STRESS, PAIN, AND MOOD IN ADOLESCENTS WITH SICKLE CELL DISEASE

By

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CHAPTER I

INTRODUCTION

Sickle cell disease (SCD) is a disease which disproportionately affects African Americans. With a prevalence of 1 in 500 African American births, SCD is associated with shortened life expectancy, neurologically related medical problems, and pain ranging in intensity from mild to severe. Among the chronic debilitating aspects of SCD, pain is the most marked characteristic of the disease.

The biology of SCD is best described at the cellular level. In healthy individuals, normal hemoglobin molecules transport oxygen from the lungs to sites throughout the body. Upon releasing oxygen, normal hemoglobin molecules remain as single units and move freely, giving red blood cells their round, pliable shape which allows the cells to move easily throughout the circulatory system. In individuals with SCD, however, a mutation on chromosome 11 causes the body to manufacture abnormal hemoglobin molecules, although some normal hemoglobin is still produced. Unlike their healthy counterparts, the hemoglobin molecules of a child with SCD only remain as individual units when bound to oxygen. Once oxygen is released, the mutated hemoglobin molecules become sticky, and group together to form a long chain. These chains of molecules morph the red blood cells into stiff, rod-like structures with a sickled shape. These misshapen red blood cells return to the lungs and reoxygenate to resemble normal hemoglobin. However, the cyclical transformation of the cells takes a toll on red blood cells, either resulting in early cell death or their becoming irrevocably stiff and brittle.
Diagnosis of sickle cell disease occurs at birth during a battery of tests that are now routine for newborns. While pain can start as early as 6 to 9 months, it is not until the age of approximately 4 years that children most commonly begin to experience the problematic symptoms of the disease. This delay is due to the presence of fetal hemoglobin (Hemoglobin-F) in infants and toddlers with SCD, which can be prolonged via medication. Hemoglobin-F prevents deoxygenated sickle cell hemoglobin from sticking to one another, thereby inhibiting the formation of sickled red blood cells.

Pain and Sickle Cell Disease

Although there are various complications affiliated with SCD, pain episodes or pain crises are the most prevalent symptom of SCD. Rigid, sickled red blood cells are unable to move smoothly throughout the smaller vessels of the circulatory system and instead become lodged within the vessels, restricting blood flow to tissues. The result is localized pain for the sickle cell patient due to oxygen deprivation in cells and constriction of blood flow through the capillaries. The experience of SCD pain can range from dull to sharp pains in the head, back, or extremities.

The pain of SCD goes beyond the aforementioned physical manifestations and biological consequences. Research has also demonstrated the significant impact that SCD pain episodes have on the lives of those with the disease. For example, in an investigation of adolescents with SCD, Gil, Carson et al. (2003) found a significant and positive relationship between adolescents’ ratings of SCD pain and increased school absences, decreased extracurricular activities, and reduced household chores. In adolescents as well as adults with SCD, pain has also been shown to be associated with
costly medical care, family stress, as well as symptoms of depression in patients and family members (Gil, Carson et al. 2003; Shapiro, Dinges et al. 1995).

Even with the significant impact that SCD pain can have on the lives of those with the disease as well as their families, very little is known about the specific triggers or precipitants of sickle cell pain episodes. Anecdotal evidence describes precipitants ranging from cold weather to decreased fluid intake to increased physical activity. These triggers lack scientific foundation, however, leaving a dearth of information within the psychological and medical literature. In order to better understand the possible precipitants of sickle cell pain, it is most helpful to first understand the broader construct of pain and the research about its onset. While the construct of pain is well studied, a complete discussion of the literature surrounding this topic is beyond the scope of the present study. There are, however, various aspects of pain which must be reviewed to better understand the potential triggers of sickle cell pain.

Acute vs. Chronic Pain

The broad concept of “pain” includes two more specific types of pain which have long been acknowledged by clinicians and researchers. Acute pain refers to pain sensations that are short in duration, while chronic pain is a term reserved for pain that is longer in duration, and is often experienced in the form of intermittent episodes of pain (Sapolsky, 1998). While the intensity of these pain types can vary, it is their temporal characteristics as well as their cellular functions that differentiate the two. Located within the nervous system are pain fibers which are of particular importance when understanding pain perception. They primarily exist in two subtypes: fast fibers which
carry information about acute, sudden pain, and slow fibers, which carry information about slow, chronic, dull pain.

Theories of Pain

To explicate the pain experience solely in terms of acute and chronic subtypes, or fast and slow fibers, is to provide an inaccurate review of a vast theoretical body regarding pain perception. Though a complete review of the multiple perspectives on pain is beyond the scope of the present paper, it is important to briefly discuss the evolution of pain theory and the frameworks that currently influence medical and psychological perspectives on chronic pain.

Restrictive Theoretical Perspectives on Pain.

Scientists viewing pain from a “restrictive” theoretical vantage point attribute the pain experience to a central point of interest, ignoring other contributing factors that may play important roles in pain perception (Novy et al., 1995). Those ascribing to mind-body dualism theory, for example, view pain as a sensory experience completely equitable to the degree of observable physiological damage (Dalquist, 1999; Turk & Rudy, 1992). Likewise, some theorists assert that psychological mechanisms alone are responsible for pain (Engel, 1959). Restrictive pain theories fail to acknowledge the impact of non-central contributors to pain, deeming them trivial and unimportant to the understanding of the chronic pain experience. Not surprisingly, restrictive pain perspectives have been subject to much scrutiny and criticism, given their incongruence with empirical data. Documented instances of individuals with identical injuries but very
different pain experiences, as well as individuals with substantial physical damage yet no reports of pain provide compelling evidence refuting the validity of restrictive theories. Such cases make it difficult to deny the significance of multiple factors in the maintenance and exacerbation of pain (Turk & Rudy, 1992)

*Comprehensive Theoretical Perspectives on Pain.*

In contrast to the restrictive perspectives on pain, various theories acknowledge pain as a multifaceted experience that cannot be explained by sole central feature. These comprehensive theories, while differing in scope, agree that pain is an experience shaped by behavioral, affective, cognitive, and physiological components (Novy, 1995). Perhaps the most representative of all the comprehensive pain theories is the gate control theory of pain presented by Melzack and Wall (1965). Though heavily based on the role of neurological pathways in pain, the gate control theory also affirms the importance of non-physiological mechanisms in pain perception. With regard to biological processes, gate control theory asserts that painful stimuli are regulated by the dorsal horn located in the spinal column, before messages are finally relayed to the brain. Dorsal horn cells modulate sensory input by balancing the activity of small and large nerve fibers. Large fibers are thought to close the sensory input gate, preventing the continued synaptic transmission to cell is the spinal cord. Conversely, small fibers are posited as being responsible for opening sensory gates and promoting the brain’s receipt of pain signals. This chain of events can prolong the pain sensation and facilitate its spread to other parts of the body. Regardless of the activity of small and large fibers, gates act as transmission
Gate control theory is not, however, solely focused on the above physiological systems. Psychological information, such as fear and even sexual arousal, can interfere with the conveyance of pain signals. Neural pathways, typically responsible for the transmission of pain information can become less responsive in the face of alternate sensory information, resulting in decreased pain sensitivity. In terms of gate control theory, the pain gates have been temporarily closed to the transmission of pain information because of the other, more salient information that occupies the pathways. Gate control theory remains one of the chief perspectives on chronic pain, however, it is not without shortcoming. Melzack, asserts, for example, that cases of phantom body pain in paraplegics provide substantial evidence in refutation of his gate control theory (Melzack, 1999). Other comprehensive pain theories include non-radical operant behavioral theory and cognitive behavioral theory (Novy et al., 1995). Neither viewpoint is based on neurological mechanisms and pathways, like gate control theory, however all three perspectives share in the notion that pain is a blend of affective, cognitive, behavioral and physiological components and at no point should one factor be considered in isolation (Melzack, 1999; Melzack & Wall, 1965, 1982).

**Stress and Pain Perception**

The neurological mechanisms underlying pain sensation are but one component of pain perception. Adding to the complexity of pain perception is the construct of stress. Stress plays what may be a surprisingly integral role in the perception and experience of
pain. Much like the acute/chronic dichotomy that describes pain categories, stress too, is broken into acute and chronic subtypes. Acute stressors are those short-lived “emergencies” that demand immediate mental and physiological attention and response. To illustrate the meaning of acute stressor, Sapolsky (1998) uses the example of physical stressors experienced in the animal kingdom whereby an animal is the victim of a predator attack and must therefore focus all physiological processes on survival. As Sapolsky writes, our “body’s responses are brilliantly adapted for handling just this sort of emergency.”

The relationship between acute stress and pain perception is often described in terms of the stress-induced analgesia phenomenon, or the decrease in pain sensitivity observed after the experience of an acute stressor. The neurochemistry of this phenomenon was first noted by Guillemin (1977) when he found that stress was related to the release of endogenous opioids. This finding was significant given that scientists had known since the early 1970’s that natural or endogenous opioids (produced by the body) and opiates (analgesics not made by the body), both similar in chemical composition, had a dulling effect on the perception of pain. By binding to opiate receptors in the brain, opioids produced by stress trigger the brain to send an inhibitory signal back to the neurons in the spinal cord which sent the initial pain information.

On the other end of the stressor continuum are chronic stressors, which include more long lasting, pervasive and often worrisome events or circumstances. These chronic stressors can take the form of micro-stressors, or small daily stressful events that create an overall moderate level of life stress. Unlike the numbing effect that acute stress can have on pain sensation, chronic stress is not associated with a decrease in pain sensitivity.
The opioid secretion associated with stress cannot be sustained throughout the course of chronic, long lasting stress and therefore their pain blocking functions are no longer effective.

Perhaps the most noteworthy evidence supporting these aforementioned stress-pain relationships comes from studies on animal populations. In a classic laboratory model of stress, Gamaro et al. (1998) subjected male and female rats to acute stress (single restraint exposure) versus chronic stress (1 hour restraint, 5 days per week for 40 days), followed by the administration of a concentrated heated light source on the rat’s tail. A flick of the rat’s tail terminated the pain paradigm, and the duration of the trial indicated the pain threshold. Significant differences were found between acute and chronic stress groups, with chronically stressed male rats exhibiting a significantly lower threshold than their control group counterparts. Conversely, both male and female rats in the acute stress condition exhibited analgesic characteristics, as their pain threshold was significantly greater than the control rats. Further investigation of the chronically stressed group showed that even long after the last restraint period, basal pain threshold in male rats remained lower than the control group, suggesting that repeated stressors influence pain sensitivity after cessation of the stressful events. These findings may have implications for pain episodes in children with SCD. Much like the daily stressors experienced by children and adolescents, a single acute stressor may not be sufficient to affect pain threshold. After repeated exposures, however, seemingly small and insignificant stressors can become important in the experience of pain.

Chronic stress, the focus of the current study, can influence other biological mechanisms, and contribute to the initial onset of pain and even illness. When
individuals experience a stressor, the two divisions of the nervous system, the sympathetic and parasympathetic, which typically work in conjunction to maintain homeostasis or optimal physiological equilibrium, are thrown into a state of imbalance. While our bodies are constructed to adjust and adapt to such environmental demands through a process termed allostasis, repeated hits (stressors) can result in allostatic load, a point at which the body can no longer support the physiological demands of chronic stress, and risk for illness increases (McEwen, 2000).

Research illustrates that stress can have deleterious effects on our biological processes and can thereby result in illness and pain. For example, in a study of 22 adults hospitalized for an SCD pain episode, 50% of the sample reported that the pain was preceded by a stressful and depressing events characterized by feelings of hopelessness, helplessness and dependency (Nadel & Portadin, 1977). While this study’s finding implicates stress as a precipitant of pain onset, the reliance on retrospective methods compromises the compelling nature of the results.

The stress-illness relationship is also evident in research beyond the scope of sickle cell disease. For example, in a study by Varni, Rapoff et al. (1996), children and adolescents (ages 5-16) with rheumatic diseases completed the Children’s Hassles Scale (CHS; Kanner et al., 1985) a measure of perceived stress, or microstressors. Pain intensity ratings were also obtained using the Visual Analog Scale from the Pediatric Pain Questionnaire (PPQ; Varni & Thompson, 1985) Children and adolescents rated present pain as well as worst pain intensity for the previous week. Bivariate analyses revealed significant positive relationships between perceived stress and current pain, the child’s worst pain, adolescents’ current pain, and adolescents’ worst pain. Multivariate
analysis further supported the pain-stress relationship revealing that for children, perceived stress (microstressors) accounted for a significant amount of variance in present pain and worst pain, and for adolescents, perceived stress (microstressors) accounted for a significant amount of the variance in present pain (Varni, Rapoff et al.). These results suggest that the microstressors of daily life cumulate and are perceived by kids and teens as significant life stressors. Furthermore, this research suggests that microstressors, no matter how small, can, over time, have the same role as larger, chronic stressors.

By continually calling upon our physiological resources to respond to repeated “emergencies,” chronic stress halts the body’s ability to attend to long term processes such as digestion, growth, and immune system functioning. Continued neglect of these processes puts the overall health of an individual at risk, and makes the stress-response a potentially damaging mechanism (Sapolsky, 1998).

**Sickle Cell Disease and the Stress-Pain Relationship**

The study of stress, pain and chronic illness is replete with research demonstrating the positive relationship among these variables (e.g., Gil et al, 2000; Kohler & Haimerl, 1990; Varni et al., 1996; Walker et al. 2001). Given the various illness populations in which such investigations have been done, it is difficult to generalize findings since each illness is unique in its presentation, prognosis, and underlying biology. This is not to suggest that one illness trumps another in severity, but that individual disease characteristics may slightly alter the role between stress and disease related pain.
With respect to sickle cell disease, children and adults experience pain symptoms unlike those associated with other chronic pain disorders. Unlike some illnesses, SCD is a life-long disease with a known organic cause. Additionally, SCD pain is linked to the constriction of small blood vessels in the circulatory system resulting in pain that is largely peripheral rather than visceral. Of the many complications associated with these vascular processes, peripheral clotting of sickled red blood cells in the brain can result in mild to severe brain infarcts which can in turn result in intellectual impairment or even death. SCD pain is also chronic as well as unpredictable in its onset, offset, location, and intensity. Patients experiencing severe pain episodes are often forced to miss important obligations such as school, activities, and work. Lastly, SCD pain has no established triggers outside of the anecdotal precipitants reported by parents and children. Together these disease characteristics compose an illness that is itself a source of chronic stress. As asserted by Sapolsky (1998), “a stressor can also be the anticipation of [something] happening.” This statement is applicable to sickle cell disease. Due to the unpredictability of pain, children may experience pervasive worry about the onset, location, duration, and severity of their next pain episode. Children, adolescents and young adults are subject to stressors secondary due to their illness in addition to the normal daily stressors that are associated with these developmental periods.

**Mood and Pain**

A growing body of literature also cites a relationship between mood and chronic pain. Research by Zautra, Burleson et al. (1994), for example, demonstrated that in adults with rheumatoid arthritis, there was a positive and significant relationship between
depression and the immuno-stimulatory hormones that illicit disease flare-ups. This relationship was also illustrated by Haythornwaite et al. (1991) in a sample of depressed and non-depressed chronic pain patients. Depressed chronic pain patients were found to report greater pain intensity, greater pain behaviors, and greater interference due to pain in comparison to non-depressed patients. Work at the Medical University of South Carolina provides research on mood and pain that is perhaps most applicable to the current investigation. In a study of adolescents with varying chronic illnesses (including SCD, asthma, Type I diabetes, spina bifida, and cystic fibrosis), Key et al. (2001) found that depressive symptoms were significantly greater for chronically ill compared to the normative sample. Furthermore, a trend toward significance was found in the frequency of elevated depressive symptoms in the asthma and SCD groups, with both groups reporting moderate to severe symptoms compared to the other illness groups (p < .08).

Research on mood and pain is rather compelling, showing a consistent relationship between the two phenomena. What continues to be questioned, however, are the underlying mechanisms responsible for this relationship. Some pediatric psychologists posit that deficits in central nervous system functioning may leave children with chronic illness more vulnerable to adjustment problems, including pain (Nassau & Drotar, 1997; Stein & Jessop, 1982). It may also be the presence of illness specific daily functional impairments, such as school absences, heightened susceptibility to sport injuries, or learning deficits, that lead chronically ill children to report more depressed mood. Even without a complete understanding of the mechanism that facilitates the mood-pain relationship, it continues to be important within the field of pediatric psychology. We will continue to see this when we look specifically at mood and sickle
cell disease pain. The reason for the relationship between mood and pain is not fully agreed upon, however, research suggests that mood states such as depressed may compromise the patients ability to adjust adaptively during pain episodes (Gil et al., 1991; Thompson et al., 1992).

**SCD Pain and Mood**

As discussed above, mood is another component that must be considered in the onset and experience of pain. Research specific to sickle cell disease further corroborates such findings. In the daily diary study conducted by Porter, Gil et al. (2000), adults with SCD rated their pain, stress, mood, and health care use. Results here revealed that higher levels of negative affect (NA) were positively and significantly related to sickle cell pain. Likewise, higher levels of positive affect (PA) were associated with lower levels of reported pain. Further, when stress, NA, and PA were entered in a single simultaneous regression equation predicting pain, stress and PA continued to show independent associations with pain, although NA did not (Porter et al., 2000). Additionally, results showed that both NA and PA individually interacted with pain to significantly predict medical care use and narcotic medication use. Other research (Gil, Abrams et al. 1989; Gil, Williams et al. 1991; Thompson, Gil et al. 1992) suggests that the mood-pain relationship can also be explained in terms of clinical mood states such as depression which compromise the adjustment during SCD pain crises.
Stress, the Cardiovascular System, and SCD

As previously described, SCD symptoms manifest in the small vessels of the cardiovascular system. It is important to note then, that the cardiovascular system has its own relationship with stress. Research in both human and animal populations corroborates this contention.

Stress is known to be related to a number of physiological changes. One such change includes the constriction of blood vessels, or vasoconstriction. The relationship between stress and coronary vasoconstriction was illustrated in research by Lacy et al. (1995) when statistically significant decreases in coronary diameter were recorded in patients with and without coronary artery disease after the completion of a 75-second simulated public speaking task. Sustained stressors, such as those experienced on a daily basis can also have deleterious effects on the cardiovascular system.

The nature of cardiovascular stress responses have clear implications for the potentially important role that stress can play in sickle cell disease. Though psychological stress has been implicated as factor which can worsen the symptoms of various chronic illnesses such as recurrent abdominal pain (Walker et al., 2001) and rheumatoid arthritis (Zautra et al., 1994), the role of stress on pain, becomes increasingly important when considering the characteristics of sickle cell and the relationship between stress and cardiovascular health. As previously, discussed, SCD manifests in blood vessels where sticky, brittle, sickle-shaped cells become lodged and cause pain. Since stress is related to the constriction, and overall heightened reactivity of the cardiovascular system under stress, it follows then, that children with SCD who experience daily stressors may be at a greater risk for the onset of vaso-occlusive pain episodes. Given the
relationship among these risk factors, the study of stress as it relates to the onset, duration, and frequency of sickle cell pain is important and was the overarching objective of the current investigation.

**Daily Diary Methodology**

To achieve the aims of the current study, the present study used a daily diary method similar to that used by both Gil et al. (2003) and Walker et al. (2001). Daily diaries are frequently used in research investigating pain and stress (Ely et al., 2002; Porter et al., 2000). Diaries allow for the assessment of behaviors and symptoms without the need for daily visits to the research lab environment. Daily diary assessment also reduce the problem of recall bias that is often found when participants are asked to report on pain, coping, and stress experiences that occurred during the previous days and weeks. Daily diaries are especially useful in populations of adolescents with SCD since pain is often mild to moderate in intensity and goes unreported to health care providers thereby compromising the validity of hospital records.

SCD daily diary studies have utilized paper and pencil diaries that are sent home with the child (e.g., Gil et al., 2003) and the child is instructed to return the diary by mail. This methodology is problematic since it is impossible for investigators to ensure that all “daily” information was in fact completed on a daily basis and no penalty is incurred to the child should he fill out all diary days at the end of the survey period.

Outside the realm of SCD research, however, investigators have utilized many methods of daily data collection. Many methods fall under the title of ‘experience sampling’, whereby electronic devices, such as pagers or Palm Pilots, are distributed to
the sample. These technologically sophisticated approaches provide rather obvious benefits such as signaling, or setting an alarm to remind the participant to complete the questions as well as time-stamping. Furthermore, electronic devices allow for ease of data entry, since most data can be downloaded directly from the device into data management software. This user-friendly daily diary method is not without its flaws, however. For example, electronic techniques of collecting daily data are subject to equipment malfunction.

The present study addressed the concerns of electronic and paper daily diaries by administering daily diaries in the form of phone interviews. Daily telephone contacts have been used previously in studying recurrent abdominal pain (Walker et al., 2001) and are less subject to problems with delayed recording of data and biases in recall. Additionally, by speaking to the participant on a daily basis, the phone interview method allows for the researcher to establish rapport, thereby, maintaining the subject’s motivation and interest to continue in the study.

Purpose of Current Research

The goal of the present study was to analyze daily patterns of stress and pain in adolescents with sickle cell disease over the course of 28 days, through the use of daily telephone interviews. Specific hypotheses related to the present investigation are as follows: (1) stress and SCD pain; (2) stress and negative mood; and (3) negative mood and pain.

1) Same day stress would be positively and significantly related to same day SCD pain.
2) Negative mood would be positively and significantly related to SCD pain.

3) Negative mood would be positively and significantly related to stress.
CHAPTER II

METHOD

Participants

Participants were 15 adolescents (6 girls, 9 boys) between the ages of 11 and 17 (M = 13.33 years, S.D. = 2.024). All of the adolescents were African American, which was appropriate given that sickle cell almost exclusively affects this race. All had been diagnosed with sickle cell disease and were monitored by a pediatric hematologist at Vanderbilt Medical Center.

Procedure

Parent (or caregiver)-child dyads participating in this study were part of a larger pilot study that included measures additional to those discussed here. Dyads were recruited for this study through the Vanderbilt University Medical Center Pediatric Hematology-Oncology Clinic. During routine clinic visits, eligible families were introduced to the study by the physician. In order to eliminate undue pressure on families to participate, families expressing interest signed a release form which allowed a member of the research team to contact them. Parents agreeing to participate visited the Stress and Coping lab with their child for a baseline visit. During this visit the parent completed informed consent procedures; assent was also obtained for older children. Once consent was obtained, the child participated in a short individual interview training session during which a member of the research team reviewed the format of the interview and explained
the response scales that would be used. Each child was sent home with a photocopy of the response scales to use for reference during the interviews. For most children, daily phone interviewing began on the Monday following the baseline visit. Each child was compensated $6 for each phone interview he/she completed, allowing for the chance to earn $168 dollars if all 28 interviews were done. Interviews were conducted on a daily basis for 28 consecutive days at a time agreed upon by the researchers and the participant typically, interviews were conducted in the late afternoon or early evening to accommodate participants’ school and activity schedules. Each participant was interviewed by a two interviewers who rotated on a weekly basis (i.e., the first interviewer would conduct interviews during the first and third week and the second interviewer would conduct interviews during the second and fourth weeks).

**Measures**

**Demographics.**

Parents/caregivers completed a demographic questionnaire indicating the age, gender, and ethnicity of their child.

**Daily Phone Interview.**

The daily diary was composed of multiple sections, several of which are relevant to the scope of the current study and are described below.
**Pain.** Anecdotal evidence from the attending physician on the research team revealed that children with sickle cell are, in fact, able to distinguish between pain sensations that are attributable to SCD and those that are not, therefore, the daily interview probed for both SCD and Other (non-SCD pain experiences). More specifically, children were asked to report on each of these pain types as they occurred on the day of the interview, as well as during the previous evening. This captured any episodes of pain that occurred after the conclusion of the previous night’s interview. Therefore, the pain portion of the interview was divided into four sections: SCD night pain, SCD day pain, other night pain, and other day pain. Information regarding the intensity of each pain episode was gathered through the use of the Wong-Baker FACES pain rating scale. This scale used facial expressions ranging from 0: “Did not hurt;” 1: “Hurt just a little bit;” to 5: “Hurts as much as I can imagine,” to aid in the child’s rating of his/her pain intensity. Each child was provided with a hard copy of the Wong-Baker scale to help them to give responses over the telephone. Duration of each pain episode was reported through the use of an eight-point duration scale with responses ranging from 1: “A few minutes,” to 8: “Most of the day.”

**Stress.** Similar to work by Varni et al. (Varni, Rapoff et al., 1996) and Walker et al. (Walker, Garber et al., 2001), stress was assessed by asking children to report on microstressors or small daily hassles in the domains of family, school, friends, and health. Participants used a 6-point hassles scale (range: 0 = did not happen to 5 = happened and bothered me a whole lot) to respond to a series of questions about daily microstressors. This Hassles Scale was comprised of microstressor questions which were derived from
the Walker et al. Daily Diary Interview (2001), with some questions being altered to be more applicable to children with sickle cell disease. Example questions included: “Did you get into an argument with your parents?” and “Did you receive a bad grade today?” In order to avoid an artificial inflation in the stress-pain relationship, this scale did not include any micro-stressors that entailed the experience of a pain episode. Subsequent use of the term “stress” in this paper will therefore refer to these hassles or microstressors.

**Mood.** Mood was assessed within a larger group of questions which also contained queries about the severity of somatic sensations. The scale used was based on the scale developed for the DDI (Walker, Garber et al. 2001). Using a 5-point scale, ranging from 0: “Not at all,” to 4: “A whole lot,” children reported on how much they felt happy, sad, excited, angry, hopeless, upset, and worried.

**Creating composite scores**

For use in data analysis, stress, mood, and pain items were combined to create composite scores for each respective domain.

**Stress.**

The interview contained several questions to assess stress. The bulk of these questions were contained in the Hassles Scale, however, the interview also contained open ended questions about stressors that occurred during the day and one question about the adolescent’s general perception of his/her daily stress. First, all response scores for all
stress questions were summed to create a composite stress score. Second, only response scores from the Hassle Scale were summed. These two composite scores were then correlated to determine the utility of including all stress questions versus only Hassle Scale questions in the stress composite score ($r = .99$, $p < .01$). Given this high Pearson correlation, only ratings from the Hassle Scale were summed to create the stress composite score to make results more interpretable.

\textit{Pain.}

Both the Sickle Cell Pain and Other Pain composite scores were calculated using a combination of pain intensity and pain duration ratings. For both day and night pain, the corresponding intensity and duration ratings were multiplied together for each participant. The resulting products for day pain and night pain were then summed to obtain one pain composite score for each interview day.

\textit{Negative Mood.}

In order to create a negative mood composite score, items were selected from the scale containing questions about both mood and somatic symptoms. The items selected queried anger, sadness, worry, hopelessness, and upset. The sum of the ratings on these items was calculated to create the composite negative mood score. In order to ensure that these items appropriately reflected the construct of negative mood and could therefore be used together in a composite score, reliability analyses were conducted with the negative mood items. The resulting coefficient alpha ($\alpha = .83$) indicated that together, all items reliably measured the construct of negative mood.
CHAPTER III

RESULTS

Descriptive Statistics

*Interview Completion.*

A total of 15 participants completed a total of 335 daily phone interviews out of a possible 420 days. Participants, therefore, had an average completion rate of 80 percent. On average, the children/adolescents completed 22 interviews each (range = 14 to 28) and 6 of the 15 participants completed at least 90% of their interviews. Below, Table 1 details the incremental percentages of interview completion rates.

Table 1. *Rates of Interview Completion*

<table>
<thead>
<tr>
<th>% of interviews completed</th>
<th># of participants (% of sample)</th>
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<tbody>
<tr>
<td>90% or more</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>85% or more</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>80% or more</td>
<td>7 (47%)</td>
</tr>
<tr>
<td>75% or more</td>
<td>11 (73%)</td>
</tr>
<tr>
<td>50% or more</td>
<td>15 (100%)</td>
</tr>
</tbody>
</table>
SCD Pain.

A pain episode was counted as either one report of SCD day pain, one report of SCD night pain, or a day when both day and night pain were reported. Across the entire sample, 72 pain episodes were reported, representing a report of pain on 21% of the interview days. This indicates an average of 4.8 pain episodes per adolescent over the twenty-eight days. This average, however, reflects wide variability, as the number of pain episodes reported by each participant ranged from 0 to 25 (see Table 3).

As noted in above, the SCD pain composite score was calculated by combining intensity and duration scores. Adolescents, on average, reported a pain intensity of 2, which on the Wong-Baker FACES scale, corresponded to “Hurts a little bit.” On the pain duration scale, the adolescents, on average, reported that their pain episodes lasted between 3 and 4 hours. The mean pain composite score was 25.9 (range = 0-80, SD = 21.15).

Negative Mood.

Across the entire sample, adolescents reported at least one negative mood symptom on 43% of all interview days. Among adolescents who reported at least one day with negative mood, he average negative mood composite score was 3.0 (range = 1-20, mode = 1). When all participants were included in analysis, the average negative mood sum score was 1.3 with a mode of zero. When number of negative mood items/symptoms endorsed were analyzed, adolescents were found to endorse a mean of 1.8 symptoms each day (range 1-5). Both distributions of negative mood composite
score and number of symptoms endorsed were highly positively skewed with the largest number of participants reporting zero symptoms and a composite score of zero.

Stress.

Each day of the interview period, adolescents rated a list of thirty-six daily hassles. Stress composite scores had a mean of 4.8 (range = 0-40, SD = 5.7). Across the entire sample, adolescents most frequently endorsed zero hassles (40% of interview days) during the interview period and endorsed one of the possible thirty-six hassles, 14.4% of the time. Each participant endorsed at least one hassle during the twenty-eight day interview period. On average participants endorsed three hassles per day (range = 0-17, SD = 3.11).

| Table 2. Descriptive Statistics for Pain, Mood, and Stress |
|-----------------|------|----------|--------|----------------|----------------|
|                 | N    | Minimum | Maximum| Mean  | Standard Deviation |
| SCD Pain        | 72   | 0       | 80     | 25.97 | 21.15            |
| Negative Mood Score | 335 | 0       | 20     | 1.30  | 2.69             |
| Hassle/Stress Score | 335 | 0       | 40     | 4.77  | 5.66             |

Hypothesis 1: Same day stress would be positively and significantly related to same day SCD pain.

As shown in the fourth column of Table 3, the relationship between stress and sickle cell pain was first analyzed using a within subjects approach, whereby correlations between stress and pain were calculated individually for each subject. The correlations
for each subject ranged from -1.00 to .714, with two subjects having significant correlations. Only one of these adolescents, however, had sufficient data points to make this correlation meaningful. For this adolescent, Hypothesis 1 was supported as days on which more stressful events or microstressors were experienced were slightly more likely to also be days on which a SCD pain episode occurred. For the other adolescent, subject only two pain data points existed, both of which fell upon the regression line, resulting in a misleading perfect negative correlation of $r = -1.00$. The next step in examining this hypothesis was a between subjects approach, whereby the stress and pain data were aggregated for the entire sample. Counter to the hypothesis, sickle cell pain and stress were not significantly correlated for the sample as a whole.

*Hypothesis 2: Negative mood would be positively and significantly related to sickle cell pain.*

When participants were analyzed individually, negative mood and SCD pain correlations were calculated for 7 adolescents, and ranged from $r = -1.00$ to $r = .443$. Two of the 7 Pearson coefficients were positive and significant, however, only one of these correlations was interpretable, due to the perfect negative correlation of Subject 18’s two SCD pain data points. For this one adolescent, more severe negative mood symptoms were associated with longer and more intense pain episodes. Consistent with the hypothesis, the correlation between negative mood and pain was significant for the whole sample, $r = .298$, $p < .05$. 
Hypothesis 3: Negative mood and pain would be positively and significantly related to stress.

As shown in the sixth column of Table 3, this hypothesis was supported in both between and within subject analyses. Subject-by-subject correlations ranged from $r = .022$ to $r = .716$. For 6 of the 15 participants, within subject analyses revealed significantly positive correlations between negative mood and stress, indicating that for these participants, more negative mood symptoms were associated with more stressful or hassle-filled days. This positive correlation remained significant when the entire sample was analyzed together ($r = .374$, $p < .01$).
Table 3. Rates and Correlations of Pain, Stress, and Negative Mood.

<table>
<thead>
<tr>
<th>Subject</th>
<th># Interview Days Completed</th>
<th># Days Of Scd Pain Reported</th>
<th>Stress-Scd Pain Correlation</th>
<th># Of Days With At Least One Negative Mood Symptom Reported</th>
<th>Stress-Negmood Correlation</th>
<th>Scd Pain-Negmood Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>25</td>
<td>r= .410*</td>
<td>10</td>
<td>r= .446*</td>
<td>r= .337*</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>3</td>
<td>r= n/a</td>
<td>7</td>
<td>r= -.022</td>
<td>r= n/a</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>9</td>
<td>r= .026</td>
<td>11</td>
<td>r= -.255</td>
<td>r= .368</td>
</tr>
<tr>
<td>4</td>
<td>26</td>
<td>0</td>
<td>r= n/a</td>
<td>6</td>
<td>r= .100</td>
<td>r= n/a</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>3</td>
<td>r= n/a</td>
<td>2</td>
<td>r= .388</td>
<td>r= n/a</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
<td>0</td>
<td>r= n/a</td>
<td>1</td>
<td>r= 0.26</td>
<td>r= n/a</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>0</td>
<td>r= n/a</td>
<td>23</td>
<td>r= -.195</td>
<td>r= n/a</td>
</tr>
<tr>
<td>8</td>
<td>22</td>
<td>6</td>
<td>r= -.073</td>
<td>16</td>
<td>r= .518*</td>
<td>r= -.100</td>
</tr>
<tr>
<td>9</td>
<td>27</td>
<td>0</td>
<td>r= n/a</td>
<td>22</td>
<td>r= .221</td>
<td>r= n/a</td>
</tr>
<tr>
<td>10</td>
<td>18</td>
<td>4</td>
<td>r= -.626</td>
<td>8</td>
<td>r= .081</td>
<td>r= -.074</td>
</tr>
<tr>
<td>11</td>
<td>22</td>
<td>0</td>
<td>r= n/a</td>
<td>7</td>
<td>r= .566**</td>
<td>r= n/a</td>
</tr>
<tr>
<td>12</td>
<td>22</td>
<td>10</td>
<td>r= -.339</td>
<td>4</td>
<td>r= .313</td>
<td>r= .174</td>
</tr>
<tr>
<td>13</td>
<td>21</td>
<td>4</td>
<td>r= .714</td>
<td>11</td>
<td>r= .716**</td>
<td>r= .443</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>5</td>
<td>r= .351</td>
<td>1</td>
<td>r= .269</td>
<td>r= n/a</td>
</tr>
<tr>
<td>15</td>
<td>29</td>
<td>2</td>
<td>r= -1.00**</td>
<td>15</td>
<td>r= .405*</td>
<td>r= -1.00**</td>
</tr>
<tr>
<td>Total</td>
<td>335</td>
<td>72</td>
<td>r= .024</td>
<td>144</td>
<td>r= .374**</td>
<td>r= .298*</td>
</tr>
</tbody>
</table>

*p<.05.  **p<.01,  ***p<.001,  ^p<.0001

Note: N/A indicates that SPSS was unable to calculate a correlation coefficient because at least one of the variables was zero.
Secondary Analyses

Because rates of pain were low for many of the participants, a series of secondary analyses were conducted separating the participants into groups based on their rates of pain. These analyses included additional correlations for those participants with high vs. low number of pain days and additional comparisons of mean levels of stress and negative mood for these groups of participants.

Table 4 presents the correlations obtained once the sample was divided into groups based on frequency of pain episodes. Adolescents were separated into “No Pain” (subjects who reported zero pain episodes over the twenty-eight days) and “Pain” (those that reported at least one pain crisis during the interview period those that reported at least one pain crisis during the interview period) groups. Of the entire sample, 5 adolescents fell into the “No Pain” group, while 10 participants reported at least one episode of SCD pain. As shown in Table 4, the correlation between stress and SCD pain was not calculated for the “No Pain” group since the pain variable was constant for these participants, mirroring the results from analyses of the entire sample. For the “Pain” group, the stress-SCD correlation did not reach significance. When Stress and Negative Mood scores were correlated, the resulting statistics were significant for both groups, with $r = .318$, $p < .01$, for the No Pain group and $r = .372$, $p < .01$, for the Pain group. Therefore, for both groups, increases in stress were associated with increases in negative mood. The Pain group showed a significant correlation between SCD pain and Negative Mood; this calculation was not applicable to the group with zero reports of pain crises. For the Pain group adolescents, this indicated that within this group more negative mood symptoms were associated with longer, more intense, and more frequent pain episodes.
Table 4. Correlations Between Stress, Pain and Negative Mood by Pain Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Stress-SCD Pain</th>
<th>Stress-NegMood</th>
<th>SCD Pain-NegMood</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pain Reported (n = 5)</td>
<td>$r = \text{n/a}$</td>
<td>$r = .318^{**}$</td>
<td>$r = \text{n/a}$</td>
</tr>
<tr>
<td>$\geq 1$ Pain Episode Reported (n = 10)</td>
<td>$r = -.013$</td>
<td>$r = .372^{**}$</td>
<td>$r = .293^{*}$</td>
</tr>
</tbody>
</table>

Secondary analyses for group differences in mean stress and negative mood score were also conducted. As shown in Table 5, there was a significant mean difference between the stress scores of the “No Pain” group versus the “Pain” group, with the “Pain” group reported higher levels of stress ($t = -2.574$, $p < .01$). Negative mood scores were compared by group in the same fashion and again revealed a significant difference in group means. Adolescents with no pain over the interview period had a mean negative mood score of .661 while for those with at least one pain episode the mean score was 1.7. The significant difference between these means indicates that adolescents who experienced pain during the interview period also experienced more frequent and more severe negative mood symptoms.

Table 5. T-Test for Equality of Mean Stress Score by Pain Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>T-Test for Equality of Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pain Reported</td>
<td>3.865</td>
<td>4.024</td>
<td>$t$</td>
</tr>
<tr>
<td>$\geq 1$ Pain Episode Reported</td>
<td>5.330</td>
<td>6.390</td>
<td>$-2.574^{**}$</td>
</tr>
</tbody>
</table>

**p<.01

**$p<.01$
Table 6.  *T-Test for Equality of Mean Negative Mood Score by Pain Group*

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>T-Test for Equality of Means</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Pain Reported</td>
<td>.611</td>
<td>1.103</td>
<td><em>t</em></td>
</tr>
<tr>
<td>≥ 1 Pain Episode</td>
<td>1.708</td>
<td>3.229</td>
<td></td>
</tr>
</tbody>
</table>

***p<.001
CHAPTER IV

DISCUSSION

The primary aim of the current study was to investigate the inter-relationship among stress, mood, and sickle cell disease pain in adolescents. In order to accomplish this, a daily dairy methodology was used, whereby participants were asked to complete a telephone interview each day for 28 days. Previous research has suggested that bother mood and stress play important roles in the experience of SCD pain (e.g., Porter et al., 2000). Based on such previous investigations, I examined the relationship between stress and negative mood, stress and pain, and finally negative mood and pain. I hypothesized that each of these relationships would be positive and significant. These hypotheses were tested using between subjects as well as within subject correlations. Group comparisons were also conducted as secondary analyses.

In looking at the relationship between stress and pain, the first hypothesis was supported in the within subject correlations for only one subject for whom greater amounts of stress were significantly associated with longer, more severe, and more frequent SCD pain crises. The correlation between pain and stress was not significant for any of other the participants, however. Further, for the entire sample this hypothesis was not supported as the correlation between stress and pain did not reach significance. The only support for an association between stress and pain came from secondary data analyses in which the mean stress levels were compared for participants who reported no episodes of pain with those participants who reported at least one day of pain. The “no
pain” group reported significantly lower levels of stress than did the “pain” group. Although this comparison provides some support for an association between the levels of stress and pain, it does not establish a temporal correspondence between stress and pain, as the data were aggregated for these two variables across days. The ability to test the first hypothesis was severely limited, however, by the relatively low number of pain episodes, as 5 participants reported no episodes of pain and the mean number of days with pain as 4.8 for the whole sample.

With regard to the second hypothesis, support was found for the hypothesized association between negative mood and pain for the entire sample (r = .298), indicating that as reports of negative mood symptoms increased, so did reports of SCD pain. This pattern could reflect a greater sensitivity to pain on those days when participants experienced higher levels of negative emotions. Alternatively, episodes of pain may have led to more negative emotions, including sadness, anxiety, and anger. This finding is consistent with results reported previously by Porter et al. (2000) who found a significant relationship between negative mood and pain in a diary study with adult sickle cell patients. The present study extends the findings of Porter et al. to children with sickle cell disease, and corroborates the association between negative mood and pain using a telephone interview method rather than a written diary method.

The third hypothesis was supported, as negative mood and stress were found to be positively associated (r = .374). This pattern is consistent with a large literature on the positive association between stress and negative emotions and more generally with emotional and behavioral problems (e.g., Grant et al., 2003). However, most research on stress and negative emotions or symptoms has been used aggregate measures of stressful
events and symptoms, rather than the type of intensive daily assessment of these constructs that was used in the present study. It is noteworthy that the correlation for stress and negative mood was significant both for those participants who reported at least one day of pain ($r = .318$) and for those who did not report any pain days ($r = .372$). This suggests that the association stress and negative emotions is a pervasive effect that is not contingent on the occurrence of pain.

Taken together with the positive correlation between negative mood and pain, these correlations suggest that stress may be indirectly associated with pain via increases in negative mood and emotions. That is, stressful events may lead to negative emotions such as sadness, anxiety, and anger/frustration and these negative emotions may in turn lead to increased sensitivity to and decreased tolerance for pain. This pattern would be consistent with previous research on the role of negative mood in pain (Porter et al., 2000; Zautra et al., 1994), but the present findings suggest that that stress may contribute to this process by increasing levels of negative mood.

The current study also sought to examine the feasibility of telephone contact as a method of assessing sickle cell pain in adolescents. Telephone contact has been used in previous studies to assess pain in children with recurrent abdominal pain by Walker et al. (2001). Similarly, daily diaries have been a popular research method for assessing mood, stress, as well as pain (Walker et al.; Gil et al., 2000). With respect to the current study, analysis of interview completion rates revealed rates that were congruent with those obtained in other daily diary investigations of sickle cell disease in children and adolescents (Porter et al., 2000; Gil et al., 2003; Walker et al., 2001). For example, in their daily study of the role of stress and mood in sickle cell pain, Porter et al. (2000)
achieved an 86.6% completion rate in a sample of 15 adolescents. Similarly, in a daily diary study of stress, mood and pain investigation whereby 37 adolescents with SCD were asked to complete written diaries, participants had a completion rate of 76% (Gil et al., 2003). These results therefore suggest that daily telephone contact is an acceptable and feasible method of assessing mood, stress and pain in adolescents with sickle cell disease. This may also be generalizable to other populations in which low base rates of pain make it necessary to assess symptoms daily. Additionally, when compared to the completion rates reported in written daily diary studies, telephone contact appears to perform equally as well, if not better. This may be due to the fact that telephone interviews provides a more tangible reminder that the interview must be completed and also facilitates the establishment of rapport between researcher and participant.

There is relatively little previous research on the base rates of SCD pain, therefore, there is little against which to compare the SCD pain rates reported in the current study. However, a 1991 article in the New England Journal of Medicine, reported that a review of 3,578 SCD patient’s medical records revealed an average rate of 0.8 pain episodes per year (Platt et al., 1991). These findings suggest that the average pain rates reported in the current study may be somewhat higher than those found in the general population. If, however, we look at the rates of pain reported in other daily diary studies done with SCD patients, we again find higher rates than those described by Platt et al. For example, adolescents in a study by Porter et al. (2000), for example, reported pain at a rate of 65.5%. Participants in the Gil et al. (2000) analysis of daily diary data reported pain on an average of 2.5 days out of 14 diary days (18%).
In order to assess the feasibility and acceptability of the telephone diary methodology in populations with sickle cell disease it was also necessary to examine the use of 28 days as an appropriate period of time for assessing SCD pain. During the development phase of the protocol for this study, consultation with the medical team in the Vanderbilt Medical Center’s Sickle Cell Clinic suggested that 28 days was a sufficient amount of time for conducting daily telephone interviews. While the completion rates suggest that this time period was feasible and acceptable to the subjects, the relatively low rate of pain days suggests that it is likely that this interview period needs to be extended for future investigations of SCD pain. In the general population SCD pain has a low base rate and therefore low rates of pain crises were reported in this study. This compromised the ability to correlate the pain variable with other variables of interest. It is therefore possible that I was unable to garner a fully accurate depiction of the relationships between SCD pain, stress and negative mood. This is further corroborated by the group comparisons that suggested a trend toward significant association between stress and SCD pain.

Although the present study provides some promising support for the use of a daily assessment method to examine pain, stress and negative mood in adolescents with sickle cell disease, there are several limitations that need to be addressed in future research. First, the 28 day interview period may have been too short to capture a sufficient number of pain episodes in this population. Future studies may need to sustain the interviews for a longer period of time to capture more occurrences of pain. Second, inspection of the means and standard deviations for each negative mood and stress revealed highly skewed distributions with the majority of the sample clustered around lower scores. This
provides further indication that a longer assessment period may be needed to capture adequate samples of important possible correlates of pain. Third, the hypotheses of the current study involved same day correlations and did not investigate the possible lagged relationship between stress, pain and negative mood on Day 1 and these same variables on Day 2. Previous written daily diary work by Porter et al. (2000) has looked at this relationship and found that a significant relationship does exist between stress on Day 1 and pain the subsequent day. Specifically, findings indicated that stress may precede pain episodes, suggesting the presence of a causal relationship between stress and pain. It is important that future analyses be conducted to investigate these relationships within the methodology of a daily telephone contact study. Finally, future studies will require larger samples to use more powerful statistical methods to assess within subject and between subject associations between stress, negative mood and pain, including multilevel modeling in which the associations for each participant can be modeled and compared across individuals.
REFERENCES


