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## An evaluation of central sensitization in patients with sickle cell disease

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### Abstract

Central sensitization (CS), nociceptive hyper-excitability known to amplify and maintain clinical pain, has been identified as a leading culprit responsible for maintaining pain in several chronic pain conditions. Recent evidence suggests that it may explain differences in the symptom experience of individuals with sickle cell disease (SCD). Quantitative sensory testing (QST) can be used to examine CS and identify individuals that may have a heightened CS profile. The present study categorized patients with SCD based on QST responses into a high or low CS phenotype and compared these groups on measures of clinical pain, vaso-occlusive crises, psychosocial factors, and sleep continuity. Eighty-three adult patients with SCD completed QST, questionnaires, daily sleep and pain diaries over a three-month period, weekly phone calls for three months, and monthly phone calls for 12 months. Patients were divided into CS groups (i.e. No/Low CS [n=17] vs. High CS [n=21]), based on thermal and mechanical temporal summation and aftersensations, which were norm-referenced to 47 healthy controls. High CS subjects reported more clinical pain, vaso-occlusive crises, catastrophizing, and negative mood, and poorer sleep continuity ( $p$ 's<0.05)

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over the 18-month follow-up period. Future analyses should investigate whether psychosocial disturbances and sleep mediate the relationship between central sensitization and pain outcomes.

**Perspective**—In general, sickle cell disease patients with greater central sensitization had higher clinical pain, more crises, worse sleep, and more psychosocial disturbances compared to the low CS group.

### Keywords

Sickle cell disease; clinical pain; laboratory pain; QST; central sensitization; sleep; catastrophizing

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## Introduction

Sickle cell disease (SCD), an inherited blood disorder, is associated with significant morbidity including severe episodic pain and, in a sizeable subset of patients, chronic pain [47]. While the mechanisms of SCD pain remain poorly understood, recent reports have implicated a process of central sensitization (CS). CS is a process whereby nociceptive signals coming from the periphery assault the central nervous system and alter the spinal cord and brain producing a chronic amplification of pain sensations [57]. This manifests clinically in a number of ways, including hyperalgesia and allodynia, enlarged area of hyperalgesia beyond the initial area of injury, and after sensations following cessation of the initial insult [57]. Rewiring of pain transmission occurs in patients with CS and a growing body of literature documents augmented central nervous system (CNS) processing in SCD. Transgenic mice models of SCD (expressing sickle hemoglobin) suggest that CS occurs through aberrant heightened spinal and supraspinal processing that is demonstrated by increased sensitivity to cold, heat, and mechanical stimuli as well as musculoskeletal pain behavior compared with control animals [15]. Ballas and colleagues [3] note that the best example of this phenomenon observed in patients with SCD is the continuation of severe pain, even following successful bone marrow transplantation, which essentially “cures” the patient of SCD. They note that resetting the aberrant wiring of the brain back to normal may take an extended period of time.

CS in humans can be assessed through the application of quantitative sensory testing (QST) using standardized, calibrated, consistently applied noxious stimuli to measure pain processing. Typical QST measures of CS include the measurement of painful aftersensations or temporal summation, which is heightened perceptual responses to repeated stimulation of identical intensity [22][57]. QST is often used to measure patient characteristics that might be associated with pain-related outcomes [28], and increased sensitivity to painful stimuli has been shown to incur risk for poor outcomes. For example, in non-SCD chronic pain conditions, lower pain tolerance [20;24] and higher levels of temporal summation [2] are associated with more frequent, intense, and disabling episodes of recent pain. The few studies that have examined QST in adults with sickle cell disease generally find enhanced sensitivity of thermal detection and reduced pain thresholds in patients with SCD [5;26;27]. A recent report found evidence of central sensitization in 60% of patients with SCD tested and a combination of central and peripheral sensitization in an additional 32% [23]. The goal of the current study was to use the extant literature to categorize patients with SCD as either showing no/low CS or high CS based on responses derived during QST and examine

differences in clinical characteristics between these two groups. We hypothesized that those in the high CS group would endorse greater pain, worse psychosocial/behavioral comorbidities and a more severe symptom experience than those in the no/low CS group.

## Methods

The current analyses are part of a larger ongoing project designed to examine pain and crises in patients with SCD and compare them to healthy-matched controls. All subjects were recruited for participation from the Sickle Cell Center for Adults at Johns Hopkins Hospital or through posted advertisements. The current analyses focused on thirty-eight adult patients with SCD, derived from a larger sample of 83 patients with SCD and classifying CS based on QST responses observed in 47 healthy controls (see Table 1 for demographic data and QST used for categorization). Major inclusion criteria for the SCD group included age  $\geq 18$  years, formal diagnosis of SCD (by confirmed genotyping or confirmation by study hematologist), no changes in dose of long- and short-acting opioids, NSAIDs or acetaminophen one month prior to pain testing (if on any of these medications) and self-identifying as black or African American (for matching purposes in the larger study). Exclusion criteria included chronic transfusions, active alcohol or substance abuse/dependence; significant cognitive impairment; unstable psychiatric illness; HIV infection, viral hepatitis, or other current infection. While not the focus of the current analyses, additional exclusion criteria for healthy controls included any acute or chronic pain, regular use of anti-inflammatory medication, opioids, or antidepressant medication; and smoking greater than 1 pack/day. While not the specific focus in the current analyses, CS data from healthy controls were used to categorize SCD patients into groups. In brief control participants were healthy African Americans, 65% were women and the group mean age = 33 (SD=9.5) with a BMI of 26 (SD=4.8).

## Procedures

Following initial telephone screening to ensure eligibility criteria were met, participants attended an in-person visit. Participants were asked to attend only when their pain was typical of their SCD pain and at no greater intensity than 5 /10 and they had not experienced a vaso-occlusive crisis in at least the previous 3 weeks. Following informed consent procedures, participants completed a standardized laboratory pain testing protocol between 9 and 11 am; upon completion they were instructed in the use of electronic diary monitoring via personal digital assistant (PDA) and informed they would receive follow-up calls for a total of 18 months (see Figure 1 for a timeline). Participants were allowed to stop or refuse any procedure at any time and all study-related procedures were approved by the Johns Hopkins University School of Medicine Institutional Review Board. Additionally, clinical characteristics (e.g. history of acute chest syndrome, presence of avascular necrosis) were obtained from the medical record.

## Quantitative Sensory Testing (QST)

**Pain threshold/tolerance**—*Heat pain threshold* (HPT<sub>h</sub>) was assessed via a Peltier element-based stimulator (Medoc, Pathway, Advanced Thermal Stimulator (ATS) thermode), on the dominant ventral forearm, using an ascending method of limits paradigm

with a 9 cm<sup>2</sup> probe and 0.5°C/sec rate of rise. Subjects underwent two trials and indicated when they first felt painful (HPTh) via button press which turned the device off. Heat Pain Tolerance (HPTo) was conducted in a similar manner, with participants indicating when they could no longer tolerate the pain from the thermal device. *Pressure pain threshold* (PPT<sub>h</sub>) was assessed via algometer (SBmedic, 1 cm<sup>2</sup> hard rubber probe), bilaterally and 2 times each, at the trapezius muscle, interphalangeal joint of the thumb, the proximal third of the brachioradialis muscle (forearm), and middle of the quadriceps insertion point [6]. Mean HPTh, HPTo (in °Celsius) and PPT<sub>h</sub> (in kilopascals) values were averaged across trials, respectively.

**Temporal Summation**—*Thermal Temporal Summation* (TTS) was assessed via response to three randomized series (temperatures: HPTh, HPTh+2, 45°C) of 10 heat pulses with each temperature rated on a 0–100 scale (0=no pain; 100=worst pain imaginable), applied to the dominant ventral forearm by the Medoc, Pathway Contact Heat-Evoked Potential Stimulator (CHEPS) [54]. A 2.5 second inter stimulus interval (ISI) and a 70°C/sec rate of rise was employed. A TTS difference score (maximal rated pulse of the series minus first pulse of the series) was created for each temperature. The thermode was moved slightly between trials to avoid overlapping stimulation sites. One additional pain rating was obtained 15 seconds following the final pulse in each series to characterize after sensations. *Mechanical Temporal Summation* (MTS) was assessed at two weights via response to an initial single stimulus, and then to a sequence of 10 stimuli of weighted punctate probes applied on a flat contact area of 0.2 mm diameter with a force of 128mN and 256mN, to the middle phalanx, dorsal surface of the dominant middle finger. Each series was delivered with an ISI of 1 second. Participants were instructed to rate the “peak” pain experienced over the train of 10 stimuli. A MTS difference score was calculated (peak rating minus initial stimulus rating) for each probe weight.

**Hot Water Immersion Tests**—Pain ratings were additionally assessed using hot water. This task is similar to cold pressor testing in terms of eliciting a pain response. Hot water was chosen to avoid the possibility of prompting a vaso-occlusive crisis and avoids baroreflex activation [48]. Participants immersed the dominant hand in a circulating water bath maintained at a tailored temperature designed to be moderately painful. The tailoring process included a series of up to 5 brief hand immersions starting at 42°C and increasing by 1–2°C until a rating of 60/100 was reached or as high as tolerable for 20 seconds. Following the tailoring procedures, a total of 3 immersions were conducted, two in the context of CPM (as described below) and one hot water tolerance test. Participants were permitted to remove their hand prior to the completion of any trial if the pain became intolerable. Pain ratings on a 0–100 scale were obtained at 30-second intervals for up to two minutes, the (uninformed) time limit during the hot water tolerance test.

**Conditioned pain modulation (CPM)**—Two PPT<sub>h</sub> readings were obtained on the non-dominant side trapezius muscle immediately prior to commencing the main hot water immersion tests. At the 20-second point during each of the hand immersion trials, a PPT<sub>h</sub> reading was obtained on the trapezius muscle. A difference value was created for CPM, such that the 2 PPT<sub>h</sub> values obtained during each of the CPT trials were averaged and the average

of the 2 baseline PPT<sub>h</sub> readings was subtracted from it (during-baseline to yield a positive number if threshold increased during hand immersion).

## Questionnaires

**Pain**—Brief Pain Inventory (BPI) items were used to assess self-reported clinical pain severity based on the patients' current, average, worst and least pain mean over the preceding week using a 0–10 scale (0 – No Pain to 10 – Pain as bad as it could be). Additionally, participants completed twice daily (daytime and evening) pain ratings using electronic diaries (described in more detail below).

**Depression**—The Center for Epidemiological Studies Depression Scale (CES-D) [35] was used to measure depressive symptomatology. Participants responded to items based on frequency of feelings/experiences during the last week on a 5-point scale (0 - rarely/less than one day to 4 - most of the time/5–7 days). Total score was calculated as the sum of responses. A score of 16 or higher identifies individuals at risk for clinical depression [29].

**Catastrophizing**—The Pain Catastrophizing Scale (PCS) [49] assesses exaggerated negative cognitive and affective response to pain. This standard version of the scale assesses trait-like responses to pain in general and consists of 13 items rated on a 5-point scale (0 - not at all to 4 - all the time) with higher scores indicating greater pain catastrophizing. Participants are instructed to indicate the degree to which he/she has specific thoughts and feelings when experiencing pain. The measure assesses three dimensions of catastrophizing: rumination, magnification, and helplessness. In the current study, we asked patients to base their answers specifically on their sickle cell pain. Total score was calculated as the sum of all responses.

The Situational Catastrophizing Questionnaire (SCQ) [19] is a six item adaptation of the PCS. It has been used by our group and others in several studies [12]. Participants completed this questionnaire immediately after each QST procedure, with instruction to reference the pain procedures while answering, these were averaged to create one situational catastrophizing score.

**Affect**—The Positive and Negative Affect Schedule (PANAS) [55] was used to evaluate mood. It is comprised of two scales, one positive and one negative, each including 10 descriptive words rated on a 5-point scale (not at all to extremely). A total score was calculated for each scale as the sum of all responses within its dimension.

**Sleep**—Participants completed the Pittsburgh Sleep Quality Index (PSQI [9]), a widely used 19-item self-report questionnaire for the evaluation of sleep quality over the previous month. The PSQI includes 7 component scales, which were examined separately and added together to yield a global sleep quality score. Global scores greater than five indicate clinical significance [9].

The Insomnia Severity Index [ISI] [4] is a seven item questionnaire focused on insomnia. Higher scores indicate greater severity, with a score of less than 10 representing no clinically significant insomnia and over 10 indicating strong likelihood of clinical insomnia [31].

**Diary Measures**—In addition to the self-report questionnaires, participants completed diary measurement of pain, vaso-occlusive crises (VOC) and sleep for three months, starting at the conclusion of their initial session. These diaries were completed on a Palm Pilot (Tungsten E2, Palm® personal electronic organizer, Sunnyvale, CA) using a customized application. Specifically, immediately upon waking, participants entered the time they went to bed, latency to sleep onset, wake after sleep onset, final awakening, and time out of bed in order to create indices of sleep continuity.

Just prior to bedtime, participants were instructed to record their average pain level for the day. Participants used an electronic slider on the PDA screen between zero (“no pain”) and 100 (“pain as bad as you can imagine”). Participants were also instructed to self-report the degree to which pain interfered with daytime activities and if they experienced a crisis that day. If they did experience a crisis, they were asked to rate their crisis pain (0–100). A proportion of diary days for which a vaso-occlusive crisis was reported [47] was calculated for each participant as an index of sickle cell disease severity.

Participants did not receive reminders to complete entries; however participants were scheduled for a one-week follow-up to check diary use, answer any questions about the diary and to identify any technical issues regarding its use. Participants received financial incentives based on the number of diaries completed. During data cleaning, entries that were not completed within 12 hours of waking or bedtime were removed to decrease recall bias.

**Telephone Calls**—Following completion of the diary period, participants were then called weekly and queried regarding their pain, mood and sleep for three months. They were then contacted monthly for an additional 12 months. Specifically, participants were asked about their normal level of pain (BPI-like measure) and pain during crises, catastrophizing, positive and negative affect, as well as questions regarding sleep continuity and duration. In total, the follow-up period lasted 18 months from their initial assessment.

## Data Analysis

The initial analyses included standardizing pre-identified QST parameters for the patients with SCD to the mean for each parameter derived from the controls. Specifically, thermal temporal summation (tailored and 45°C), mechanical temporal summation and TTS after sensations were standardized by subtracting the healthy control mean from each individual patient with SCD’s value and dividing by the control standard deviation for each task ( $(X - \mu)/s$ ). Z-scores that were greater than one standard deviation above the healthy control mean of each task were noted. Patients with SCD that scored greater than 1 standard deviation on at least two tasks were categorized into the “high CS” group. Those that were within 0.25 standard deviation of the healthy control group on all tasks were categorized into the “low CS” group. Additionally, a summary score was created that combined the remaining QST variables (QST index), to reflect general sensitivity. A series of t-tests and chi-square tests (for categorical data) were conducted to compare SCD CS groups on measures of pain, psychosocial/behavioral and crisis measures. No imputation was conducted for missing variables.



## Results

### Demographic, Clinical and Clinical Pain Information

Demographic and clinical information for both groups are presented in Tables 1 and 2. The high CS group tended to be older ( $p=.09$ ), had a significantly higher body mass index (BMI) and were more often taking long and/or short acting opioids ( $p$ 's  $< 0.03$ ). The groups differed on a variety of indices of pain, including pain severity from the BPI ( $p=0.001$ ), diary pain ratings averaged over the three months ( $p=0.003$ ), and average number of days reporting a VOC ( $p=0.044$ ; see Table 3). Non-crisis pain was rated more severe in the high CS group across the three months of weekly ( $p=0.018$ ) and 12 months of monthly phone calls ( $p=0.009$ ). In addition to more severe clinical pain, the high CS group reported more calls made to providers and a greater number of medical visits ( $p=0.003$  and  $p=0.028$ , respectively).

### Psychosocial Variables

Although reports of SCD pain catastrophizing were similar between the high and no/low CS groups, situational catastrophizing in response to pain testing was enhanced among the high CS group ( $p < 0.001$ ; Table 4). Consistent with this, catastrophizing was also more frequently reported in the high CS group on PDAs and during the weekly and monthly telephone assessments ( $p$ 's  $< 0.01$ ). While negative and positive affect did not differ between groups during QST, the high CS group reported lower positive affect from three to 18 months of follow-up phone calls ( $p$ 's  $< 0.05$ ). This group also reported greater negative affect in the three months of daily diaries following testing ( $p = 0.026$ ) and during months six through 18 of monthly phone calls ( $p = 0.026$ ).

### Sleep Characteristics

As shown in Table 5, the CS group reported greater sleep disturbance across a number of indices of sleep. This group reported poorer overall sleep as reflected by the PSQI global score as well as multiple PSQI components ( $p$ 's  $< 0.05$ ) and insomnia (from the ISI,  $p=0.005$ ). These summary reports of sleep disturbance were consistent with the pattern of sleep disturbance reported by the high CS group during the home monitoring period, including daily PDA diaries and weekly and then monthly phone calls ( $p$ 's  $< 0.05$ ). Although no group differences emerged in sleep duration between groups ( $p$ 's  $> 0.05$ ), sleep fragmentation was two times greater in the high CS group on the PDAs (though only trended towards statistical significance), weekly ( $p=0.029$ ) and monthly phone calls ( $p=0.006$ ). These differences remained significant even when controlling for group differences in BMI.

### QST Measures

Laboratory pain measures are displayed for each group in Table 6 and normalized and presented graphically in Figure 2. The QST index (composite score of each QST measure, except those that comprised the CS categorization) varied by group ( $p = 0.002$ ). Significant differences between the low and high CS groups were observed in several QST measures including pressure pain threshold at the trapezius, thumb and quadriceps, and temperature of

the hot water task (tailored to a perceptual level;  $p$ 's < 0.05). [Insert Table 6 and Figure 2 about here]

## Discussion

In comparing QST defined low and high central sensitization groups, we observe differences in pain and psychosocial/behavioral patterns between groups. Specifically, the high CS group reported greater clinical pain at the time of testing and on non-crisis days during the daily/weekly/and monthly follow-up, as well as a greater percentage of crisis days during the daily diary monitoring period. Additionally, this group reported enhanced catastrophizing in response to pain testing and worse sleep continuity on a number of parameters and assessment methods. Not surprisingly, other QST measures differed between groups as well, reflecting an overall greater sensitivity in the high CS group. Consistent with this pattern of greater pain sensitivity and disturbed psychosocial/behavioral function, the high CS group reported more contacts with health care providers, either by telephone or in person.

The phenomenon of central sensitization occurs when nociceptive input creates a sustained, reversible increased responsivity of central nociceptive neurons [57]. CS has been hypothesized to affect 17.5–35.3 % of chronic pain patients [41], thus it is not a completely overlapping phenomenon. This sensitization can be quantified in humans using different laboratory pain assessments, including, temporal summation (wind-up like pain) and after sensation, employed here. These indices were chosen, as opposed to others in our QST battery, as they are two of the most commonly assessed QST measures in relation to CS [57], are mediated by different underlying central mechanisms [34;60] and have been documented to have clinical and diagnostic value [21;40]. The method of standardized scores (z-scoring approach) is recommended to evaluate individual patients and patient groups on patterns of QST and determine where they fit in regard to normative ranges [36;37]. Our findings are consistent with the extant literature indicating increased laboratory and clinical pain and greater psychosocial/behavioral sequelae among individuals showing central sensitization. Using fairly stringent criteria (greater than 1 standard deviation above the mean of healthy controls on 2 of the chosen QST tasks), we classified CS in approximately 25% of our sample of SCD patients. This contrasts with a recent study reporting components of CS present in over 90% of patients with SCD [23]. Differences in methodology likely contribute to this discrepancy. We used healthy controls to quantify abnormal responses, whereas Ezenwa et al. [23] used a decision tree based on patient responses to painful vs. non-painful sites. Thus, these different methodologies may have assessed different aspects of CS-ours focused on local summation and theirs on widespread characteristics.

One potential explanation for the differences observed between the low and high CS groups could be that of opioid-induced hyperalgesia (OIH), given that those in the high CS group were far more likely to be on long and/or short-acting opioids (57% vs. 18%). The concept of OIH is an important one that has received much discussion in the pain management literature. We are unable to determine the potential role for OIH in contributing to the increased sensitivity seen in the high CS group, as we do not have data regarding pain levels and pain sensitivity prior to initiation of opioids. This important iatrogenic effect of opioids



is a particularly challenging topic to study in sickle cell, as complications of the disease typically require early, and sometimes extensive, exposure to opioid therapy intermittently over years. The use of ketamine, the noncompetitive NMDA receptor antagonist, in recent case reports of acute pain management of sickle cell crises [52] that have successfully reduced opioid dosing while enhancing pain management support the potential importance of OIH in sickle cell patients.

The underlying mechanism(s) and predisposing factors for developing CS are receiving increased attention and include genetic [45;46], neurophysiological [39], psychosocial [33] and behavioral [25;61] conceptualizations. Recent data suggest that targeting individuals with dysfunctional CS pain modulatory mechanisms with specific interventions may be beneficial [7;11;58]. For example, painful diabetic neuropathy patients with reduced CPM (a proxy for endogenous opioid tone) reported enhanced pain reduction from duloxetine, while the drug was less effective in those with more efficient CPM [59]. In another study, post-caesarean pain patients with enhanced CS (quantified via temporal summation) experienced the greatest analgesic effect from ketamine [58]. These findings provide increasing support for using QST-derived CS profiles to identify specific subgroups for which medications may be most effective, as suggested by others [58]. Whether this approach can be used to manage pain in SCD is an important area for future study.

A growing literature documents the bidirectional association between sleep and pain [25] and several reports have documented that experimentally-induced sleep deprivation promotes hyperalgesia [42] and increases spontaneous pain while reducing central pain modulation in healthy participants [43]. The current differentiation between CS groups in sleep disturbance over an extended follow-up period is quite striking. Patients in the high CS group reported overwhelmingly poorer sleep than those in the low CS group and these differences appear stable over time. These findings are consistent with a growing literature documenting a specific relationship between sleep disturbance and CS indices in clinical pain samples [10;18;42]. It is important to note, however, that our analyses are unable to speak to the temporal relationship between these constructs. For example, it is unclear if sleep disturbance predisposes someone to develop central sensitization or whether the process of central sensitization produces downstream effects on sleep continuity. However, reviews of the existing literature infer a stronger impact of sleep on pain sensitivity than vice versa [25] and we have shown in our larger SCD sample that diary reports of sleep fragmentation in particular precedes increases in next-day clinical pain [32]. Given the broad health benefits of good sleep [50] and the potential for improvements in sleep to reduce clinical pain [44], testing whether improved sleep in SCD reduces clinical pain and possibly CS is an important next step in understanding the potential causal contribution of sleep disturbance to central sensitization in SCD.

The high CS group reported greater situational catastrophizing as well as reports of pain catastrophizing in daily life during follow-up. Surprisingly, we did not observe differences in depressive symptoms or SCD-related pain catastrophizing between CS groups. Maladaptive psychological characteristics, including pain catastrophizing, have been previously associated with identifiable CS clusters in OA patients [16], and several reports have specified pain catastrophizing as an important component in central sensitization

[1;8;38;53]. Although only tested in healthy volunteers, current data suggest that situational catastrophizing is not an artifact produced by the enhanced pain experienced by the high CS group during laboratory pain testing. We have shown that increases in pain are not predictive of increases in catastrophizing, but increases in catastrophizing are predictive of increases in pain in the laboratory using healthy volunteers [13;14]. Also using healthy volunteers, Salomons and colleagues [38] found that eight sessions of brief cognitive training in healthy volunteers reduced pain unpleasantness and central sensitization, but not pain catastrophizing; however, reductions in secondary hyperalgesia, their index of central sensitization, were correlated with reductions in pain catastrophizing in the experimental treatment group. Their findings suggest that changes in central sensitization may be related to changes in pain catastrophizing and that CS may be modulated by altering pain-related thoughts.

One potential limitation of our work is the method we used to classify high vs. no/low CS, which created extreme groups using a healthy control group for standardization and classification. The reference group was limited to 47 healthy African American volunteers from our local community and may not be fully representative of the African American/black population. One clear indicator of this is the sample age of 33 years which is consistent with our sample of SCD patients, but not representative of the larger community. Other groups using a similar method [36;37;51] standardize patients to samples of hundreds of healthy volunteers. We were able to identify a sample of 17 patients with SCD who essentially looked comparable to these healthy volunteers in terms of pain sensitivity and CS indices. Other clinical groups, such as fibromyalgia have individuals who show little to no central sensitization using QST [17;30;56]. An issue for future research to examine is whether our approach of using extreme groups is replicable and produces continued insight into the factors that contribute to central sensitization and its sequelae. Another limitation may be the small sample identified here to create these extreme groups. While not statistically significant, conditioned pain modulation was higher (in the expected direction) among the low CS group. Enhanced descending pain inhibition could be a protective factor; however we may have had too little power, given our small sample size, to truly elucidate differences in CPM. An additional limitation of the current work is a potential confluence of the temporal relationship between situational catastrophizing and the QST measures used to classify groups. Specifically, situational catastrophizing is measured during the execution of QST and subjects are asked to report thoughts/emotions in response to the pain of testing. As noted above, we have shown that changes in catastrophizing in healthy volunteers precede changes in pain, rather than vice versa, but this needs to be replicated in clinical samples, such as SCD patients.

Despite these limitations, the current data suggest greater clinical pain, health care utilization, pain catastrophizing and sleep disturbance in high CS patients with SCD as compared to no/low CS SCD patients. We present an innovative approach to categorizing patients into CS groups which needs to be replicated and extended to other patient groups for further validation. Application of this method to other pain populations may produce valuable information regarding psychosocial factors associated with central sensitization, either causal or sequelae. Future studies may wish to examine CS differences and combined psychosocial/behavioral influences in healthy participants and chronic pain patients and

investigate whether sleep and psychosocial disturbances mediate the relationship between central sensitization and pain outcomes.

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### Highlights

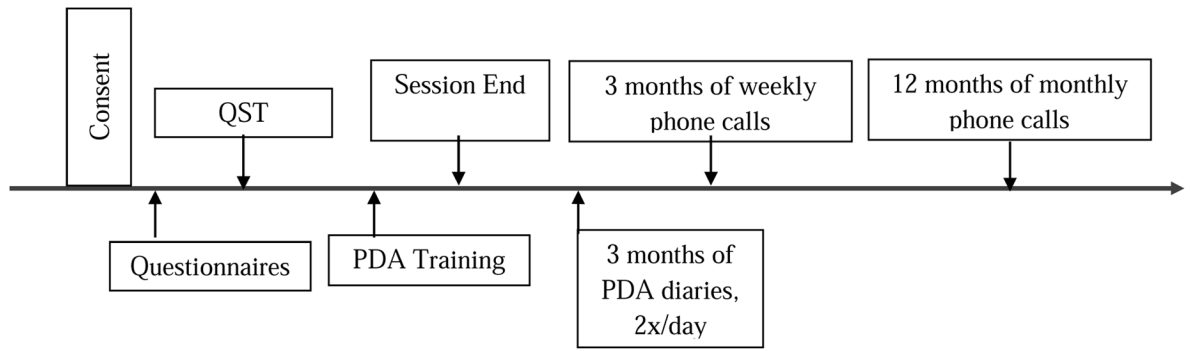
- Sickle cell patients were split into low vs. high central sensitization groups.
- High central sensitization (CS) subjects reported worse SCD outcomes.
- The high CS group reported more clinical pain, vaso-occlusive crises, and poorer sleep
- The high CS group also reported higher catastrophizing and negative mood

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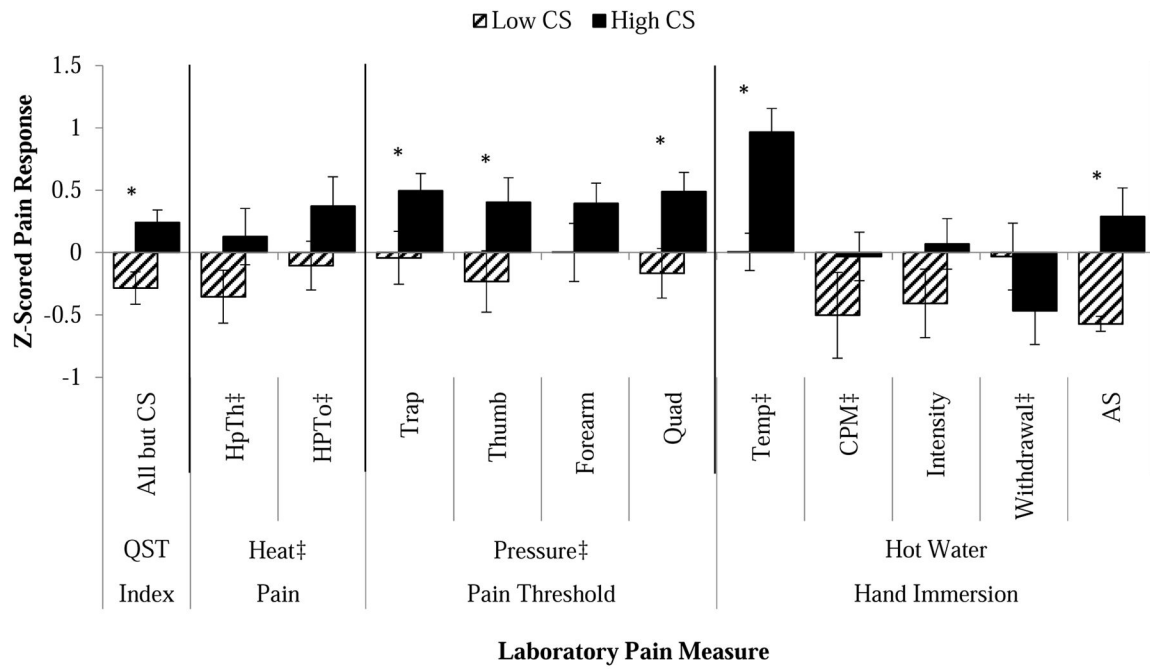
**Figure 1.**  
Timeline

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**Figure 2.** Normalized means and standard error for laboratory pain methods displayed by group. \* $p < 0.05$ . Difference between groups. Measures denoted with ‡ were reversed (multiplied by  $-1$ ) in order to keep directionality consistent. QST Index is a summary of all parameters presented, HPT<sub>h</sub> = Heat Pain Threshold, HPT<sub>o</sub> = Heat Pain Tolerance, PPT<sub>h</sub> = Pressure Pain Threshold, Temp = Water Temperature, CPM = Conditioned Pain Modulation, Intensity = Pain ratings to hot water, AS = After Sensation to hot water.

**Table 1**

Demographic variables [Mean (SD) / % (n)]

<b>Demographic Variables</b>	<b>Low CS N=17</b>	<b>High CS N=21</b>	<b>p value</b>
Age (mean $\pm$ SD)	35.6 (10.6)	42.8 (13.1)	0.08
Female	70.6% (12)	76.2% (16)	0.49
<b>Education Level</b>			
High School/GED	11.8% (2)	23.8% (5)	0.24
Some College/Technical School	35.3% (6)	42.8% (9)	
Bachelor's degree	53.0% (9)	33.4% (7)	
<b>Occupational Status</b>			
Employed (full or part time)	70.6% (12)	42.9% (9)	0.11
<b>Marital Status</b>			
Single/Divorced/Separated	64.7% (11)	81.0% (17)	0.34
Married/Living with partner	35.3% (6)	19.0% (4)	

**Table 2**

Clinical characteristics [Mean (SD)]

Clinical Variables	Low CS N=17	High CS N=21	p value
Body Mass Index	24.5 (3.2)	27.4 (4.6)	0.04*
Systolic Blood Pressure	112.6 (11.0)	116.0 (14.9)	0.44
Diastolic Blood Pressure	69.8 (10.2)	70.5 (10.6)	0.83
Heart Rate	80.3 (11.0)	80.5 (13.1)	0.95
Nicotine Use (smoking)	0% (0)	28.6% (6)	0.42
Genotype			
SS	70.6% (12)	57.1% (12)	0.47
S-Beta zero	5.9% (1)	9.5% (2)	
SC	17.6% (3)	33.3% (7)	
Unknown	5.9% (1)	0% (0)	
History of Acute Chest Syndrome	41.2% (7)	42.9% (9)	0.59
Presence of Avascular Necrosis	29.4% (5)	33.3% (7)	0.54
Taking Hydroxyurea	35.3% (6)	19.0% (4)	-
Taking long-acting opioids	17.6% (3)	57.1% (12)	0.013*
Taking short-acting opioids	52.9% (9)	85.7% (18)	0.027*

\* (p&lt;.05).

**Table 3**

Pain variables by group [Mean (SD)]

Clinical Pain Variables	Low CS (n=17)	High CS (n=21)	p value
<b>Pain</b>			
Pain Severity (BPI)	0.9 (1.3)	2.8 (1.8)	0.001***
Interference (BPI-Extended)	1.5 (2.7)	3.1 (2.4)	0.06
<u>Pain from PDA (0–100; average over 3 months)</u>			
	n=16	n=20	
<u>Proportion of PDA's completed (total completed days/total possible days)</u>	0.78 (0.2)	0.76 (0.3)	0.80
<hr/>			
Non-Crisis Pain	8.8 (14.5)	26.1 (20.5)	0.008**
VOC Pain	35.6 (23.4)	52.1 (21.0)	0.11
Average Number of days reporting VOC	0.09 (0.1)	0.23 (0.2)	0.044*
Average length of Crises	0.8 (1.1)	1.5 (1.0)	0.045*
Number of calls to providers	1.8 (3.0)	4.5 (6.0)	0.11
Number of medical visits	1.6 (1.8)	4.9 (6.1)	0.05
Number of Crises	5.4 (9.2)	12.3 (12.7)	0.08
<hr/>			
<u>From Weekly Calls (0–10; average over 3 months)</u>			
	n=14	n=18	
<u>Number of weekly calls completed (of 12)</u>	10.6 (2.9)	11.0 (1.6)	0.66
<hr/>			
Non-Crisis Pain	1.4 (1.4)	2.9 (1.8)	0.018*
VOC Pain	5.0 (1.8)	5.8 (1.7)	0.31
Average Number of Crises/Week	0.034 (0.06)	0.09 (0.1)	0.13
Number of calls to providers	0.6 (0.8)	1.4 (1.5)	0.23
Number of medical visits	0.7 (0.8)	1.1 (1.4)	0.55
<hr/>			
<u>From Monthly Calls (0–10; average over 12 months)</u>			
	n=13	n=17	
<u>Number of monthly calls completed (of 12)</u>	10.5 (2.8)	9.8 (2.3)	0.44
<hr/>			
Non-Crisis Pain	1.6 (1.5)	3.5 (2.1)	0.009**
VOC Pain	5.3 (1.9)	6.2 (1.5)	0.18
Average Number of Crises/Month	0.9 (0.9)	1.3 (1.1)	0.24
Number of calls to providers	1.0 (1.4)	4.5 (3.2)	0.003**
Number of medical visits	1.5 (2.1)	4.2 (3.5)	0.028*

\* (p&lt;.05),

\*\* (p&lt;.01),

\*\*\* (p .001).



**Table 4**

Psychological characteristics by group [Mean (SD)]

Psychosocial Variables	Low CS (n=17)	High CS (n=21)	p value
Depression (CESD)	11.6 (11.6)	17.5 (12.8)	0.15
Catastrophizing (PCS)	24.6 (15.4)	26.4 (11.7)	0.69
Situational Catastrophizing (SCQ)	0.4 (0.3)	1.4 (0.9)	<0.001 ***
Positive Affect (PANAS)	35.4 (8.6)	34.1 (8.4)	0.64
Negative Affect (PANAS)	11.1 (1.2)	12.7 (3.6)	0.09
<b>From PDAs (average over 3 months)</b>			
Catastrophizing	5.0 (8.2)	22.1 (20.2)	0.003 **
Positive Affect	63.7 (16.3)	56.8 (17.4)	0.230
Negative Affect	15.5 (14.7)	27.5 (15.7)	0.026 *
<b>From Weekly Calls (average over 3 mo)</b>			
Catastrophizing	3.8 (3.3)	12.1 (10.3)	0.007 **
Positive Affect	6.9 (1.3)	5.7 (1.5)	0.024 *
Negative Affect	2.5 (1.6)	3.4 (1.7)	0.12
<b>From Monthly Calls (average over 12 mo)</b>			
Catastrophizing	4.8 (4.7)	17.1 (12.5)	0.002 **
Positive Affect	7.2 (1.5)	5.8 (1.4)	0.014 *
Negative Affect	2.6 (1.7)	4.1 (1.8)	0.026 *

\* (p&lt;.05),

\*\* (p&lt;.01),

\*\*\* (p .001).

BPI: Brief Pain Inventory, CESD: Center for Epidemiological Studies Depression Scale, PCS: Pain Catastrophizing Scale, SCQ: Situational Catastrophizing Questionnaire, PANAS: Positive and Negative Affect Schedule.

**Table 5**

Sleep parameters by group [Mean (SD)]

Sleep Variables	Low CS (n=17)	High CS (n=21)	p value
PSQI Components			
1. Subjective Sleep Quality	0.8 (0.5)	1.5 (0.8)	0.007**
2. Sleep Latency	0.9 (0.9)	1.8 (1.1)	0.01*
3. Sleep Duration	0.5 (0.7)	1.3 (1.2)	0.01*
4. Habitual Sleep Efficiency	2.6 (1.0)	2.0 (1.3)	0.10
5. Sleep Disturbance	1.4 (0.7)	2.0 (0.7)	0.006**
6. Use of Sleep Medications	0.1 (0.3)	1.0 (1.2)	0.007**
7. Daytime Dysfunction	0.9 (0.7)	1.3 (0.9)	0.14
Global Score	7.1 (3.1)	10.9 (4.0)	0.003**
ISI	5.4 (6.1)	12.5 (8.2)	0.005**
<u>Sleep from PDA</u> † (average over 3 months)			
Sleep Efficiency (%)	89.6% (6.7)	77.1% (17.7)	0.011*
Wake After Sleep Onset (in minutes)	17.5 (24.3)	35.6 (29.5)	0.057
Sleep Onset Latency (in minutes)	16.8 (12.9)	37.4 (25.1)	0.005**
Sleep Duration (in hours)	7.2 (1.2)	7.9 (3.7)	0.53
<u>From Weekly Calls</u> (average over 3 months)			
Sleep Continuity Disturbance	0.9 (.9)	1.9 (1.3)	0.029*
Sleep Duration	6.7 (0.9)	6.2 (1.5)	0.34
<u>From Monthly calls</u> (averaged over 12 months)			
Sleep Continuity Disturbance	1.1 (0.9)	2.2 (1.0)	0.006**
Sleep Duration	6.5 (1.2)	5.7 (1.1)	0.068

\* (p&lt;.05),

\*\* (p&lt;.01).

PSQI: Pittsburgh Sleep Quality Index, ISI: Insomnia Severity Index.

† Does not include VOC nights.

**Table 6**

Quantitative Sensory Testing (QST) measures by group [Mean (SD)]

QST Variables	Low CS (n = 17)	High CS (n=21)	p value
<b>QST used to categorize groups</b>			
<b>Thermal Temporal Summation</b> difference scores			
at Heat Pain Threshold	0.5 (1.3)	9.7 (10.6)	
at Heat Pain Threshold +2 °C	0.9 (2.6)	8.7 (13.6)	
at 45°C	0.06 (0.2)	9.6 (9.8)	
After Sensation Ratings (TTS, 0–100)	0.2 (0.7)	29.7 (21.6)	
<b>Mechanical Temporal Summation</b> difference scores			
128 mN (Probe 5)	2.2 (5.2)	25.0 (18.0)	
256 mN (Probe 6)	5.5 (6.7)	30.0 (25.2)	
<b>Summary Measure</b>			
QST Index	-0.3 (0.5)	0.3 (0.3)	0.007**
<b>Thermal Pain</b> in °Celsius			
Threshold (HPT <sub>h</sub> )	42.1 (2.5)	40.7 (3.0)	0.14
Tolerance (HPT <sub>t</sub> )	44.9 (1.9)	43.8 (22.5)	0.14
<b>Pressure Pain Threshold</b> in kilopascals (kPa)			
Trapezius	276.8 (102.2)	213.8 (74.0)	0.034*
Thumb	336.4 (108.8)	268.5 (94.9)	0.050
Forearm	261.9 (109.1)	217.3 (84.8)	0.17
Quadriceps	612.9 (204.9)	448.8 (176.4)	0.012
<b>Hot Water Hand Immersion Tests</b>			
Temperature of Hot Water (in °Celsius)	46.2 (1.3)	44.3 (1.8)	<0.001***
CPM Difference Trapezius (difference score)	94.4 (91.1)	64.1 (57.5)	0.22
Hot Water Pain Ratings (0–100)	50.6 (29.8)	63.3 (24.5)	0.16
Hot Water Tolerance (in seconds)	43.9 (35.1)	57.8 (38.4)	0.26
After Sensation Ratings (hot water; 0–100)	2.6 (4.0)	16.0 (16.4)	0.002**

\*  
(p<.05),\*\*  
(p<.01),\*\*\*  
(p .001).

Difference Scores represent the maximal rated pulse (for Thermal Temporal Summation) or following the train of 10 stimuli (for Mechanical Temporal Summation) of the series minus first pulse of the series. CPM: Conditioned Pain Modulation. CPM Difference represents pressure pain thresholds at the trapezius obtained during water immersion of the hand minus baseline trapezius pressure pain thresholds. QST Index: Quantitative sensory testing index z-scores all QST variables (except those used to categorize groups) and combines them into one general sensitivity index.