Acute Pain Speeds Skin Barrier Recovery in Healthy Men and Women

Running Head: Pain and Skin Healing

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Abstract

Objective. Psychological stress is known to impair skin barrier recovery, but little is known about the impact of pain on skin healing processes. Our primary goals were to examine the degree to which acute pain affects recovery from skin barrier disruption, and the potential mediating impact of cortisol and catecholamines. ***Methods***. Healthy non-smokers aged 18-43 (N=53, 65% women) underwent a 3-minute cold pressor pain stimulus to their foot. Tape-stripping of forearm skin occurred at two separate locations: before (site 1) and after (site 2) the pain stimulus. Transepidural water loss (TEWL) was assessed at baseline (pre-stripping), immediately post-stripping, and at 75 minutes to determine skin barrier recovery. Cortisol and catecholamine responses were obtained from multiple saliva and plasma samples, respectively. ***Results***. Contrary to expectations, greater pain was associated with faster skin barrier recovery, even after controlling for demographics, mood, anxiety, and other factors. Those who reported higher pain showed faster recovery at site 2 compared to a) individuals who experienced lower pain; and b) their own recovery at site 1. Greater increase in norepinephrine (but not in cortisol) was also associated with faster recovery at site 2, and mediated the impact of pain on recovery. ***Discussion***. Results bolster evidence that acute pain can affect immune-related processes. It is possible that acute pain may speed recovery from dermal abrasions, although pain is likely to impair recovery from more severe wounds. As pain is an important potential target for clinical intervention, further investigation of pain, stress, and healing processes is warranted.

Keywords: Acute Pain, Psychological Stress, Psychoneuroimmunology, Cortisol, Catecholamines; Wound Healing

Introduction

      Psychological stress can slow healing of laboratory-induced wounds across a variety of different types of wounds (e.g., from minor to more substantial skin wounds as well as wounds of oral mucosal tissue) and stress paradigms (e.g., both chronic stress and relatively brief stressors) [1-3]. For example, students healed standardized mucosal punch biopsy wounds on the oral hard palette an average of 40% more slowly during an academic examination period than during vacation [4]. In a chronic stress model, women who were taking care of a relative with dementia – a long-term process marked by psychological stress – took 9 days longer to heal a small punch biopsy wound on the arm of their skin as compared to controls matched on age and income [5]. The causal impact of psychological stress in such human studies is supported by animal models showing a negative effect of induced stress on dermal healing [6-8] with clearly delineated physiological mechanisms [3]. However, no study to our knowledge has examined the impact of perceived pain from an experimentally induced physical pain stressor on healing. Physical pain, like psychological stress, can trigger immunological changes that are relevant to wound healing [9], such as increases in glucocorticoids and proinflammatory cytokines; in addition, physical pain can trigger the release of prostaglandins, and other molecules related to inflammation [10,11]. Because pain, negative emotion, and psychological stress often co-occur and provide different targets for potential intervention, it would be helpful to elucidate the unique impact of pain on healing.

      Pain experience – which is, of course, common following laboratory wounding procedures as well as surgical procedures – is correlated with slower healing [12,13]. In one relatively well-controlled study, women who reported greater pain following an elective surgical procedure took longer to heal a laboratory-induced punch biopsy wound [14]. However, it is

unclear to what extent the effects of pain are distinguishable from mood and psychological stress [12]. Acute pain report is strongly and positively correlated with perceived stress as well as depressed mood, hostility, and anxiety [15-17], which are in turn associated with slower healing themselves [18,19].

Research on surgical recovery suggests that pain may have an independent impact on physiological outcomes relevant to healing [20,21]. For example, although opiate pain medication is immune suppressive if taken in the absence of pain, opiate pain medications that are taken (or administered) to adequately control for pain can positively affect healing rates following surgery [20]. Thus, it possible that pain itself (as opposed to general stress perception or negative mood) may affect healing. Further, stress symptomatology may even interact with pain experience to influence healing, particularly chronic stress related to anxiety and depression that may aggravate emotional and inflammatory responses to pain [22].

Pain, such as elicited experimentally with a cold pressor task (immersing the foot or hand in ice water), is known to produce a small to moderate increase in cortisol [23], along with a robust sympathetic nervous system response [24,25]. Both glucocorticoid secretion and catecholamine release, particularly during early stages of healing, represent physiological pathways by which psychological stress has been linked with slower wound healing in experimental animal models [3,12,26]. Several human studies also support a role for glucocorticoids in mediating stress and healing connections [27,28]. Thus, following an experimental pain stimulus, changes in either cortisol or catecholamines are potential mediators of a pain and healing relationship.

The goal of the present research was to examine the effects of acute physical pain on recovery from skin barrier disruption. Skin barrier disruption is a mild form of skin wounding

from which individuals typically recover relatively quickly, as compared to skin wounding

procedures where the epidermis (outer layer of skin) is punctured. The function of skin is not

only to protect the host (e.g., against infection) but also to hold in moisture; skin barrier function

is thus essential for survival [29] and skin barrier recovery is a critical factor in many diseases

(e.g., atopic dermatitis, psoriasis) [30] and in dermal healing [31]. Experimental skin barrier

disruption can be achieved via repeated stripping of tape from the skin until a set amount of

moisture loss is detected. Healing is then assessed using measurements of the amount of water

loss from the skin. Using such procedures, Garg et al. [31] showed that skin barrier recovery was

impaired among students during an academic examination period compared to vacation. Other

stressors, such as a relatively brief laboratory-induced social stressor (a modified Trier Social

Stress Test), sleep deprivation, or marital dissolution have also resulted in slower recovery of

skin barrier function among healthy adults [32-35]. These effects were generally greatest in the

individuals who reported the most stress.

The degree to which healing is influenced by pain from an experimentally induced

physical pain stressor has not been previously reported. Individuals vary in how they respond to

even a standardized pain stimulus, with many individuals finding it to be very stressful or painful

and others finding it to be much less so [36]. We hypothesized that greater reported pain in

response to cold water exposure would be associated with slower skin-barrier recovery,

independent from effects of negative mood or other related factors. Further, we expected that

pain and negative mood would interact such that individuals with both higher acute pain

experience and evidence of anxiety or depressed mood symptomatology would show the slowest

recovery. Finally, we examined whether catecholamine and/or cortisol changes to the cold

pressor partially mediated effects of pain experience on skin barrier repair.

Methods

Participants

Participants were 53 healthy men and women, non-smokers aged 18-43 (mean age = 24.43, SD = 6.15), for whom we had complete skin barrier recovery data from a larger study to examine effects of exposure to certain odors on endocrine and immune function [37]. Community advertisements were used to recruit participants, who were then screened for (and excluded if they had) perfume allergies, problems with smell or taste, respiratory symptoms or problems, asthma, or excessive alcohol or caffeine use. Also excluded were individuals taking cardiovascular medications (e.g., statins or beta-blockers) or with evidence of health problems involving obvious immunological or endocrinological components. The Ohio State University Biomedical Research Review Committee approved the project and all participants gave written informed consent prior to participation.

Procedures

The larger study from which participants were recruited examined effects of exposure to certain odors across 3 separate visits to a General Clinical Research Center (GCRC) [37]; data from an odor-neutral control visit were used for the present analysis, and there was no order of condition effect on results presented here. Figure 1 illustrates the timing and order of key events in the study protocol. Participants arrived at the GCRC at 8:00 AM, having fasted from midnight the night before. After standard intake procedures, an indwelling catheter was inserted by a nurse and participants were then given a standard breakfast. Next, participants were given standardized questionnaires, which included assessments of mood. Participants were exposed to cold water with a cold pressor procedure (described in greater detail below) at 11:00. Both before and after the cold pressor, at 10:15 and 11:45, mild wounding was induced by disrupting the skin barrier

on the underside of the forearm (the one in which the catheter was not inserted); the two strippings were done on the same forearm but in different locations a few inches apart, with skin barrier recovery assessed using transepidural water loss (TEWL), as described below.

As shown in Figure 1, six plasma samples for catecholamines were obtained via catheter at 1) baseline (>1h after breakfast and before any study events), 2) just prior to the first tape-stripping session, 3) just before the cold pressor, 4) 10 minutes after the cold pressor, 5) 45 minutes after the cold pressor, and 6) just after the final tape stripping and before lunch. In addition, saliva was collected at six time points (concurrent with all of the plasma timepoints except for immediately post cold pressor). Saliva was collected using a salivette (Sarstedt, Newton, North Carolina), an untreated sterile cotton roll that was placed in the subject's mouth for approximately 2 minutes to ensure saturation.

Measures

Pain. Following a 15-minute period of sitting quietly, participants immersed their foot in warm water (37ºC) for 1 minute, to ensure that everyone's foot started at the same temperature, and then immediately into ice water (4ºC) for 3 min. Participants were asked to rate how much discomfort they experienced during the cold pressor task on a scale from 0 (no discomfort) to 10 (greatest discomfort).

Wound Recovery. Skin barrier disruption before and after pain was achieved with standardized tape-stripping methods [38]. After initial baseline measurements of TEWL from the area about to be stripped, cellophane tape (3M Scotch-type; St. Paul, MN) was applied repeatedly to remove the superficial layer of skin. Tape stripping at each of two time points stopped when TEWL was elevated to at least $20g/m^2/h$, which took 6-50 tape applications due to individual variability; TEWL was assessed with computerized evaporimetry equipment, the

DermaLab (CyberDERM, Media, PA). Also via TEWL, the degree of skin barrier recovery was assessed 75 minutes after each tape stripping procedure. Following commonly used methods, skin barrier recovery was computed as percent recovery toward the baseline TEWL using the formula: [(immediate post stripping TEWL – 75 minute TEWL) / (immediate post stripping TEWL - baseline TEWL)] *100.

Endocrine Data. All saliva and plasma samples were centrifuged and then frozen at -70C in aliquots until assay, as described in greater detail previously [39,40]. All samples were analyzed within the same assay run after the participants had completed the study; all assays were run in duplicate and had excellent sensitivity and specificity with intra-assay and interassay coefficients of variation of less than 8%. Saliva was assayed using the Cortisol Coat-A-Count RIA (Siemens Medical Solutions Diagnostics, Los Angeles, CA). Plasma catecholamines (epinephrine and norepinephrine) were obtained by HPLC with ElectroChemical Detection using Standards and Chemistry (alumina extraction) from Thermo-Alko (Beverly, MA).

Depressed Mood and Anxiety Symptomatology. The Depressive Symptoms subscale (12 items) and the Anxious Symptoms subscale (11 items) of the Mood and Anxiety Symptom Questionnaire (MASQ) [41] were used to measure recent depressed and anxious sympotomatology. Participants were asked to what extent in the past week they had experienced symptoms of anxiety (e.g., shortness of breath, shaking hands) and depression (e.g., felt that nothing was interesting or enjoyable) on a scale from 1 (*not at all*) to 5 (*extremely*). These subscales are reliable and have good convergent validity with other scales of anxiety and depressed mood [41].

State Mood. State mood was measured with the two 10-item subscales of the Positive and Negative Affect Schedule (PANAS) [42]. These subscales are typically independent of one

another and have been well-validated against other state mood measures [42]. These subscales were administered several times during the protocol; the scales immediately following the cold-pressor task were used in the present analysis.

Other Psychosocial & Demographic Characteristics. Perceived social support was measured with the Interpersonal Support Evaluation List [ISEL; 43], a 40-item scale which asks about four types of support: self-esteem, appraisal, tangible, and belonging on a four-point scale from 1 (*definitely false*) to 4 (*definitely true*). Items are summed, with higher scores reflecting overall higher perceived support. Loneliness was measured with the New York University Loneliness Scale [44], which is comprised of 8 items that ask about loneliness explicitly, including how lonely the individual feels, how often he or she feels lonely, and how often he or she has felt lonely in the past. The possible total score ranges from 0-31 with higher scores indicating greater loneliness. The Marlowe-Crowne Social Desirability Scale [45], a 33-item true-false scale, was used to assess the tendency to try to maintain an idealized, positive self-concept. Socioeconomic status was assessed with the MacArthur Scale of Subjective Social Status, which is comprised of three items on a ladder scale [46]. Relationship status was coded as either 1 (divorced, separated, never married) or 2 (currently married or living as if married).

Statistical Analyses

Bivariate correlations were calculated for key study variables. Hierarchical linear regression was used to examine whether pain was a unique predictor of healing; for example, demographic factors were examined in the first step, followed by anxiety and depressive symptomatology in the second step, and pain from the cold pressor in the third and final step. Linear regression was used to determine whether gender, anxiety, or depressive symptomatology moderated effects of pain on healing, using interaction terms generated by multiplying pain by

each of those factors. Comparisons between those with higher and lower pain were made via independent sample t-tests for linear variables and Chi-square tests for non-linear variables. A paired t-test was used to compare skin recovery before and after the pain stressor among those who reported higher pain. Log-transformations were used for cortisol and catecholamine data to correct for their right skewed distributions. Two additive measures of cortisol secretion over time were calculated using all of the timepoints and either the formula for cortisol area under the curve (AUC) with respect to ground or AUC with respect to increase [47]. Linear regression was used to determine whether cortisol or catecholamine responses mediated associations between pain and skin barrier recovery, using guidelines set forth by Baron and Kenny [48].

<div align="center">Results</div>

Preliminary analyses

 Sample characteristics. The sample was comprised of 66% women. A majority (60.4%) of participants identified as being White/Caucasian, with 20.7% identifying as Black/African-American, 13.2% Asian, 1.9% Pacific Islander, and 3.8% other. The majority were either single, separated, or divorced (81.2%), with the remainder currently married. Participants were well-educated overall, with 96.2% having at least some college, and 47.1% having a college or advanced degree.

 Skin barrier recovery. As would be expected, TEWL decreased at 75-minutes after the initial stripping from where it was immediately after the tape stripping at both the first, $F(52) = 272.11$, $p < .001$, and second tape stripping sites, $F(52) = 323.77$, $p < .001$, with approximately 50% average recovery at each follow-up point. Pain from the cold pressor was not related to the number of tape strips required to meet the initial wounding criterion, $r = -.05$, $p = .72$, and those reporting higher pain to the cold pressor did not require more tape strips than those reporting

lower pain at either the first or second tape stripping time point, $t(51) = -.36$, $p = .72$ and $t(51) = -.09$, $p = .93$, respectively.

Bivariate correlations. At the first tape stripping site, which was stripped prior to the pain stimulus, pain from the cold pressor (as a continuous variable) was not associated with either skin barrier disruption (via TEWL) 75 minutes after tape stripping ($r = .05$, $p = .71$) or with percent recovery ($r = .04$, $p = .81$). However, at the second tape stripping site, which was stripped after the pain stimulus, pain from the cold pressor was associated with less skin barrier disruption 75 minutes after tape stripping, $r = -.32$, $p < .05$ and faster recovery (greater percent recovery at 75 minutes post tape stripping), $r = .26$, $p < .05$. Table 1 presents the correlations among key measured indicators, including percent recovery from both sites, pain, and factors related to pain report. In addition to pain, skin barrier recovery at the second tape-stripping site was also associated with younger age ($r = -.27$, $p < .05$) but was not significantly associated with any other variable, including gender, positive or negative mood, depression or anxiety symptoms, age, social desirability, or loneliness. Greater pain was associated with female gender, $r = .34$, $p < .05$, and with younger age, $r = -.31$, $p < .05$.

Unique effects of pain on skin barrier recovery

The continuous variable for pain was entered as the last step in a hierarchical regression analysis, with demographic factors age, body mass index (BMI), gender, socioeconomic status ranking (SES), and marital status (yes/no) entered in the first step. Pain from the cold pressor remained a unique predictor of faster skin barrier recovery at the second (post-pain) site after controlling for all demographic factors, $t(51) = -2.35$, $p < .05$, $\beta = -.35$. Next, state negative and positive mood were entered into the second step in a similar regression analysis, with the demographic factors as the first step and pain as the third and final step: Pain remained

significant after the addition of state negative and positive mood, $t(48) = -1.98, p < .05, \beta = -.32$. There was too much overlap between mood indicators and anxiety/depression symptomatology variables to enter them all into the same regression analysis to predict recovery; when doing so, no variable emerged as a significant independent predictor. However, pain also remained a significant predictor of recovery in a separate regression analysis controlling for demographic factors in the first step and both depressive and anxiety symptoms in the second step.

Characteristics by high/low pain report

To better illustrate and explore the above findings, high and low pain rankings were assigned based on a median split, with ratings of 0-7 ranked as "lower" pain ($n = 23$) and ratings of 8-10 ranked as "higher" pain ($n = 30$). As shown in Figure 2, those who reported higher pain showed faster skin barrier recovery at the second tape stripping site than those who reported lower pain, $t(51) = 2.28, p < .05$; these groups showed no difference in skin barrier recovery at the site of the first tape stripping, $t(51) = -.78, p = .44$. In addition, using a paired t-test, we compared the percent healing at 75 minutes post-stripping between the first and second tape stripping sites. Those who reported higher pain had significantly faster recovery at the site that was wounded after the cold pressor (site 2), as compared to their own recovery at the site that was wounded before the cold pressor (site 1), $t(28) = -.20, p < .05$; no such differences in recovery before and after the cold pressor occurred in individuals reporting lower pain.

To aid in interpretability of these findings by group, Table 2 presents means and standard deviations on key study variables, demographic factors, and other psychosocial factors between those reporting higher pain and those reporting lower pain to the cold pressor. In addition to differences in age and gender that would be expected based on bivariate correlations reported earlier, those who reported higher pain were significantly less likely to be married, $\chi^2(1,53) =$

6.72, $p < .01$. Those who reported more pain scored lower on social desirability, $t(51) = 2.06$, $p < .05$ and reported greater loneliness, $t(51) = -2.14$, $p < .05$. Social desirability and loneliness were added as covariates to linear regression analyses to examine the unique impact of pain (as a continuous variable as it was run in the earlier regression analyses) on skin barrier recovery; the addition of neither variable reduced the unique impact of pain on skin barrier recovery.

Changes in cortisol and catecholamines and their relation to skin barrier recovery

Cortisol and pain. Change in cortisol from just prior to pain to 45-minutes post-pain was marginally associated with greater reported pain as a continuous variable, $r = .23$, $p = .10$. Those who reported higher pain than others in response to the cold pressor showed a different pattern of cortisol response as well, $F(2,42) = 4.46$, $p < .05$; those reporting higher pain showed an increase in cortisol at 45-minutes post-cold pressor followed by recovery, whereas those who reported lower pain to the cold pressor did not show an increase in cortisol in response to the stimulus.

Cortisol and Skin Barrier Recovery. Cortisol levels at none of the individual time points, including 45, 75 and 130 minutes post-pain, were significantly associated with percent recovery at either tape stripping site. The overall pattern of cortisol responsiveness over the test session, as measured by two different assessments for area under the curve, was also not associated with recovery at either site. The amount of change in cortisol from just prior to pain to 45-minutes post-pain was marginally correlated with slower recovery at the first site, $r = -.25$, $p = .09$, and was not correlated with recovery at the second site, $r = -.03$, $p = .83$. However, the ability of change in cortisol to predict recovery at the first site was reduced to non-significance when examined in a linear regression analysis that included demographics, $t(51) = -1.61$, p = .12.

Catecholamines and Pain. Change in norepinephrine (NE) and epinephrine (EPI) from just before the cold pressor to both 10 minutes and 45 minutes-post cold pressor was computed

and examined for associations with pain. Change in neither NE or EPI was significantly associated with pain report from the cold pressor. There were no significant interactions between pain grouping (higher or lower pain report) and change in N/EPI levels to the pain stimulus.

Catecholamines and Skin Barrier Recovery. Change in NE and EPI from just before the cold pressor to both 10 minutes and 45 minutes-post cold pressor were examined for relation with skin barrier recovery. Of these, only change in NE at 10 minutes post-stress was marginally associated with faster recovery at site 2, $r = .24$, $p = .09$, with greater increases associated with faster recovery. Change in NE to the pain stimulus (from just prior to pain to 10-minutes post-pain) was next examined in a linear regression analysis to predict recovery at the site 2, after controlling for age, gender, BMI, SES, and marital status; in this analysis, greater increase in NE to the pain stimulus was associated with significantly faster recovery at site 2, $t(51) = 2.09$, $p < .05$. We next ran a linear regression analyses to see if NE increases in response to pain mediated the effect of pain on skin barrier repair at site 2; consistent with mediation [48], when change in NE was entered as the second step, with the demographic factors in the first step and pain in the third step, pain was no longer a significant predictor of recovery, $t(50) = .92$, $p = .36$.

Gender effects

Gender did not significantly moderate effects of pain and the unique association between higher pain and slower percent recovery at site 2 was significant for both men and women. Neither chronic anxiety nor depressive symptoms significantly moderated effects of pain on recovery within either gender.

Discussion

This is the first research to our knowledge to examine the effect of pain experienced from a mild, laboratory-induced pain stimulus (a cold pressor) on skin barrier recovery, a measure of

the skin's ability to heal from a superficial wound caused by tape-stripping. Controlling for gender, age, marital status, socioeconomic status, BMI, as well as either state mood or both depressive and anxiety symptoms, pain experience was uniquely associated with faster skin barrier recovery. Follow-up analyses with dichotomized higher/lower pain report showed that similar recovery was observed among those who reported higher and lower pain to the pain stimulus at the site where tape stripping occurred *prior* to the cold pressor. However, at the site where tape stripping occurred *after* the pain stressor (on a separate area of the forearm), those who reported higher pain showed faster recovery from skin barrier disruption compared to: a) individuals who experienced lower pain; and b) their own recovery from the skin barrier disruption that occurred prior to the pain stressor. Those who reported higher pain from the cold pressor showed an increase in salivary cortisol surrounding the cold pressor, suggesting that they did indeed experience the pain stimulus as more stressful. The association between pain and recovery was unaffected by other psychosocial factors, such as loneliness or social desirability. Together, these results suggest that something about the pain experience *per se* was responsible for the effect on recovery, rather than a characteristic of those reporting higher or lower pain.

The finding that greater pain experienced during a pain stressor was associated with faster skin barrier recovery was unexpected, as research has shown that laboratory-induced social stressors can impair skin barrier recovery in healthy volunteers [32-34]. However, the present study differed from these past studies in a few ways. First, it utilized a cold pressor (pain) task as the stressor. As a briefer stressor with a physiological component, the cold pressor task may function as a more acute stimulus than laboratory social stressors, as it is less likely to cause substantial or prolonged psychological distress. In addition, pain has qualitative differences from other stressors in that it can signal injury (or the perception of injury); hence, the effects of pain

on immune functioning may be qualitatively different from other stressors. In addition, the timing of the stressor relative to tape stripping and recovery measures was different when compared to past studies examining the effects of social stressors. In those studies, the stressor took place between the initial tape stripping and final recovery, which was assessed at approximately 2 hours [34] or 3 hours post-stress [32,33]. In the present study, the time between stressor and recovery assessment was either 45 minutes (site 1) or 2 hours 15 minutes (site 2). Thus, the timing at site 2 (where the tape stripping took place after the stressor) coincides more with previous studies; in contrast, at site 1 (where the tape stripping took place before the stressor) there was likely insufficient time (45 minutes) for the pain stimulus to affect recovery. Differences between the two sites may also have occurred given that pain was introduced mid-way through the cascade of physiological events that typically occur following skin barrier disruption, which is reviewed below.

Norepinephrine response to the pain stimulus was associated with faster skin barrier recovery at site 2 (where higher pain was associated with faster recovery), after controlling for demographics. Importantly, the effect of pain on recovery became non-significant after accounting for norepinephrine response shortly (10 min) after the stressor; thus, the change in norepinephrine in response to pain appeared to account for the effect of pain on faster skin barrier repair. Norepinephrine has been shown to modulate stress and healing outcomes in animal research [26]. In contrast, neither cortisol levels nor change in cortisol to the pain stimulus was associated significantly with skin barrier recovery after controlling for demographic factors (age, gender, BMI, and marital status). This finding diverges from animal research showing that stress-induced impairment of skin barrier function is partly dependent on glucocorticoids [49] and human studies utilizing other types of healing models (e.g., blister

wounds) that have corroborated the importance of glucocorticoids in the healing process [1,27,28]. However, consistent with our present findings, one prior study examined the effect of a Trier Social Stress Test on skin barrier repair in healthy women and reported that there were no significant associations between cortisol changes and skin barrier function [32]. It is possible that neither cold pressor nor experimental social stress reliably produces a cortisol response strong enough to observe a consistent relationship between cortisol and skin barrier recovery. Further, pain is likely to lead to a less robust HPA-axis response than psychosocial stress [50,51].

Together, our results showing a significant role for norepinephrine but not cortisol in the association between pain and skin barrier repair suggest that the physiological mechanisms by which pain and psychosocial stress affect skin barrier repair are different. It may be that other biological changes in response to pain are related to skin repair, such as cytokines or prostaglandins [12] – neither of which we were able to test in the current analysis. Skin barrier disruption results in increases in both proinflammatory cytokine production [52] and the proliferation of keratinocytes (the predominant cell type in the epidermis) [53] in the locally affected tissue. Interestingly, factors that promote inflammation (e.g., TNF-α, TLR-2 activation) appear to aid in barrier function recovery [54,55], whereas factors that inhibit inflammation (e.g., IL-4 as well as HPA-axis activation to acute stress, both of which can be anti-inflammatory) appear to hinder it [56]. Pain has been shown to induce/augment the secretion of proinflammatory cytokines in the periphery [11,57,58] and norepinephrine has been shown to potentiate the activity of proinflammatory cytokines [59]. Thus, inflammation is a possible (though untested) mechanism through which greater pain perception might have related to faster barrier recovery in the present study. In contrast, acute psychological stress may lead to slower healing via HPA axis activation and its anti-inflammatory effects.

In terms of timing, it is possible that acute pain may help 1) initiate the inflammatory phase of skin repair; and/or 2) promote leukocyte trafficking to sites of immune activation. Acute stressors in rodents can lead to changes in leukocyte distribution that are observed within 30 minutes of a stressor, and these changes have been related to enhanced innate immunity in a variety of target organs including skin [60-62]. Pre-surgical stress in knee surgery patients similarly has been related to a redistribution of leukocytes which, in turn, are related to shorter post-surgical recovery times [63]. Such immune changes (e.g., leukocyte trafficking) can be adaptive in the short term in that they help the body better prepare for immediate immune challenges [60,62]. However, in certain contexts they can lead to harmful inflammatory responses and worsen health outcomes; for example, psoriasis or skin allergy responses might well be aggravated by the same immune responses to acute stress that may improve skin barrier repair [64]. It is also possible that it is not adaptive to heal as fast as possible, particularly when the wound is not life-threatening, is relatively sterile, and when fast healing involves using limited resources quickly. Results of the present study should thus not be interpreted as evidence that acute stress or pain is helpful overall in terms of immune responses or even healing, but may be helpful in certain contexts and under certain conditions.

Our hypothesis that pain might interact with symptoms of depression or anxiety was not supported. Although there was adequate variability in responses to these two scales, our sample was not recruited on the basis of depression or anxiety. It is possible that more clinical levels of anxiety or depression might interact with pain to predict healing outcomes. Indeed, it has been reported that dysphoric individuals are over 3.5 times more likely than non-dysphoric individuals to exhibit slower healing of oral mucosal wounds [65].

An important limitation of the present research is that it was conducted as part of a larger

study that was not experimentally designed to test effects of pain. The physiological effects of the cold pressor may have differed between individuals who reported higher or lower pain in ways that could have affected skin barrier function. Although we measured two important physiological responses to the cold pressor – catecholamines and cortisol secretion – it would have been ideal to have additional time points to more fully capture the peaks and the temporal dynamics in response to pain, particularly a post-pain cortisol measure obtained earlier than at 45-minutes post-pain. Having continuous heart rate and heart rate variability data to provide more sensitive measures of autonomic nervous system reactivity would also have been ideal. However, by using two separate tape-strippings that took place before and after the cold pressor (on the same forearm but in different locations), we were able to demonstrate that the same individuals who reported greater pain to the cold pressor experienced faster recovery of skin barrier function if they were wounded after experiencing pain as compared to before. This research also examined pain independently of state mood and chronic stress symptomatology (anxiety and depressive mood), important but often overlooked covariates.

Overall, these results bolster evidence suggesting that acute pain can affect processes related to immune function. Specifically, findings suggest that brief laboratory-induced pain may speed recovery after mild dermal abrasions in healthy adults and that this association may be explained by increases in norepinephrine in response to pain. The direction of these findings was unexpected and should thus be interpreted with caution. For instance, it is unlikely that pain speeds or improves recovery from more severe wounds; indeed, previous research suggests that pain experience is likely to impair such recovery, as the adequate pharmacological control of pain alters immunity in favor of quicker recovery from surgery [20,21]. Additional research is needed to replicate and extend the present findings, to better understand issues related to timing

and mechanisms, and to determine whether results extend to other populations, other pain

stimuli, and other wound healing paradigms.

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Table 1. Correlations Between Key Study Variables

	1	2	3	4	5	6	7	8	9	10	11	12
1. % Recovery Site 1[a]	–											
2. % Recovery Site 2[a]	.23	–										
3. Pain	.04	.26*	–									
4. Gender[a]	-.01	.08	.34*	–								
5. Age	-.13	-.27*	-.31*	-.13	–							
6. BMI	.09	.03	-.08	-.10	.22	–						
7. Marital Status[b]	-.10	-.18	-.14	.14	.45***	.01	–					
8. Loneliness	-.13	.16	.14	-.24	-.03	.19	-.33*	–				
9. Social Desirability	-.21	-.06	-.17	-.04	.21	-.10	.09	-.03	–			
10. Positive Mood	-.25	-.09	-.04	-.01	.03	-.14	.02	-.27*	.12	–		
11. Negative Mood	.14	.18	.20	-.01	-.15	.29*	-.01	.40**	-.10	-.35**	–	
12. Depressed Symptoms	-.03	.17	.03	-.16	.09	.32**	-.09	.16	-.15	-.38*	.11	–
13. Anxiety Symptoms	.06	.17	-.01	-.05	-.05	.18	-.09	.36**	-.29*	-.22	.27*	.43***

* $p < .05$. ** $p < .01$. *** $p < .001$. [a]Percent recovery from baseline (75 minutes after tape-stripping); [b]Gender is coded such that

1=male, 2=female; Marital Status is coded such that 1=no, 2=yes (currently married or living as if married).

Table 2. Differences Between Individuals Reporting Lower and Higher Pain

|	Lower Pain Mean (SD)	Higher Pain Mean (SD)
Gender (% women)	56.5%	73.3%
Marital Status (% not married)	65.2%	93.3%**
Race (% White)	65.2%	60.0%
Age	26.96 (7.44)	22.50 (4.11)**
SES	5.91 (1.38)	5.62 (1.74)
Body Mass Index	25.67 (5.92)	24.64 (5.48)
Depressed symptoms	18.26 (4.84)	18.33 (6.16)
Anxiety symptoms	17.22 (3.86)	16.93 (3.15)
Social Support	101.65 (11.60)	101.90 (12.69)
Loneliness	15.70 (2.49)	17.67 (3.85)*
Social Desirability	17.26 (4.88)	14.40 (5.10)*

$* p < .05.$ $** p < .01.$

Figure 1. Timeline of Key Study Events
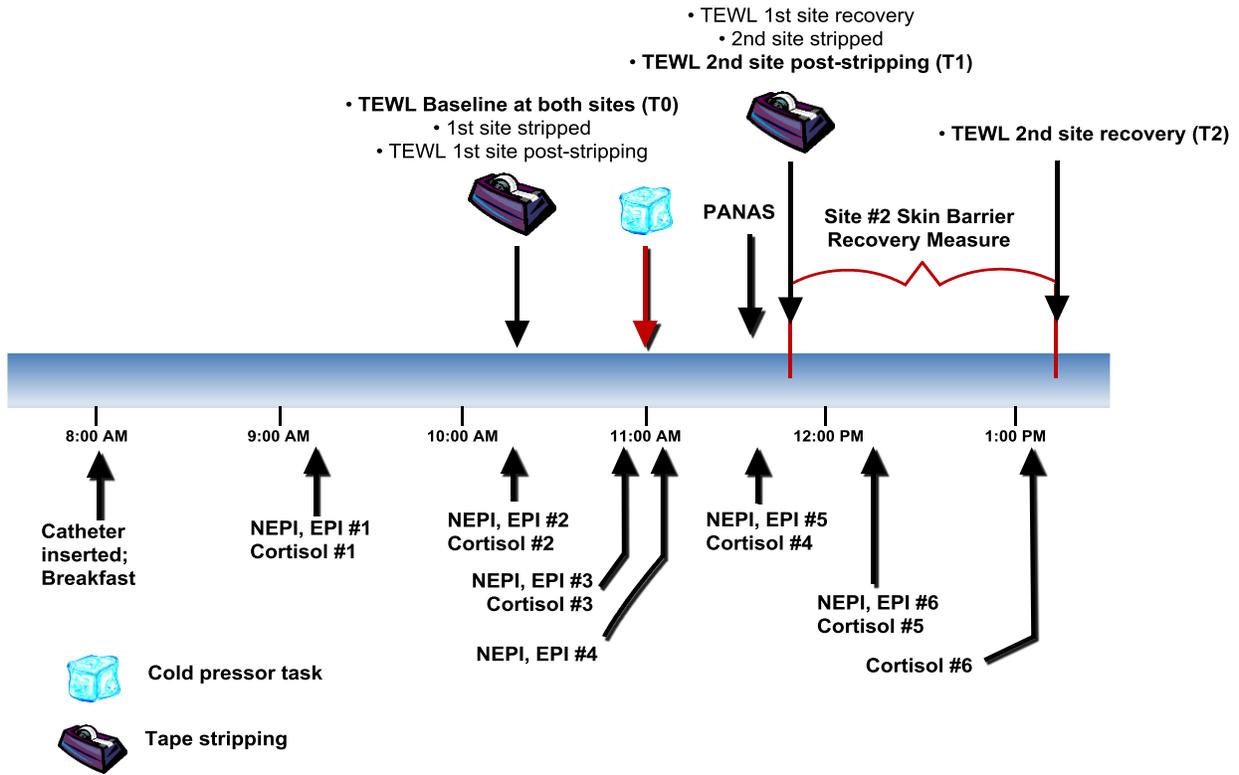
Note. The timing of the assessments at the first tape stripping site involved T0 and T1; the second stripping site involved T1 and T2. Baseline measures for both sites were conducted at T0. The time from the TEWL assessment immediately post-stripping to the recovery time point at each site was 75 minutes.

Figure 2. % Skin Barrier Recovery by Tape Stripping Site and Pain Group
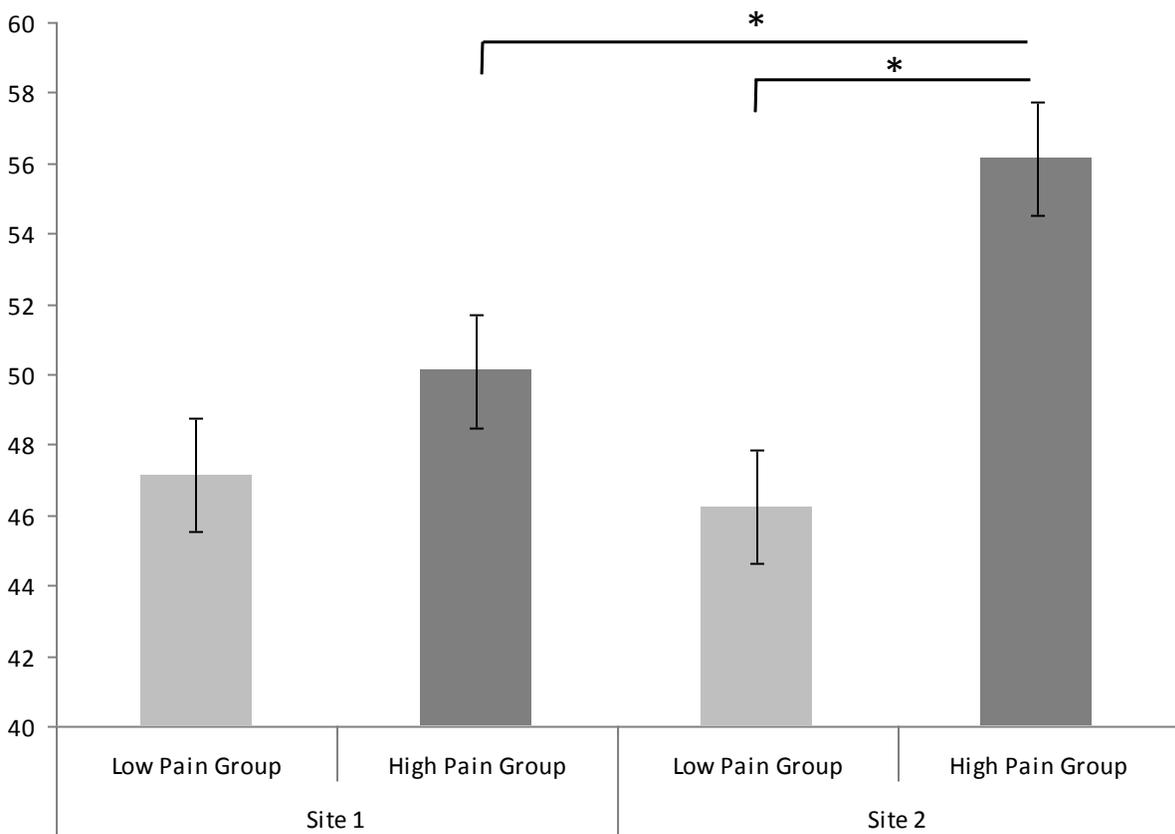
Note. Error bars represent standard error of the mean (SEM).
* = $p < .05$.