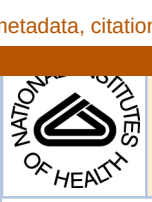

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Detecting the Emergence of Chronic Pain in Sickle Cell Disease

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Abstract

Context—Sickle cell disease (SCD) is an inherited hematological disease marked by intense pain. Early in life the pain is episodic, but it becomes increasingly chronic in many cases. Little is known about this emergence of a chronic pain state.

Objectives—The goal of this study was to determine whether adult SCD patients whose pain is still largely episodic show early signs of the disturbed pain processing (hyperalgesia, increased temporal summation) and cognition (hypervigilance and catastrophizing) that are characteristic of a chronic pain state.

Methods—SCD patients (n=22) and healthy controls (n=52) received noxious pressure stimulation for up to three minutes, and periodically reported pain intensity and unpleasantness on 0–10 scales, allowing the rate of pain increase (temporal summation) to be determined. Pain intensity discrimination also was measured, and attitudes toward pain were assessed.

Results—There were no overall differences in pain ratings or temporal summation between patient and control groups. However, patients' experimental pain ratings tended to increase with age, and those reporting a history of very painful episodes showed particularly rapid temporal summation of pain unpleasantness. Patients were significantly impaired at discriminating intensities of noxious stimulation. Patients were more hypervigilant than controls, but catastrophizing was elevated only during pain episodes.

Conclusion—Most SCD patients whose pain remits entirely between episodes are not in a chronic pain state, but some—those who are older and have a history of highly painful episodes—appear to be transitioning into it. These early signs of disturbed processing may aid clinicians seeking to forestall disease progression.

Keywords

Chronic pain; sickle cell disease; hyperalgesia; temporal summation; catastrophizing

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Disclosures

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Introduction

Sickle cell disease (SCD) is a debilitating, life-long condition, the most prominent symptom of which is intense, fluctuating pain. There are several genetically distinct forms of this hematological disease, but all involve abnormalities of hemoglobin. The disease is most prevalent among people of African descent; approximately one in 500 African Americans is born with SCD.[1]

SCD pain typically emerges in the second half of the first year of life, as red blood cells with the protective fetal form of hemoglobin wane, replaced by cells that are capable of sickling (deforming), impeding blood flow, and thus producing ischemia, hypoxia, and possible tissue damage. The clinical presentation of SCD pain is complex.[2] Early in life it may be largely episodic; however, tissue necrosis, central nervous system changes, and other factors, perhaps including the cumulative impact of pain itself, can induce an increasingly pronounced chronic component of SCD pain later in life.[3] The discovery of ways to prevent or postpone this gradual deterioration is an important goal of SCD research.[4]

Research on other painful conditions indicates that chronic pain often entails abnormalities in the structure and function of cerebral cortex, disturbances of judgment, memory, and emotion, and other changes.[5,6] Many chronic pain patients show signs of central sensitization,[7–9] such as widespread hyperalgesia (abnormally intense pain from a noxious stimulus)[10–13] and exaggerated temporal summation (increase of pain with repetition or prolongation of a noxious stimulus).[10,12,14–16] Both symptoms can occur far from the region in which the chronic pain is located.[13,14] It has been suggested that central sensitization may emerge during the temporal evolution of SCD pain as well,[3] but until now this possibility has not been tested experimentally.

Much of the research on SCD pain has asked patients to report on their clinical pain, so that researchers can determine its characteristics and its relationship to demographic variables and psychosocial processes.[4,17–20] In contrast, only a few studies[21,22] have measured the responsiveness of SCD patients to experimental pain stimuli. Research on experimental pain complements the study of spontaneous clinical pain in that it allows direct comparison between the pain sensitivities of patients and healthy controls.

In the present study, we used experimental pain paradigms to answer several questions: 1) Do some SCD patients show signs of central sensitization, or other disturbances of pain processing? 2) Is central sensitization more likely to occur during a pain episode than between episodes, showing that it is dependent on short-term, transient factors? 3) Alternatively, is central sensitization related to long-term factors, such as a patient's age or a history of intense pain episodes? A positive answer to this third question would raise the intriguing possibility that manifestations of central sensitization, such as hyperalgesia and enhanced temporal summation, could be early signs of a gradual transition to a chronic pain state. In addressing these questions, we examined both the intensive and affective dimensions of pain, because both can be disturbed in individuals with chronic pain. 4) Finally, we asked whether attitudes and cognitive processes related to pain, such as fear, hypervigilance, and catastrophizing, are elevated in SCD patients, and if so, whether this elevation is specifically associated with pain episodes.

Materials and Methods

Subjects

There were two groups of subjects: those with, and those without, SCD. SCD participants were all patients at the University of North Carolina (UNC) Sickle Cell Clinic, which is a

part of the Duke-UNC Comprehensive Sickle Cell Center. Approval for this study was granted by the UNC Biomedical Institutional Review Board. Twenty-six individuals with SCD were enrolled, but three of these were pilot subjects, and the participation of a fourth was terminated when it became clear that he had substantial chronic pain from lupus, in addition to SCD pain. The remaining 22 participants (13 females) with SCD ranged in age from 18 to 54 (mean=32.6 years). All were African American. All but three had the most common and generally most severe form of the disease, homozygous sickle cell anemia (HbSS); of the others, two had hemoglobin SC disease (HbSC) and the third had sickle β^+-thalassemia. Questionnaire scores and experimental measures for these three were comparable to those of other participants in the SCD group.

Participation was limited to those patients who had discrete episodes of vaso-occlusive SCD pain, with relatively pain-free intervals between episodes. Importantly, patients were excluded if they had pain from SCD (or any other cause) that was unremitting, that is, patently chronic. Other exclusionary criteria were the presence of diabetes, seizures, or heart disease. Of the 22 patients, 19 reported that they had experienced between one and five episodes of SCD pain during the past six months, lasting an average of 4.7 days, with pain intensity averaging 7.1 on a 0–10 scale. Patients reported that their most painful episode of the last six months averaged 9.4 on a 0–10 scale.

Recruitment of the patients was accomplished through a two-step process. First, a research nurse known to the patients (SJ) let potential candidates for participation know that the study was taking place and asked whether they would be interested in learning more about it. The experimenter (NK) met with interested patients in a private room during a clinic visit to explain the study and ask if they wanted to participate. If so, written informed consent was obtained.

Fifty-seven healthy controls were enrolled. Of these, one was a pilot subject, and the participation of four was terminated when it became clear that they had substantial ongoing pain, which they attributed to recent or much earlier injuries; these individuals were excluded from the analyses. The 52 remaining control participants (29 females), like the patients, ranged in age from 18 to 54 (mean=29.7 years). Because all SCD participants were African American, we recruited only African-American control participants. They were recruited with flyers posted on campus and in UNC Hospitals. Potential participants telephoned or emailed the experimenter, who explained the study to them, and scheduled the first session. When they arrived, the experimenter again described the study, and obtained written informed consent. It was a requirement that they not have SCD; other exclusionary criteria were the same as for the patients.

All experimental sessions were carried out in a private examination room in the Clinical and Translational Research Center (CTRC) within UNC Hospitals. Sessions lasted 90–100 minutes, and subjects were compensated at the rate of $60 per session.

When possible, subjects participated in two sessions. For the patients, one of these sessions was during a pain episode, and the other was during a relatively pain-free (“baseline”) period between episodes. A total of 14 SCD participants completed two sessions. Seven completed the baseline session first, and the episode session was first for the other seven.

A patient’s first session was often on the same day that he/she enrolled, taking place after a clinic appointment. However, clinic appointments usually did not coincide with pain episodes, so to arrange for some SCD participants to have their “episode” session first, they were monitored in follow-up communication by the experimenter, after giving informed consent but before participating. When they reported being in an episode, they were invited to come to the CTRC for their first session. “Episode” sessions generally took place during

the early or late stages of an episode, rather than during its peak. Sessions did not take place if participants did not feel well enough to come to the CTRC, or if they were currently inpatients. Nevertheless, patients were in substantial pain during their episode session: Those who participated in two sessions gave substantially higher ratings of their current clinical pain intensity on a 0–10 scale at the beginning of their episode session (mean=4.64, standard deviation [SD]=1.54) than for the baseline session (mean=0.11, SD=0.29) [t(13)=10.10, $P<0.0001$]. To check for order effects, control subjects were also asked to participate in two sessions; 41 of the 52 did so.

Participants were asked to list their current pain medications at each session. All SCD patients reported analgesic use at the time of their episode session, and in all cases but two (87.5%), this consisted of, or included, a narcotic, such as oxycodone (six patients), oxycodone/acetaminophen combination (four patients), or morphine (received in the hospital by three patients). Some took over-the-counter (OTC) analgesics such as ibuprofen in addition. During baseline sessions, 27.3% of patients took no analgesics, but the proportion reporting current narcotic use, although lower than during an episode, was still substantial (68.2%). In contrast, analgesic use was modest in the control group, with 13.5% of individuals taking OTC medications, and none taking narcotics.

We made no attempt to discourage participants from taking their usual medications in advance of a session: To do so would have risked unacceptable suffering, disrupted steady-state conditions, and made it impossible to recruit patients with severe SCD pain. However, differences in medication between patients and controls, and between episode and baseline sessions for the patients, may have affected group differences in responsiveness to experimental pain, and constitute an important subject for future study.

Apparatus

A top priority in choosing our method of experimental pain induction was to avoid provoking or exacerbating clinical pain in SCD patients. For example, cold pressor pain (immersion of a hand or foot in very cold water) is inappropriate given the clear clinical and epidemiological evidence that cold can exacerbate SCD pain.[19,23] Ischemic pain is likewise contraindicated as an experimental approach, given the possibility of triggering a vaso-occlusive episode. Warmth is used therapeutically in some cases of SCD,[2] but the effects of noxious levels of heat are unknown.

Therefore, we restricted noxious stimulation to the use of the Forgione-Barber stimulator[24] (local dull pressure), the only method that has been repeatedly demonstrated to be safe and effective for patients with this disease.[21,22] The Forgione-Barber apparatus pressed a rounded Plexiglas edge (radius of curvature, 2.5 mm) downward onto the dorsal surface of a finger (middle phalanx of either the index or middle finger). The lowest force exerted by the edge was 0.8 N; weights were added for individual experiments (as described below) to increase force, to a maximum of 3.8 N. Cardboard baffling blocked the subject's view of the stimulator and the weight being applied, as well as the distal part of his/her hand.

Procedure

Psychometric Instruments—Each session began with the subject completing a number of questionnaires. These included a demographic questionnaire that asked subjects whether they had SCD, and if so, what the average intensity of a typical pain episode was, on a 0–10 scale; next, a current pain questionnaire asked them to rate (again on 0–10 scales) the intensity and unpleasantness of their pain "right now," and to list their current pain medications. Subjects then completed the Fear of Pain Questionnaire-III (FOP),[25] which asks respondents how fearful they are of the pain associated with 30 aversive experiences

(for example, biting your tongue while eating). They next completed the Pennebaker Inventory of Limbic Languidness (PILL),[26] a diverse symptom inventory that serves as a measure of hypervigilance. Finally, they completed the Pain Catastrophizing Scale (PCS),[27] indicating the degree to which they have various negative thoughts and feelings about pain (for example, "I feel I can't go on," "I keep thinking about how much it hurts") when they are in pain. (The PCS was not administered in the first few sessions of the study.)

Temporal Summation—The experiments then began with the temporal summation experiment, using the Forgione-Barber stimulator. During a run, the weighted ridge rested on a finger continuously for three minutes; the experimenter lowered it onto the finger at the start of the run, and lifted it off at the end. Because pressure pain at moderate levels of pressure builds up slowly, we applied the stimulus continuously during a trial, rather than using a series of brief presentations as is often (but not always[28]) done with thermal or electrical stimulation. Continuous pressure stimulation has been shown to produce robust temporal summation that is the result of a combination of peripheral and central factors.[29,30]

Participants were notified that they could stop the experiment at any time. Ten seconds after the start of the run, and at 20-second intervals thereafter, the subject was prompted to give a rating of the current pain from the stimulus, on a scale extending from 0 ("no pain") to 10 ("the most intense pain imaginable"). The experimenter explained that the scale was a continuous one, with the use of fractions or decimals being allowed. Between the intensity ratings, that is, at 20 seconds after the start of the run and at 20-second intervals thereafter, the subject was prompted to rate the current unpleasantness of the experimental pain, on a scale from 0 ("not at all unpleasant") to 10 ("the most unpleasant pain imaginable"). A complete run thus produced a series of nine intensity and nine unpleasantness ratings.

Following a practice run lasting less than one minute, the subject participated in three runs, using three different levels of force (1.8, 2.8, and 3.8 N). The order of these three stimuli was randomized across sessions and participants. A different finger was used for each of the four runs (including the practice run); the order of the four fingers (index and middle fingers of the left and right hands) was generated randomly prior to the session.

Because we wished to avoid inflicting severe pain, particularly when patients were experiencing pain episodes, a run was terminated if a subject gave an intensity rating exceeding 7.5, and any pending runs with greater force were not carried out. In addition, if a pain intensity rating exceeding 7.5 was elicited by the middle (2.8 N) or weakest (1.8 N) stimulus, later components of the session using the Forgione-Barber stimulator were not carried out. If this occurred in the first session for control subjects or SCD subjects not in an episode, they were not asked to come back for a second session. However, if a subject with SCD met this "stopping criterion" during a first session while they were in a pain episode, he or she was invited to return for a later, baseline session, to account for the possibility that experimental pain might be less during baseline than during a pain episode.

Pain Discrimination—Following the temporal summation experiment, subjects participated in a pain discrimination task. The ability to discern changes in pain intensity is of practical importance, especially for SCD patients as they decide how to respond to pain episodes. Research has shown that psychosocial processes such as negative thinking can affect pain discrimination in SCD patients.[21,22] On each of a series of trials, a stimulus at either of two force levels (2.3 N or 3.3 N) was presented with the Forgione-Barber stimulator. The stimuli were randomly interspersed, and the subject was asked after each trial whether the stronger or weaker stimulus had been presented. A confidence-rating procedure[31] was used, the subject responding on a scale from 1 (indicating that he/she was sure the weaker stimulus had been presented) through 2 (thought it was the weaker stimulus)

and 3 (thought it was the stronger stimulus) to 4 (sure it was the stronger stimulus). The experiment began with two "learning" trials in which the weaker and the stronger stimuli were presented once each, and identified as such; these were followed by four practice trials, in which feedback was given. Another 20 trials followed, with no feedback, and these were used for the analyses. The index finger of the right hand was always used in this experiment.

Statistical Analyses

A multilevel regression model (mixed model) approach was employed for analysis. Because the study design calls on individuals to provide multiple observations on the same variable (for example, scores on a given questionnaire) at different times, it violates key assumptions of analysis of variance-type models and conventional multiple regression. Observations taken from the same participant correlate more strongly with each other than those taken from separate participants; using a multilevel statistical approach allows one to control for this interdependency in the data and consequently to make unbiased estimates of the effects of the predictors.[32]

Additionally, a multilevel model approach can be used without restricting the dataset to only individuals who have completed all measures at all time points, as in repeated-measures analysis of covariance. Thus, this approach allowed us to collect data from participants who for various reasons (for example, disease severity, limited availability) were not able to participate in two visits.

However, to assess fully whether differences in responses at first and second sessions were a result of an order effect, it was necessary to examine first, in isolation, data from participants who completed two sessions, using paired *t*-tests. No order effects were observed, for any of the measures we examined. Therefore, we continued with the primary analyses using the multilevel modeling approach, without retaining session number as a predictor. These analyses included data from all participants, even those who completed only one session.

Multilevel model analyses were performed using the PROC MIXED procedure in SAS® version 9.2 (SAS Institute Inc., Cary, NC).[33] Nestedness was accounted for statistically through the inclusion of random intercepts in the models. Random intercepts estimate the variance in the outcome variable that is a result of within-subject factors, including the correlation between observations from the same individual. This variance is accounted for when the estimates of regression coefficients for conventional predictors, also termed the "fixed effects," are calculated. The multilevel models were estimated using a variance components covariance structure; degrees of freedom were estimated using the Kenward-Roger method,[34] which is appropriate for relatively small samples as it corrects for inflated F-test values.

Results

Psychosocial Measures

Three psychosocial constructs – fear of pain, pain catastrophizing, and hypervigilance – were examined, using standardized questionnaires (Table 1). In each case, we sought to determine whether the characteristic was more strongly demonstrated by one group of participants (patients vs. controls) than the other, and whether, for the patients, the characteristic was present to a different degree during pain episodes than during a baseline period.

The mean PCS score for SCD patients (20.4) was somewhat higher than that for controls (14.9), but this difference was not significant [$F(1,49)=2.10$, $P=0.15$]. However, patients had

significantly more catastrophizing during a pain episode than when they completed the questionnaire during a baseline session [$F(1,39)=14.11$, $P=0.0006$].

Hypervigilance, as measured by the PILL, was significantly greater in the patients than in the controls [$F(1,54)=5.45$, $P=0.023$], but did not differ between the patients' baseline and episode sessions [$F(1,49)=1.12$, $P=0.29$].

FOP score was not significantly dependent on either the presence/absence of SCD [$F(1,54)=1.63$, $P=0.21$], or, for the SCD participants, on the presence of a pain episode at the time of a session [$F(1,49)=3.33$, $P=0.074$].

Temporal Summation Experiment

Almost all subjects, in both groups, showed robust temporal summation, that is, an increase in the intensity and unpleasantness of pain caused by a steadily applied noxious stimulus. Four measures of pain were derived from each subject's ratings in this experiment: mean intensity, mean unpleasantness, the rate of increase of intensity, and the rate of increase of unpleasantness. Four separate multilevel models were created, to determine whether these four measures (which served as dependent variables) were consistently higher in some conditions than others or in some subjects compared with others.

Calculating the Four Measures—Mean pain intensity was calculated by averaging the ratings at all nine time points within a run. Complicating this first step was the fact that several subjects in both groups gave ratings higher than 7.5 with the 3.8N and/or 2.8N stimulus, causing about 20% of runs to be ended before nine ratings were given. Because gradual increases in intensity ratings were observed in virtually all of these trials, calculating the mean using only the values the participant gave before the stop criterion could substantially underestimate the amount of pain that a full run would have elicited. To prevent this underestimation, remaining values were determined by linear extrapolation. For example, if a subject gave intensity ratings of 2, 4, 5, 6.5, and 8, the response of 8 caused the trial to be terminated. From the last two responses given, 6.5 and 8, the values at later time points would be 9.5 for the first missing rating, then 10, the highest possible, for the remaining ratings. Mean pain unpleasantness was calculated in the same way.

Pain intensity ratings, averaged across sessions and individuals within each group, are shown in Fig. 1; pain unpleasantness ratings (not shown) were similar. Pain ratings were quite low (in some cases zero) for the 1.8N stimulus, indicating that this stimulus was only barely noxious – little more than a tactile stimulus. The 2.8 and 3.8N stimuli, in contrast, produced substantial pain in most participants. Statistical analysis was, therefore, confined to the two higher levels of stimulus force.

The amounts of temporal summation of pain intensity and unpleasantness were expressed as the rates of increase of these two quantities during a run. Regression-line slopes for individual runs were calculated using only ratings given by the participant (that is, without extrapolated values).

Multilevel Models—For purposes of analysis, a separate three-level model was constructed for each of the four pain measures; the models were identical except for the dependent variable. In each model, one of the predictors, stimulus force, varied within session (Level 1); four others – the three questionnaires and the presence/absence of a pain episode – varied across sessions for some subjects (Level 2); three others – sex, age, and presence/absence of SCD – varied only across subjects (Level 3). We included sex as a predictor because of the extensive literature on sex differences in pain sensitivity,[35] and

included age because SCD episode frequency and intensity have been shown to depend on it.[4,23,36,37]

Not surprisingly, stimulus force was a consistent predictor of mean pain intensity [β=1.43, F(1,120)=96.9, P<0.0001] and unpleasantness [β=1.62, F(1,118)=109.3, P<0.0001], as well as of the rate of increase in intensity [β=0.23, F(1,119)=27.0, P<0.0001] and unpleasantness [β=0.24, F(1,118)=31.2, P<0.0001]. In other words, the 3.8 N stimulus consistently evoked stronger and more rapidly building pain than the 2.8 N stimulus (Fig. 1).

Sex was another significant predictor, with females giving higher, and more rapidly increasing ratings than males, a result consistent with prior research.[35] For example, women's mean pain intensity ratings were about one unit higher (on the 0–10 scale) than men's, β=−1.15, F(1,63.6)=5.66, P=0.020. The rate of increase of pain intensity was also higher in females [β=−0.25, F(1,61.6)=6.46, P=0.014], as was the rate of increase of unpleasantness [β=−0.23, F(1,61.3)=6.45, P=.014]. Sex was not a significant predictor of mean unpleasantness, however. These results apply to the study sample as a whole, rather than indicating a distinguishing characteristic of SCD patients.

It is noteworthy that presence/absence of SCD was not a significant predictor of any of the four measures. Thus, whereas some patients gave indications of hyperalgesia (see below), this was clearly not true for the group as a whole. This finding is consistent with the similarity between groups shown in Fig. 1. Presence/absence of an episode in the patients was likewise not a significant predictor in any of the models.

Age was a significant predictor of temporal summation of both pain intensity [β=0.01, F(1,62.2)=4.74, P=0.033] and pain unpleasantness [β=0.01, F(1,61.6)=5.24, P=0.025], greater age being associated with more rapid temporal summation. Age was not a significant predictor of the mean level of intensity or unpleasantness for the overall study sample. Inspection of the data suggested, however, that pain intensity was related to age among the patients, but not among control subjects. This possibility was evaluated by repeating the mean-intensity analysis using only the data of the SCD group. In this analysis, age approached significance, with older subjects tending to report higher intensities of pain from the experimental stimuli, β = 0.09, F(1,12.6)=3.99, P=0.068.

Psychosocial measures were not strong predictors of experimental pain ratings. The only finding that approached significance was a positive relationship between PCS scores and mean intensity ratings for the overall study sample, β=0.04, F(1,113)=3.81, P=0.053.

Finally, to explore the role of patients' pain history, we analyzed the relationship between the recalled painfulness of previous SCD episodes (mean=7.07, median=7, SD=1.58), and their ratings of the pain elicited by the experimental stimulus. Their ratings of the average intensity of a typical pain episode significantly predicted the rate of temporal summation of pain unpleasantness [β=0.14, F(1, 17.8)=4.60, P=0.046], and predicted mean pain unpleasantness at a level approaching significance [β=0.69, F(1,19.1)=4.06, P=0.058]. These findings are illustrated in Fig. 2, where pain unpleasantness is plotted separately for subjects whose reported episode severity was above or below the median. Similar analyses for pain *intensity* did not yield significant results.

In summary, the temporal summation experiment showed that the experimental pain ratings of the SCD patients, whose clinical pain is still predominantly episodic rather than chronic, are on average quite similar to those of control participants. However, there are indications of an emerging sensitization in some patients: Older individuals tend to give increased ratings of experimental pain intensity (a trend not seen in control participants), and patients

with a history of severe pain episodes are more likely to report that their experimental pain builds up rapidly in unpleasantness (that is, the affective dimension of pain).

Pain Discrimination

The SCD participants were significantly impaired in comparison with the healthy controls on the pain discrimination task. In this task, two stimulus intensities (2.3 and 3.3N) were presented in a randomized 20-trial sequence, and on each trial the subject judged whether the stimulus was the weaker or the stronger. We found that the subject's confidence in his/her judgments (indicated by a preponderance of the response options 1 and 4, rather than 2 and 3) was not associated with clinical status [$F(1,47)=0.86$, $P=0.36$)] or pain state [$F(1,47)=0.96$, $P=0.33$]; responses were, therefore, classified simply as correct or incorrect, and accuracy (% correct) calculated. Accuracy scores ranged from 55 to 100%, with a mean of 84.5% (SD=10.1); a breakdown of scores by diagnosis and current pain status is given in Table 1. Analysis of the results for subjects who participated in the discrimination task twice showed that there was no effect of session, $t(47)=0.32$, $P=0.75$. Therefore, it was possible to apply the multilevel model regression analysis to the data of all subjects, ignoring session number. This analysis revealed that participants with SCD were significantly less accurate than controls [$\beta=-0.07$, $F(1,47)=7.29$, $P=0.0096$]. A comparison of scores of SCD patients between baseline and episode sessions showed no effect of current pain status, $F(1,9)=1.15$, $P=0.31$.

Discussion

Scaling and Temporal Summation of Pressure Pain

This study is the first rigorous comparison of experimental pain in patients with SCD and healthy control participants. Attitudes toward pain were also assessed in both groups, specifically hypervigilance, fear of pain, and catastrophizing.

The main question we addressed is whether the repeated painful episodes that characterize sickle cell disease induce changes in central processing that are signs of a chronic pain state, such as hyperalgesia and enhanced temporal summation of pain.[10–16]

We found temporal summation, and average pain ratings of experimental pain, to be comparable in SCD patients and controls (Fig. 1), and to be uninfluenced by the presence of an episode. In other words, the patients as a group did not show significant central sensitization. Individual differences among the patients, however, revealed two indications that those with a heavier cumulative pain burden may be moving toward a chronic pain state.

First, we found that age played a marginally significant role in predicting mean pain intensity ratings in the SCD patients only, with older patients tending to give higher ratings. The fact that the control group did not show an effect of age is consistent with earlier research.[38] Our data suggest that hyperalgesia gradually emerges in SCD patients, perhaps as a result of increasing tissue necrosis, central nervous system changes, and/or other factors.

Second, patients who reported a history of intensely painful SCD episodes also tended to find the experimental pain to be strongly unpleasant, and to build up rapidly in unpleasantness (Fig. 2). This result appears to support the recent hypothesis[3] that some chronic SCD pain reflects neuroplastic changes induced by earlier painful vaso-occlusive episodes. In addition, our finding that unpleasantness was differentially affected is consistent with the suggestion, in a recent review of human brain mechanisms of pain, that "chronic pain states have stronger cognitive, emotional, and introspective components than acute pain

conditions".[39] Thus, heightened negative affect in response to a noxious stimulus may be a key early sign of the emergence of a chronic pain state.

Taken as a whole, the results of the temporal summation experiment indicate that although most SCD patients whose pain is confined to episodes do not manifest central sensitization, a subset – those who are older and who report a history of more severe episodes – are starting to show this characteristic of the chronic pain state.

Pain Discrimination

SCD patients were significantly worse than healthy controls at discriminating between two intensities of noxious stimulation. The explanation for this difference between groups is unclear, given their (on average) similar pain intensity ratings in the temporal summation task. Since pain discrimination requires working memory, modest but significant impairments on this and other neurocognitive skills in SCD patients may be a factor.[40] The difference in discrimination performance, although small, is potentially important because impaired discrimination could reduce a patient's ability to detect small increases in pain that signal the onset of an episode, and thus to take appropriate action. It is already known that reducing catastrophizing can lead to improved discrimination;[22] other approaches to eliminating the impairment also should be explored.

Pain-Related Cognition

Attitudes toward pain also were found to be affected in SCD. Hypervigilance was enhanced in the patients, relative to the controls, but did not depend on whether the patients were in a pain episode. Given the fact that most of the patients gave normal experimental pain ratings, their elevated hypervigilance is surprising, because hypervigilance has been found to be accompanied by perceptual amplification in persons with fibromyalgia or temporomandibular disorders.[11,41,42] Further research will be needed to determine whether this association is a distinctive characteristic of idiopathic disorders.

Catastrophizing showed no overall difference between the two groups, an unexpected result in light of the report by Citero et al.[17] that SCD patients demonstrate substantial catastrophizing. We did, however, find catastrophizing to be significantly greater in the patients when measured during an episode than in a baseline session. This double dissociation between psychological processes and clinical variables – with hypervigilance being related only to diagnosis and catastrophizing only to current pain status – provides valuable insight into some of the ways SCD patients cope with episodic pain. Patients' consistently higher levels of hypervigilance suggest that they are typically alert for signs that an episode is approaching, or (if present) is getting worse. Additionally, patients' higher report of pain catastrophizing during an episode suggests that they feel more helpless and less able to exert control over pain, when they are in fact experiencing severe clinical pain.

Limitations of the Present Study

It is important to note that, in the interest of patient welfare, we made no effort to control SCD patients' use of analgesics during their participation. Because most patients used similar medications during episode and baseline periods, statistical analysis of the impact of medication on pain report was not possible. Controlling or limiting medication use among participants may prove necessary in future research.

Because of limited resources, it was not possible to carry out genetic screening of healthy control participants. It is possible that some of these individuals were carriers of the sickle-cell gene. While sickle-cell trait is in most respects a benign condition,[2] it will be important to determine in future work whether it has any impact on pain processing.

Another limitation of the present study is that we restricted our patient sample to individuals whose pain remitted entirely, or nearly so, between episodes. We did this in order to look for early signs of central sensitization in persons who did not (yet) have frank chronic pain. A fuller understanding of the emergence of chronic pain in SCD will clearly require examination of a larger and more diverse sample of patients.

Conclusions

The results of the present study show few group differences in pain processing between SCD patients whose pain is largely episodic, and healthy control participants (a difference in pain intensity discrimination being a notable exception). However, aspects of the pain responsiveness of certain subgroups of SCD patients, specifically, those who are older or who have a self-reported history of especially painful episodes, suggest the presence of central sensitization. These disturbances of pain processing indicate that the pain of these individuals, although temporally episodic, is qualitatively somewhat chronic in the sense that it does not bear a normal relationship to the properties of the noxious stimulus. Our findings are consistent with the view that the emergence of chronic pain in SCD is driven by earlier experience with nociceptive pain.[3] Further experimental inquiries, particularly among SCD patients with unremitting pain, may shed additional light on the emergence of chronic pain processing disturbances in this disease.

A practical implication of the study, for those who treat SCD pain, is that patients are able to report pain precisely and consistently, even during a pain episode. Patients with SCD at times face doubts that their pain reporting is accurate, given that the direct cause of SCD pain is usually “invisible.” These doubts can impact patient care in a number of ways, including hesitation to prescribe potent analgesics.[43] Our results suggest that such doubts are largely unwarranted.

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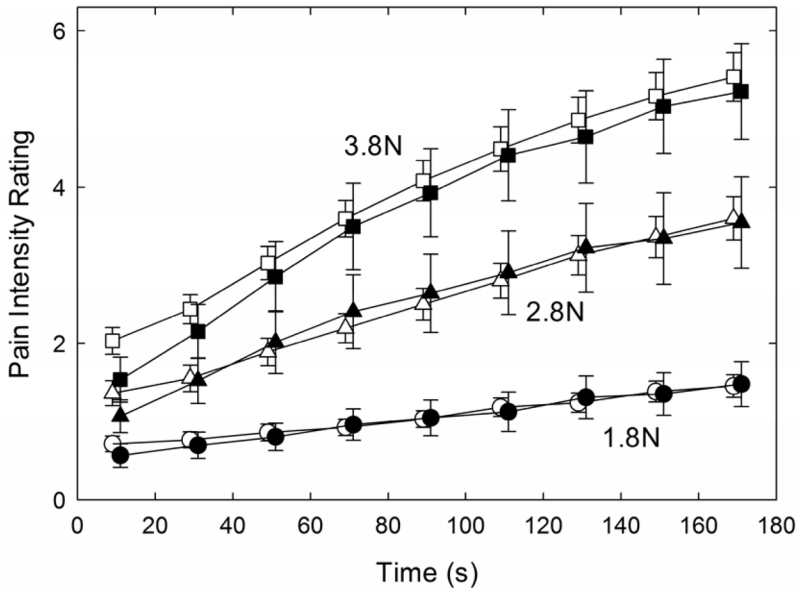

Fig. 1.

Mean pain intensity ratings for trials with SCD participants (filled symbols) and healthy controls (open symbols), as a function of time since the start of the run. Force applied by the Forgione-Barber stimulator is the parameter. For clarity, the data have been slightly offset horizontally. Error bars indicate ±1 S.E.M.

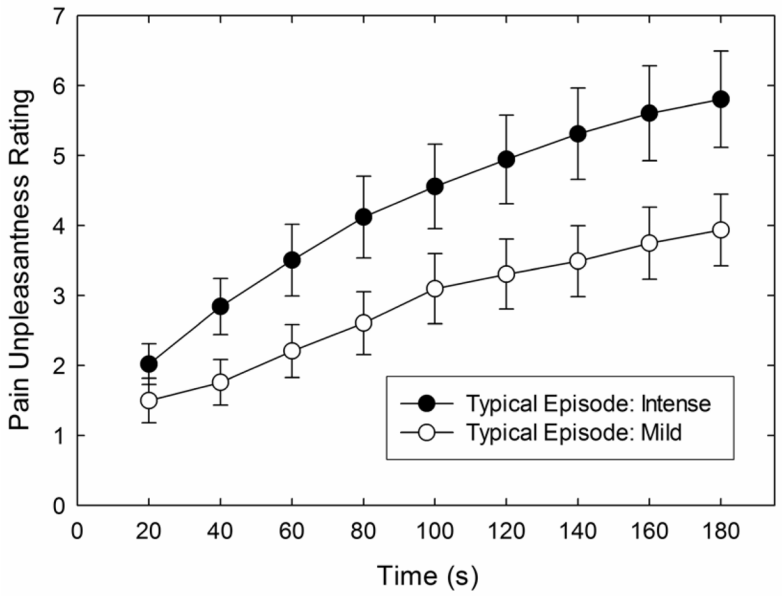

Fig. 2.

Mean pain unpleasantness ratings as a function of time from the start of the run, for SCD patients whose recalled average pain intensity of a typical SCD episode was above (filled symbols) or below (open symbols) the median. Data for the 2.8 N and 3.8 N force conditions have been combined before averaging across subjects. Error bars indicate ±1 S.E.M.

Table 1

Mean (SD) Scores on Questionnaires and Pain Discrimination Task, by Subject Group and SCD Session Type

	HCs	SCDs all sessions	SCDs baseline	SCDs episode
PCS	14.9 (10.0)	20.4 (10.8)	18.0 (8.0)	23.2 (13.1)
FOP	85.5 (17.9)	76.6 (24.6)	77.8 (24.8)	75.1 (25.1)
PILL	12.1 (8.1)	17.3 (8.4)	17.6 (8.9)	16.9 (7.8)
Pain Disc (% Cor)	85.8 (8.4)	81.0 (13.3)	78.8 (14.7)	83.8 (11.0)

SD = standard devision; SCD = sickle cell disease; HC = healthy control; PCS = Pain Catastrophizing Scale ; FOP = Fear of Pain Questionnaire; PILL = Pennebaker Inventory of Limbic Languidness.