interaction term coefficients: surface area 0.99; 95% CI: -15.73-13.75; p=0.89; magnitude -1.81; 95% CI: -6.93-3.31; p=0.49).

Discussion

The current study aimed to clarify the relationship of induced secondary hyperalgesia (SH) to distress and persistent pain status, in people with HIV. The primary hypothesis was that self-reported distress would temporally predict the surface area and magnitude of induced SH. This hypothesis was upheld: distress was positively associated with both the surface area and the magnitude of induced SH. The secondary hypothesis was that individuals with persistent pain would display greater induced SH compared to those who reported being pain-free. This hypothesis was not upheld: participants with persistent pain showed no difference in the surface area of SH compared to pain-free participants, and although those with pain displayed a marginally lower magnitude of SH, we interpret this relationship as likely to be spurious because there was no evidence to reject the null hypothesis once unblinded participants were excluded from the analysis.

The strength of the relationship between distress and induced SH in this sample suggests this relationship is worthy of attention. To support interpretation of the size of this relationship, figure 5 visualises the average increase in SH surface area that was associated with a 1-unit increase in distress, at the extremes observed in this study (0-19cm^2 and 99-118cm^2). In contrast, a 6-unit increase in SH magnitude per 1-unit change in distress is below the accepted threshold for clinically significant changes in pain ratings (20.9 to 57.5 mm), as observed in individuals with chronic temporomandibular disorder [37]. In our sample, the average increase in SH magnitude was relatively low and ranged from -17 to 57mm. However, HFS likely falls short of modelling the total nociceptive load initiated by clinical tissue injury, given that HFS lacks the peripheral sensitisation that would be recruited

by actual tissue injury [64,124]. Unlike clinical SH, experimental SH is short-lived and the experimental context of HFS also lacks other cues for threat value that would enhance signalling in real-life scenarios of tissue injury [10]. Therefore, under real-life conditions, distress may support a greater increase in central neuronal responsiveness than that observed in this study, although this possibility remains to be tested. The alternative – but not mutually exclusive – possibility is that distress-driven enhancement of responsiveness occurs by dampening inhibition. However, inhibitory processes were not the focus of the current study, and there is evidence that the response to high-frequency electrical stimulation captures both facilitatory and inhibitory activity [98].

** Figure 5 approximately here**

Our results both support and extend previous work showing that distressing events, and interventions to ameliorate the lasting consequences of distressing events, influence neuronal hyperresponsiveness related to pain. Healthy adults with higher adversity scores show greater temporal summation than those with lower adversity scores [89], and women with higher counts of stressful life events display larger areas of capsaicin-induced SH than peers with lower counts [134]. Distress-focused interventions can also influence SH: in women with a history of trauma, an emotional disclosure intervention initially increased, but later reduced, experimental SH along with negative affect and pain-induced negative emotions (at 1 day vs 1 month) [135]. Similarly, cognitive training to reduce pain catastrophising and improve pain coping resulted in less SH than non-pain-focused training [106], and handholding or passive support from a romantic partner has been shown to reduce induced SH [34,54]. Our findings extend this literature by confirming the relationship between psychological state (rather than event exposure) and central neuronal hyperresponsiveness. While this does not confirm causality - distress could arise secondary to or in parallel with nociceptive responsiveness - the findings underscore the clinical importance of addressing both distress and pain when present together.

Our secondary hypothesis was that participants with persistent pain would show greater induced central neuronal hyperresponsiveness than participants without pain. Surprisingly, our data did not support this, despite reports of central neuronal hyperresponsiveness in other persistent pain conditions, including fibromyalgia [18,33], chronic whiplash [125], unilateral shoulder pain [107], chronic pelvic pain [61], rheumatoid arthritis [84], and osteoarthritis [72]. Spinal long-term potentiation is one of the mechanisms proposed for these findings (alongside impaired descending inhibitory control) [45,64,66,123]. HFS has been shown to induce similar behavioural changes in humans and rodents, and to cause spinal long-term potentiation-like changes in the rodents [98]. Although this evidence supports the suitability of the HFS model, we did not find more HFS-induced SH in people with persistent pain than in people with no pain. Previous work on central neuronal hyperresponsiveness in people with HIV is limited to homotopic sensitisation and has demonstrated links between temporal summation of painful stimuli and either viral suppression [44] or persistent pain status [95] – although the latter was found in a predominantly male sample with mixed levels of viral suppression. Homotopic and heterotopic processes seem to rely on different substrates, as shown by the lack of association between temporal summation and the area or magnitude of HFS-induced SH in healthy humans [98]. The current findings suggest that heterotopic spinal LTP-like processes are unlikely to distinguish between people with HIV based on persistent pain status, and suggest that future comparisons of central neuronal hyperresponsiveness between people with and without persistent pain should control for distress as a potential confounder.

There are two possible alternative explanations for our finding that participants with HIV and persistent pain did not display greater neuronal responsiveness than pain-free participants. The first possibility is that neuronal hyperresponsiveness is somatotopically localised to synapses receiving information from the specific body site(s) where clinical pain occurs [73]. Although we induced SH at a standardised, pain-free site to detect globally increased neuronal responsiveness such as that commonly hypothesised to underpin widespread pain

[51], we would have missed any somatotopically localised hyperresponsiveness. However, a recent study relating susceptibility to induced SH to post-thoracotomy pain also used the forearm as an induction site and did confirm a relationship, suggesting hyperresponsiveness was not somatotopically localised – although the analysis did not control for distress [45]. The second possibility is that our between-group comparison of SH may have been underpowered to detect a difference because our sample size was pragmatically determined.

Our finding that self-reported distress temporally predicts greater induced SH has potential implications for clinical care. Although our findings may be specific to people with undetectable HIV and do require replication in other groups, this seems unlikely in light of the known links between distress and pain in other groups [22,43,117]. That distress may heighten neuronal sensitivity to nociceptive challenges suggests that distressed individuals may be vulnerable to worse outcomes following real-life noxious events such as surgery. This aligns with evidence linking distress and distress-related factors to elevated risk of poor postoperative outcomes including acute post-operative pain, increased opioid use and delayed recovery from surgery [63,71]. That heterotopic LTP-like processes may partly underpin this relationship paves the way for mechanistically targeted interventions to address distress in patients approaching surgery or other painful events [85,140]. Although non-pharmacological interventions show significant promise for reducing preoperative anxiety (e.g., reasonable evidence proposes music as a promising intervention [2]) greater clarity on the mechanistic pathways targeted by these interventions would support optimised selection and clinical delivery, and insight into their relevance to pain.

The current study has three relevant limitations. First, our method of screening for the surface area of SH could have missed areas of SH on the lateral or medial sides of the forearm. We screened along the proximal-distal axis based on the findings of previous studies reporting either a greater surface area along the proximal-distal axis than the medial-lateral axis [40], or no differences [31]; indeed, some studies assess along only the proximal-

distal axis [88]. Given that our piloting of various assessment methods has revealed an overestimation of surface area when no screening is used before radial line stimulation, we prioritised specificity, but we acknowledge that we could have missed unusual anatomical distributions of SH. Second, many ratings of HFS trains were not recorded by our system, which compromised our exploratory analysis of the painfulness of the HFS induction. Third, the study was conducted in people with HIV, and therefore needs replication in the general population. However, it is important to note that HIV is so prevalent in South Africa that people with HIV are not easily distinguished and are reasonably representative of the general population [59]. An important strength of this study is that we induced SH in a clinical population, not just pain-free controls, which is an important translational step towards clarifying the clinical relevance of induced SH. The execution of this study also enacted principles of transparent science: we published the study protocol, locked the analysis plan, reported deviations from the protocol, made analysis scripts publicly available, and openly discussed model assumptions and actions taken to address any violations.

Conclusion

This study found that distress positively predicted both the surface area and magnitude of induced SH in people with suppressed HIV, and this was consistent across participants with persistent pain and participants with no pain. Alongside the evidence that heightened SH reflects enhanced nociceptive responsiveness and arguments that heightened nociceptive responsiveness may predispose people to problematic pain, our findings suggest that distress may be a worthy target of interventions in people approaching painful events such as surgery. Although there is little basis to think this finding is specific to people with HIV, its relevance to people without HIV is yet to be tested.

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Figure captions

Figure 1: Study procedure. The green box indicates self-reported assessments, and the white box indicates secondary hyperalgesia (SH) induction and assessments. The self-reported assessments were separated from the SH induction and assessments by either a short break or up to 7 days. The five red blocks indicate the high frequency electrical stimulation trains. The red circle centrally located on the radial lines on the forearm indicates

the cathode, with each of the 8 lines on the skin spaced 45 degrees apart and the black dots forming the lines 1cm apart (not drawn to scale). The area shaded in orange shows the surface area of SH.

Figure 2: Flowchart of participants enrolled and taken to the analysis.

Figure 3: Scatterplots (A-D) overlain with the best-fitting straight line (ribbon = 95% CI), not the regression model. Each dot represents a participant's score at one of three time points. Panels A and B show relationships between distress and secondary hyperalgesia (SH) surface area for the whole sample (n = 45; primary hypothesis) and stratified by group, respectively. Panels C and D show relationships between distress and SH magnitude for the whole sample and stratified by group, respectively. Magnitude is expressed as the change in rating from the mean of the three baseline assessments to each follow-up assessment. The horizontal red dotted line indicates no SH.

Figure 4: The surface area (A) and magnitude (B) of secondary hyperalgesia (SH) over time. Each dot represents a participant's score at one of three time points. Magnitude is expressed as the change in rating from the mean of the three baseline assessments to each follow-up assessment. The horizontal red dotted line indicates no SH.

Figure 5: Represents 19cm2 increases at the two extremes of surface area observed, to illustrate the estimated effect of a 1-point increase in distress on surface area secondary hyperalgesia (SH). (A) shows a difference between 0 and 19cm2 (left to right); (B) shows a difference between 99 and 118cm2 (left to right). The areas shaded in blue and green show the mapped surface area of SH. Coloured dots mark areas with distinct changes in sensation, and the red circle indicates the cathode's position. Figure not drawn to scale.

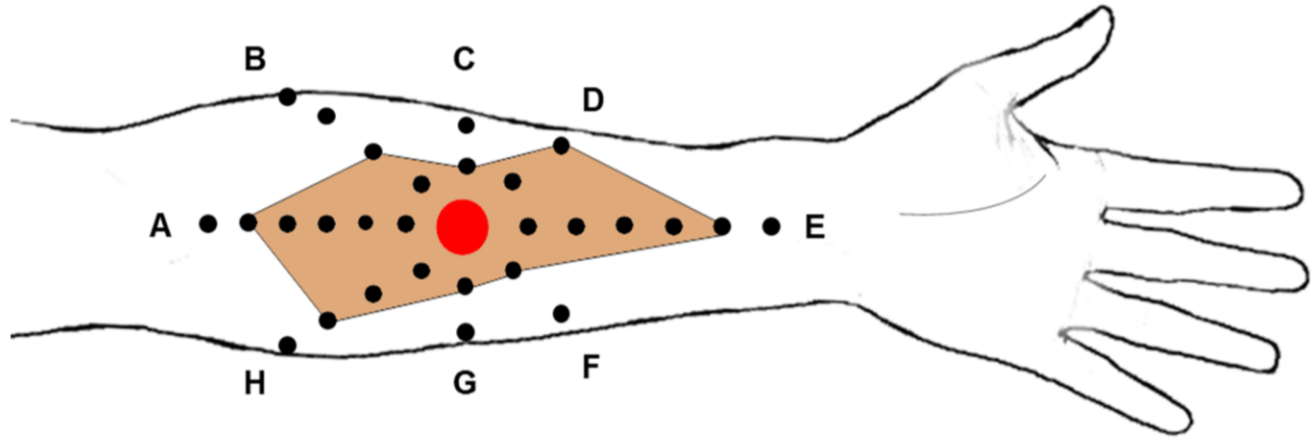
Table captions

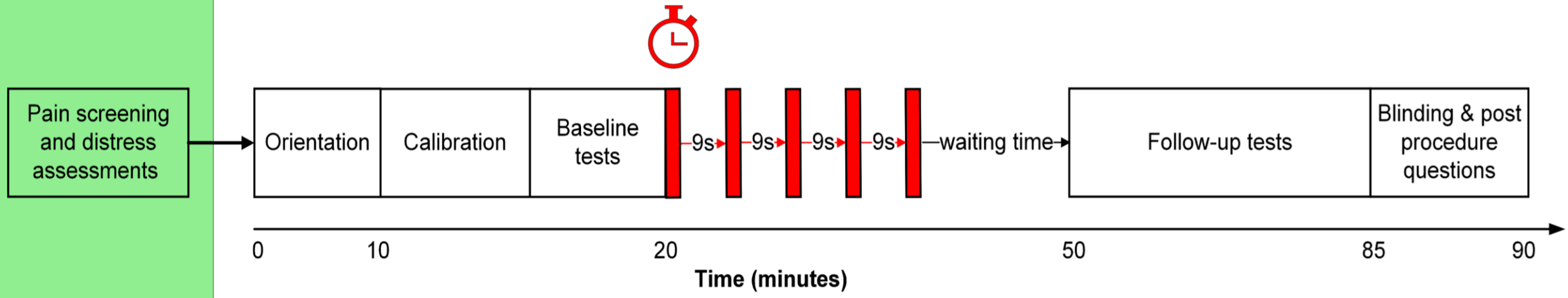
Table 1: Descriptive data (n=45). The group with persistent pain reported higher distress severity, and higher baseline ratings to pinprick stimulation (not reported) than the pain-free group. After imputation, between-group comparison of ratings of HFS trains showed a difference that was not present in the data before imputation. No other significant differences were noted between the groups. HSCL-25: Hopkins 25-item symptom checklist; MOS-SSS: Medical Outcomes Survey Social Support Scale; BPI: Brief Pain Inventory; NA: Not Applicable.

Table 2: Bootstrapped covariate-adjusted robust models predicting surface area and magnitude of secondary hyperalgesia (SH). pid: individual participant code.

Self-reports

SH induction and assessments





Enrolment

Entered procedure **n=63**

Data inspection

Datasets inspected **n=63**

Excluded **n=11**
1: Procedure terminated
1: Ineligible to participate
2: Data not saved due to electricity failure
2: Reported having epilepsy, but inadvertently included in the study by recruiter error
4: Reported different pain status between screening and study assessment
1: Received the SH induction on the same arm used for venepuncture without a 7-day waiting period

Analysis

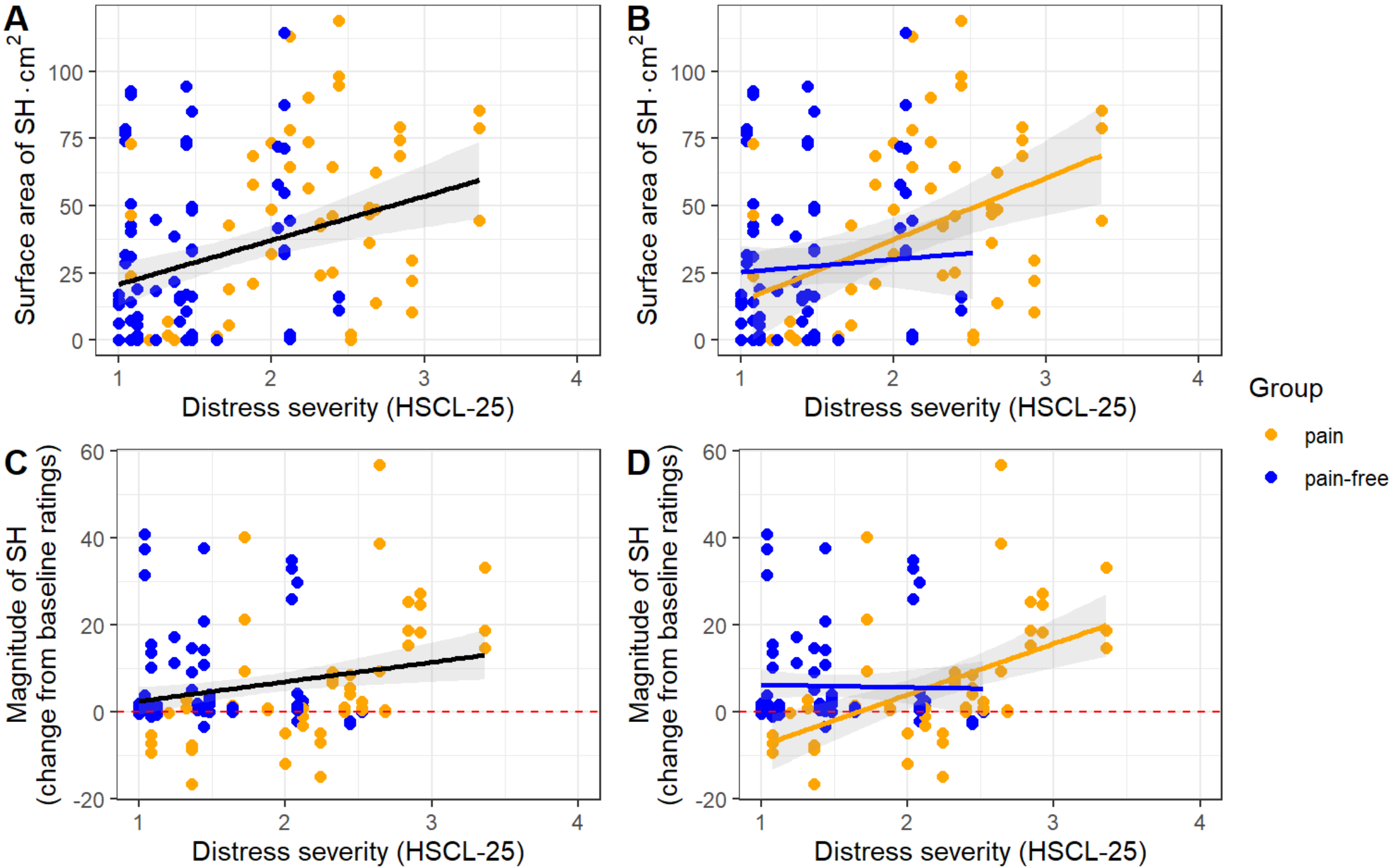
Participants taken to analysis **n=52**

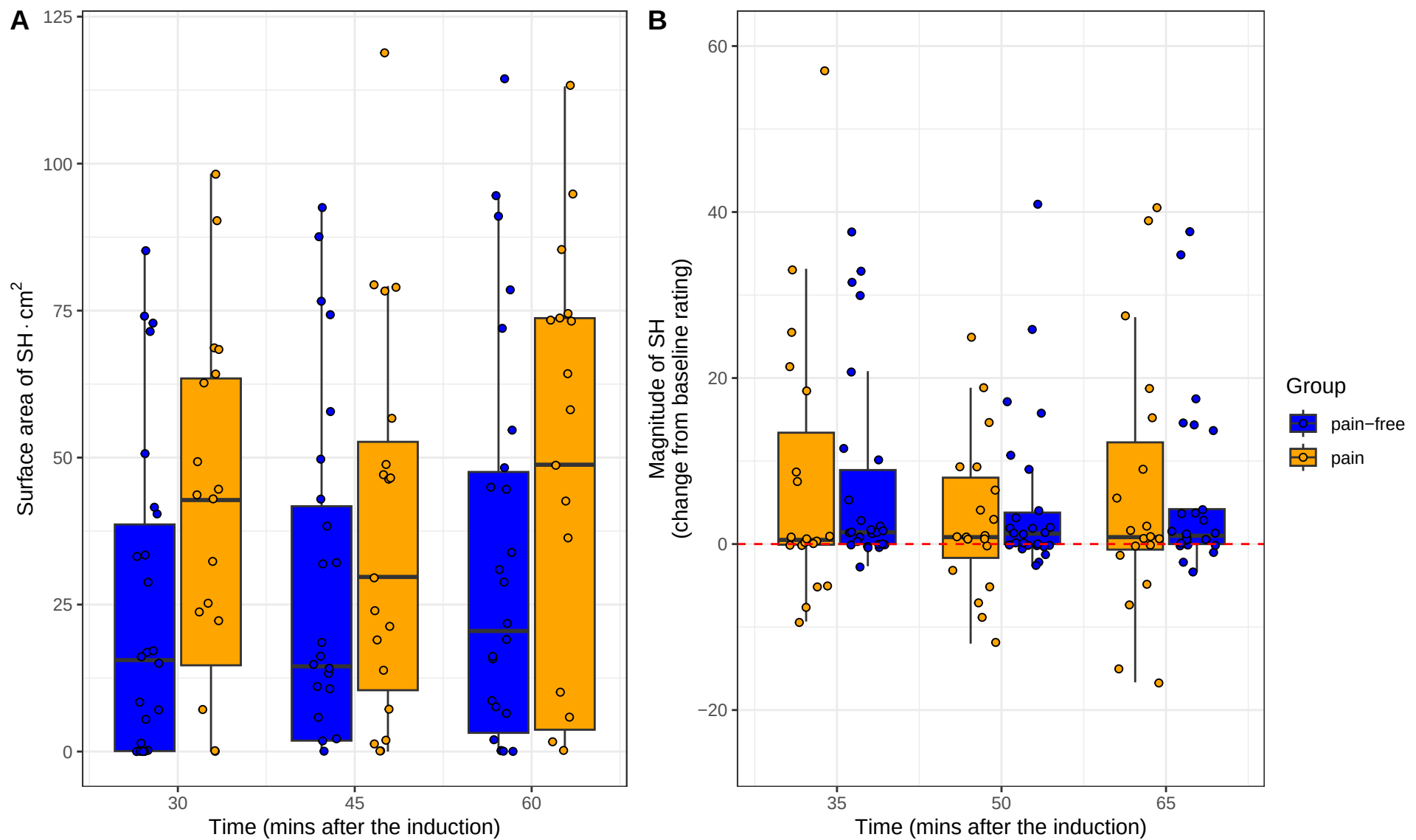
completed n=45

withdrew n=7

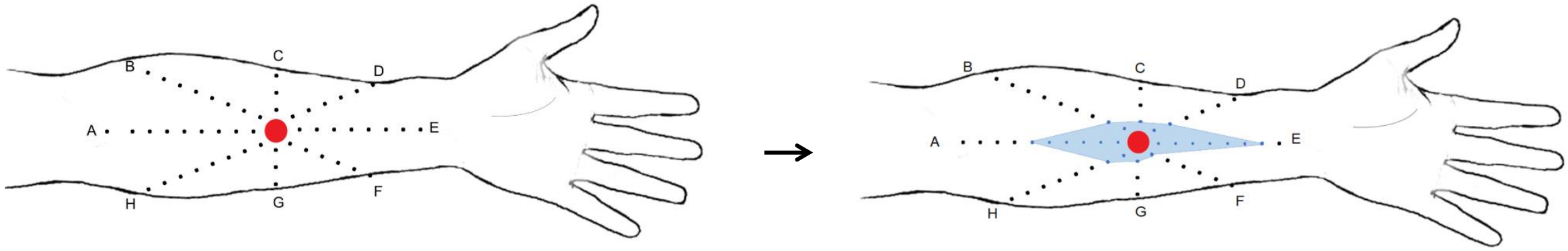
Main analyses **n=45**
(n=43 assessor blinding assessment; missing confidence level rating n=2)

Exploratory analysis **n=52**

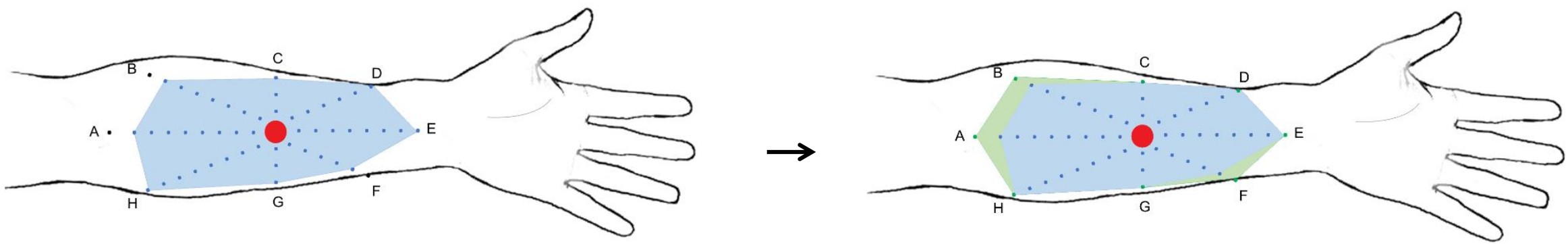

A
B
C
D
Surface area of SH · cm^2
Magnitude of SH (change from baseline ratings)
Distress severity (HSCL-25)
0
25
50
75
100
-20
20
40
60
1
2
3
4
Group
pain
pain-free


A
Surface area of SH · cm2
125
100
75
50
25
0
30
45
60
Time (mins after the induction)
B
Magnitude of SH
(change from baseline rating)
60
40
20
0
−20
35
50
65
Time (mins after the induction)
Group
pain−free
pain

A



B



	Pain (N=19)	Pain-free (N=26)	Total (N=45)	p-value
Age (years)				0.765
Median	43.00	41.00	41.00	
Q1, Q3	36.00, 48.50	34.25, 46.75	35.00, 47.00	
Range	30.00 - 58.00	31.00 - 64.00	30.00 - 64.00	
Mean (95% CI)	43.11	42.92	43.00	
SD	8.65	9.62	9.12	
Sex (n (%))				0.478
female	12 (63.2%)	19 (73.1%)	31 (68.9%)	
male	7 (36.8%)	7 (26.9%)	14 (31.1%)	
Current used for HFS (mA)				0.853
Median	0.12	0.16	0.14	
Q1, Q3	0.08, 0.19	0.09, 0.17	0.09, 0.18	
Range	0.04 - 0.27	0.04 - 0.26	0.04 - 0.27	
Mean (95% CI)	0.14	0.14	0.14	
SD	0.07	0.06	0.06	
Distress severity HSCL-25: mean score 1-4)				< 0.001
Median	2.24	1.38	1.48	
Q1, Q3	1.68, 2.58	1.08, 1.60	1.12, 2.24	
Range	1.08 - 3.36	1.00 - 2.52	1.00 - 3.36	
Mean (95% CI)	2.14	1.46	1.75	
SD	0.64	0.47	0.64	
Social support (MOS-SSS: mean score 1-5)				0.441
Median	4.75	4.88	4.88	
Q1, Q3	3.44, 5.00	4.39, 5.00	3.94, 5.00	
Range	2.00 - 5.00	2.12 - 5.00	2.00 - 5.00	
Mean (95% CI)	4.19	4.47	4.35	
SD	0.97	0.88	0.92	
Pain severity for pain in the past week (BPI mean score 0-10)				
Median	5.25	NA	5.25	
Q1, Q3	4.12, 6.00	NA	4.12, 6.00	
Range	3.00 - 7.50	NA	3.00 - 7.50	
Mean (95% CI)	5.13	NA	5.13	
SD	1.30	NA	1.30	
Pain severity for pain for the past 3 months (BPI				

	Pain (N=19)	Pain-free (N=26)	Total (N=45)	p-value
mean score 0-10)				
Median	5.00	NA	5.00	
Q1, Q3	4.00, 5.88	NA	4.00, 5.88	
Range	3.25 - 8.25	NA	3.25 - 8.25	
Mean (95% CI)	5.21	NA	5.21	
SD	1.53	NA	1.53	
Pain interference for all pain in the past week (BPI mean score 0-10)				
Median	5.00	NA	5.00	
Q1, Q3	3.93, 6.14	NA	3.93, 6.14	
Range	3.00 - 9.43	NA	3.00 - 9.43	
Mean (95% CI)	5.39	NA	5.39	
SD	1.93	NA	1.93	

	Surface area of SH		**Magnitude of SH**	
Predictors	*Estimates*	*CI*	*Estimates*	*CI*
Intercept	3.98	-30.91 – 38.87	-3.42	-13.93 – 7.09
Distress severity	19.10 *	2.85 – 35.34	6.24 *	1.28 – 11.21
Group (pain)	-1.88	-24.03 – 20.27	-6.92 *	-13.70 – -0.13
Current used for HFS	-117.83	-257.02 – 21.36	-29.36	-71.42 – 12.71
HFS painfulness	0.13	-0.25 – 0.51	0.03	-0.10 – 0.17
Time difference between distress & SH assessments	1.07	-1.06 – 3.20	0.05	-0.60 – 0.71
Baseline mean pinprick ratings			0.25 *	0.02 – 0.48
Random Effects				
σ^2	178.63		2.99	
τ_{00}	737.41 $_{pid}$		71.19 $_{pid}$	
ICC	0.81		0.96	
N	45 $_{pid}$		45 $_{pid}$	
Observations	135		135	
Marginal R^2 / Conditional R^2	0.192 / 0.842		0.240 / 0.969	

** p<0.05 ** p<0.01 *** p<0.001*