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Autonomic Nervous System Reactivity: Children With and Without Sickle Cell Disease

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Abstract

Background—Previous studies of healthy children have demonstrated a link between autonomic nervous system (ANS) reactivity and health outcomes, but there is limited research on whether ANS reactivity is similar for children with chronic conditions.

Objective—To determine if ANS reactivity differs for children with sickle cell disease (SCD) compared to a community sample of children without SCD.

Method—In two cross-sectional, descriptive studies, 32 public school children without chronic health problems were compared with 33 children with SCD. The children were 5-8 years old and they completed standardized protocols measuring ANS responses (respiratory sinus arrhythmia and pre-ejection period) during rest and challenge conditions in social, cognitive, sensory, and emotion domains. Reactivity was calculated as the difference between challenge response minus rest for each domain and overall.

Results—There were differences in the distributions of the samples in parent education and child age, so these variables were adjusted for in subsequent analyses. The community sample showed parasympathetic withdrawal (low respiratory sinus arrhythmia scores) and greater parasympathetic reactivity (low respiratory sinus arrhythmia difference scores and percentage of negative scores) compared with the children with SCD in the social ($p < .05$) and sensory domains ($p < .05$). The children with SCD showed greater sympathetic reactivity (low pre-ejection period difference scores) compared with the community children in the cognitive domain ($p < .05$) and a greater percentage of children with SCD versus the community children showed negative pre-ejection period difference scores (sympathetic reactivity) in the social domain ($p < .05$). The community

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sample, but not the children with SCD, showed changes in respiratory sinus arrhythmia across domains ($p < .05$).

Discussion—Children with SCD may display a different pattern of ANS responses to laboratory challenges compared with children without SCD from the same community.

Keywords

sickle cell disease; autonomic nervous system reactivity; pediatric chronic disease

Autonomic nervous system (ANS) reactivity, a measure of an individual's psychobiologic response to challenges in the environment, has been shown to be associated with physical, behavioral, and mental health symptoms in physically healthy children (El-Sheikh, Kouras, Erath, Cummings, Keller, & Staton, 2009; Merikangas, Avenevoli, Dierker, & Grillon, 1999; Obradovic, Bush, Stamperdahl, Adler, & Boyce, 2010). Increased ANS reactivity responses to laboratory challenges compared with resting states have been associated with high illness rates; internalizing and externalizing behavior problems; and mental health symptoms including anxiety, withdrawal, and overall poor adjustment (El-Sheikh et al., 2009; Merikangas et al., 1999; Obradovic & Boyce, 2009). It is not known whether these ANS response patterns are the same for children with chronic physical conditions. Understanding children's psychobiologic responses to their environments may guide nursing interventions and research with children with chronic health conditions.

Biological Sensitivity to Context

Respiratory sinus arrhythmia (RSA), a measure of the parasympathetic nervous system, and pre-ejection period (PEP), a measure of the sympathetic nervous system, are cardiac measures of the two branches of the autonomic nervous system. Total RSA is an index of the interbeat interval accounting for variations in heart rate due to respirations. Low RSA measures indicate parasympathetic withdrawal and correspond with an increase in heart rate. Resting and reactivity measures of RSA are associated with children's psychobiologic capacity to regulate responses to positive and negative demands from their environment (Beauchaine, Katkin, Strassberg, & Snarr, 2001). The PEP, derived from cardiac impedance measures of basal thoracic impedance (Z_0), changes in impedance (dZ), and the first derivative of pulsatile changes in transthoracic impedance over time (dZ/dt), is the time between the onset of ventricular depolarization and the onset of left ventricular ejection of blood in the aorta. Low PEP measures indicate sympathetic activation and correspond with high heart rate.

Ellis and Boyce's (2008) theory explains that children who have high reactivity are exhibiting not only psychobiologic responses to their environment but also a heightened *biological sensitivity to context*. There is an interaction between children's biologic sensitivity to context such that under conditions of adversity they may have negative health outcomes but under conditions of support and protection they may show positive health outcomes. These ANS responses to resting and challenging conditions may encompass central neural and peripheral neuroendocrine responses that are integrated into a complex system that prepares the child to respond to challenges. These neurophysiological mechanisms are related to psychological, behavioral, and health processes (Obradovic & Boyce, 2009).

Childhood Chronic Conditions

There has been an increased prevalence of childhood chronic conditions over the past few decades (Perrin, Bloom, & Gortmaker, 2007) and nurses with advanced clinical skills play a

key role in the care of these children and their families (O'Conner-Von, Looman, Lindeke, Garwick, & Leonard, 2009). In 2007, it was estimated that 15-18% of children in the United States were affected with a chronic condition, more than twice the number affected in the 1980s, due to widening disparities related to poverty, urban living, and unhealthy lifestyles (Perrin et al., 2007). Cumulative social disadvantage (poverty, low parent education, and single parent) is associated strongly with the odds of a child having a chronic condition (Bauman, Silver, & Stein, 2006) and with disability associated with chronic conditions. The chronic stressors associated with low socioeconomic status may influence well-being and disease risk through stress-related pathways (McEwen & Gianaros, 2010). Socioeconomic status may influence health outcomes for children if family relationships are in conflict and limited in positive communications, if parents and children experience a sense of helplessness and limited control, and when children and parents process information negatively (Chen, Matthews, & Boyce, 2002)--all factors that can be influenced by genetics. Chen et al. (2002) also identify potential social risk factors linking socioeconomic status with health outcomes, including limited access to quality health care and social support, poor housing, and violent neighborhoods.

The relation between ANS reactivity and health for children with chronic physical conditions has been examined related to asthma (Miller & Wood, 1997, 2003) and recurrent abdominal pain (Dorn et al., 2003; Olafsdottir, Ellertsen, Berstad, & Fluge, 2001). A study with 24 children ages 8-17 years with asthma found that ANS reactivity (heart rate, respiration rate) in response to emotion-evoking videos was associated with increased airway reactivity and decreased pulmonary function when the video content was sad (Miller & Wood, 1997) compared with video content eliciting happiness. Children 8-16 years old with recurrent abdominal pain ($n = 14$) showed greater ANS reactivity (heart rate and systolic and diastolic blood pressure) to a social stress challenge compared with 14 physically healthy children (Dorn et al., 2003). In another study (Olafsdottir et al., 2001), 25 children 7-15 years old with recurrent abdominal pain were similar to 23 healthy children in sympathetic nervous system function (measured as skin conductance level reactivity [SCLR]) and parasympathetic function (measured as RSA).

Methodological issues with these studies include small sample sizes and wide age ranges from childhood through adolescence. Heart rate and systolic and diastolic blood pressure are nonspecific measures of ANS responses that do not allow a distinction between parasympathetic and sympathetic activity and thus lack precision in characterizing biologic mechanisms underlying the stress response.

There is evidence that ANS reactivity and associations with biobehavioral outcomes is similar for children and adults (Quigley & Stifter, 2006). For example, in a review by Porges (2007), it was noted that poor modulation of parasympathetic responses was associated with depression and social anxiety in adults and behavioral regulation problems in children. Decreased parasympathetic reactivity was associated with greater emotional expressiveness in preschoolers, with reduced risk for externalizing behaviors in adolescents, and with lessened negative emotional arousal in response to stressors in adults. The psychophysiological literature also has implicated sympathetic mechanisms in the development of cardiovascular risk, diabetes, and obesity (Porges, 2007). Stress reactivity is conceptualized as a moderator of the relation between family and environmental risk factors and clinical, behavioral, and psychological outcomes for children, given that the impact of environmental adversity is not uniform for children or adults.

Sickle Cell Disease

Sickle cell disease (SCD) provides a potential model for the study of psychophysiological reactivity in children with chronic health conditions given the wide variations in clinical manifestations and mental health symptoms that have been observed in children with SCD (Key, Brown, Marsh, Stratt, & Recknor, 2001; Miller et al., 2000). Sickle cell disease is an autosomal recessive condition that affects hemoglobin structure and function. It results from a single base change on the beta globin gene of the red blood cell that produces misshapen beta subunits. These subunits misalign into rigid strands in the absence of oxygen and the rigid strands give the red blood cell a characteristic sickle shape. Sickled red blood cells have difficulty flowing through blood vessels and they have a life span of 20 days compared to the 120-day life span of normal red blood cells (National Institutes of Health, National Heart, Lung and Blood Institute, 2002). Sickle cell disease is one of the world's most common inherited diseases, with over 200,000 infants born annually worldwide with a sickle hemoglobin disorder. In the US, the prevalence of all sickle cell disorders (homozygous [SCD-SS], heterozygous [SCD-SC], thalassemia [SCD-S beta], and other variants) is 1 in 375 African American and 1 in 900 Hispanic births. Complications of SCD begin as early as 6 months of age, continue throughout life, and include chronic anemia, susceptibility to infection, stroke, acute chest syndrome, and, most commonly, pain. Treatments of SCD include transfusions--which come with the risks of alloimmunization, infection, and iron overload (Prabhakar, Haywood, & Molokie, 2010)--and hydroxyurea (Heeney & Ware, 2010), the only FDA approved treatment for the complications of SCD-SS.

The clinical complications of SCD have been attributed largely to the effects of vasoocclusion as the sickle shaped red blood cells have difficulty passing through the blood vessels, and as the blood cells have increased adhesibility to each other and the vessel walls. Chronic vasculopathy can result, and has been implicated more recently in sickle cell pathophysiological processes (Hebbel, Osarogiagbon, & Kaul, 2004). The experience of pain and of daily and illness-related stress have been associated with poor mental health symptoms in patients with SCD (Benton, Ifeagwu, & Smith-Whitley, 2007).

Findings from two studies of ANS reactivity in SCD suggest a possible heightened ANS response to challenge. In one study, an increased prevalence of heart rate variability was found in relation to cardiovascular autonomic dysfunction tests for 24 adults with SCD-SS compared with 63 healthy adults (Romero Mestre, Hernandez, Agramonte, & Hernandez, 1997). The researchers hypothesized that ANS dysfunction might contribute to the sudden deaths observed in SCD-SS. More recently (Sangkatumvong, Coates, & Khoo, 2008), five young adults with SCD-SS and five healthy adults were challenged with transient hypoxia (five breaths of nitrogen, mimicking episodes of hypoxia that occur naturally during sleep) and the adults with SCD showed parasympathetic withdrawal while the healthy controls did not show any change in parasympathetic response to the hypoxia challenge. The researchers hypothesized that parasympathetic responses to hypoxia in SCD could be the result of compensatory mechanisms in response to chronic hemolytic anemia designed to increase oxygen delivery to tissues. They also speculated that chronic subclinical vaso-occlusion may affect the sensitivity of chemoreceptors in patients with SCD-SS analogous to the effects of chronic intermittent hypoxia seen in animal models and in patients with sleep apnea.

In a pilot study of 19 children with SCD-SS ages 5-9 years, Pearson et al. (2005) found that children with higher RSA reactivity (parasympathetic withdrawal during challenge conditions compared to rest) had significantly more sickle-cell-related clinical complications than children with less RSA reactivity. Children with higher PEP reactivity (sympathetic

activation during challenge compared to rest) showed more externalizing behavior symptoms than children with less PEP reactivity.

The studies of ANS responses in adults with SCD offer some improvements in methodology with the inclusion of comparison groups. Inconsistencies and discrepancies among studies of ANS responses are beginning to be addressed with attention to the nature of the challenges and of the responses, allowing for greater specificity in describing parasympathetic and sympathetic activity (El-Sheikh et al., 2009; Obradovic et al., 2010). Constricting age ranges within studies improves internal validity and takes developmental issues and varying environmental stressors into consideration.

Some studies have shown the importance of environment, including income and neighborhood stressors, in the experience of pain intensity and functional disability for children with SCD (Hoff, Palermo, Schluchter, Zebracki, & Drotar, 2006; Palermo, Riley, & Mitchell, 2008). In keeping with the biological sensitivity to the context model, the child's diagnosis of SCD, accompanied by unexpected painful episodes, repeated medical procedures, and life-threatening complications might be expected to heighten autonomic responses to perceived threat within their environment (Kell, Kliever, Erickson, & Ohene-Frempong, 1998). Therefore, they might have an increased reactivity to environmental challenges compared with a sample of children without SCD, particularly if the sample of children with SCD were experiencing moderate, chronic stress.

Of particular interest when considering autonomic responses in children with SCD is the emerging literature on sympathetic responses in relation to the experience of pain and the development of chronic pain syndromes (Chapman, Tuckett, & Song, 2008). Sympathetic responses in acute pain lead to vasoconstriction, which could enhance the effects of vasooclusion in SCD. Chapman et al. (2008) argued that a simple neural model of pain has failed to guide effective clinical practice in the treatment of chronic pain. They advance a psychophysiological systems view of pain integrating ANS, endocrine, and immune processes into a *supersystem*. Dysregulation of the supersystem is postulated as occurring, at times, in response to social stressors. This vulnerability to dysregulation is variable and the most comprehensive understanding of the interplay between social context and children's adaptation requires consideration of children's sensitivity to context at the psychological, behavioral, physiological, and genetic levels (Obradovic & Boyce, 2009). In the development of conceptual models that can form the basis of clinical interventions for children with SCD, the focus in this presentation is on one aspect of the supersystem: ANS responsiveness.

Also, a categorical, rather than a noncategorical approach, was selected in studying the selected chronic disease population (SCD) who have a wide range of clinical outcomes, but that have the same underlying pathophysiology that may be particularly vulnerable to the effects of ANS responsiveness. Improving the understanding of one component of the stress response system in SCD, and how it relates to clinical outcomes, may inform future study of the underlying mechanisms of the stress-illness relation for other chronic conditions. Other researchers have suggested that, while noncategorical perspectives are important in the study of chronic conditions, so that general effects are not attributed to individual disease states, illness-specific issues do arise, supporting the need for both approaches (e.g., Gannoni & Shute, 2010; Hoff et al., 2006; Newacheck & Halfon, 1998; Turkel & Pao, 2007).

By understanding how children with SCD respond to environmental stress, and how that response is similar or different compared with healthy children, the advanced practice nurse can assist families to support those children who are most vulnerable to the effects of adverse experiences. More refined interventions can be developed as the nurse determines

whether the need for regulation of biological processes predominates or psychological interventions to improve self-regulation should be the focus of intervention. The advanced practice nurse is a consistent figure in the life of a child with SCD or another chronic condition (Wagner et al., 2001). In this role, the advanced practice nurse can provide education and support to families of children identified with particular vulnerabilities to the effects of stress.

Findings are reported in this presentation from two studies assessing ANS responses to challenge; for Study 1, among physically healthy children, and for Study 2, among children with SCD. Both groups of children were from the same geographic region. The middle childhood period was the focus of study given the importance of identifying emerging problems early in life in order to develop interventions to reduce the prevalence of later psychopathology. The two studies together were focused on the research question: Does ANS reactivity differ for children with SCD compared with a community sample of children without SCD?

Method

Study 1 - Community Sample

The study design was cross-sectional, using a convenience sample.

Sample—Thirty-two children ages 5-7 years attending three kindergarten and three 1st grade classrooms in a public school were recruited to participate in 2000-01. Parents were notified about the study through a mailing or informational meeting sponsored by the school's parent-advocate group, and a convenience sample volunteered to participate. Exclusion criteria were cardiovascular disorders such as hypertension or congenital heart disease; handicapping or debilitating chronic conditions, such as cerebral palsy, mental retardation, blindness, or deafness; and children taking daily prescription medications. The Committee for Protection of Human Subjects of the sponsoring university approved the consent and assent forms and procedures. Informed consent was obtained from parents and assent to participate was obtained from the children.

Procedure

Reactivity protocol: The 20-minute protocol was conducted with each child during the course of a school day, in a quiet room separate from the classroom. The reactivity protocol has demonstrated validity and reliability and is designed to elicit autonomic responses to challenges across social, cognitive, sensory, and emotion domains (Alkon et al., 2003; Obradovic et al., 2010). Resting measures were obtained while a researcher read calming stories, each lasting 2 minutes, to the child before and after the other tasks. The child completed two challenge tasks lasting 2 minutes each, followed by a neutral intertask period of 2 minutes, then completed two more challenge tasks lasting 1-2 minutes each. The protocol ended with a second calming story, lasting 2 minutes, read aloud to the children.

The social challenge was a structured interview about the child's family, friends, and likes and dislikes; the cognitive challenge involved repeating number sequences of one to six digits in length; the sensory challenge, a taste identification of two drops of concentrated lemon juice placed on the tongue; and the emotion challenge consisted of a brief video clip selected to elicit mild fear.

Physiological measurements: Physiological responses were collected continuously throughout the protocol using the Biopac MP150 System (NICO100C, Biopac Systems, Inc., Goleta, California) and Mindware software (Mindware Technologies, Gahanna, Ohio) was

used to collect, filter, and score the data. Four impedance electrodes were placed in the standard tetrapolar configuration on the child's neck and chest and ECG electrodes were placed on the right clavicle and lower left rib. Any missing physiological data was due to acquisition problems such as equipment malfunction or electrode misplacement or displacement, or scoring problems such as movement during acquisition that interfered with signal quality. The RSA and PEP scores were calculated and averaged for each minute of data collection, and ANS reactivity measures were summarized as difference scores (challenge minus resting condition). Negative RSA reactivity indicates more parasympathetic withdrawal during the challenge compared to the rest condition. Negative PEP reactivity indicates more sympathetic activation during challenge compared to the rest condition.

Demographic information: Parents completed a demographic questionnaire, providing information about family size and structure; race and ethnicity; and parent education, income, and marital status.

Study 2 - Children with SCD

This was a cohort study design, using purposive sampling, where the population, location and individuals eligible for enrollment were selected.

Sample—Thirty-three families with children 5-8 years old with any form of SCD seen at a regional comprehensive sickle cell center were recruited to enroll in a larger cohort study of stress reactivity in SCD by mail or in person in 2006 - 08. A purposive sampling design was used, where the population, location, and individuals eligible for enrollment were selected. Inclusion criteria included children in the target age group with any diagnosis of SCD seen at the sickle cell center. Exclusion criteria included a condition that prevented the child from being engaged fully in the protocol (e.g., autism, blindness, or severe developmental disability). The institutional review board of the sponsoring hospital approved the study procedures. Informed consent was obtained from parents or guardians and assent to participate was obtained from the children.

Procedure

Reactivity protocol—The children completed the stress reactivity protocol in a quiet room at the clinic on the day of a routine medical appointment or at another convenient time. The protocol was completed before any potentially stressful medical procedure such as a blood draw, immunization, or transfusion that might change the child's state of physiological arousal. The protocol was similar to the one conducted with the community children with the exact challenge tasks in the social, cognitive, sensory, and emotion domains. Neutral intertask periods were paired with each challenge task. As with the community children, the ANS indices RSA and PEP were obtained.

Demographic and clinical information—Parents provided information about family size and structure; race and ethnicity; and parent education, income, and marital status. Medical records were reviewed for complications associated with disease severity. Children were scored as having severe disease or not, based on modified criteria from Miller et al. (2000). Children were rated with severe disease if they experienced one of three adverse events: stroke or stroke risk (identified with abnormal Transcranial Doppler values); frequent pain—at least two pain events per year for 2 consecutive years; recurrent acute chest syndrome—at least one episode of acute chest syndrome per year for 2 consecutive years. Notation was made of therapies such as chronic transfusions and hydroxyurea.

Data Analysis

Data were analyzed using Stata 9.2 with statistical significance level set *a priori* at $p < .05$. Descriptive statistics were computed for each demographic and outcome variable for the community and SCD groups separately. Difference scores for RSA and PEP were calculated for each domain (social, cognitive, sensory, emotion). Overall difference scores were calculated as the mean of the challenge-specific means minus the first resting condition. For continuous variables, mean differences between the community sample and the children with SCD were examined using Student's *t* tests, with Satterthwaite's correction applied when the assumption of equal variances was not met. Analysis of covariance models controlled for differences in child age and parent education. For categorical variables, differences between the two samples were examined using chi-square or Fisher's Exact tests. Patterns in physiological responses across domains were examined using analysis of covariance models (controlling for child age and parent education) with repeated measures. Greenhouse-Geiser corrections for degrees of freedom were employed to adjust for sphericity violations.

Results

Sample Characteristics

Over half of both samples of children were girls (Table 1). Both groups had a mean of four people in the home and similar percentages of primary caregivers (2/3 of whom were mothers) working outside of the home and married or living with a partner. The two groups were not statistically different with regard to annual household income. The children with SCD were significantly, and on average, 1 year older (7.1 years, $SD = 1.1$) than the community sample of children (6.2 years, $SD = 0.6$). The samples were significantly different on parent education with the majority of the parents of children with SCD with some college or a college degree while the parents of the community children had similar numbers of parents in each category of high school or less, some college and advanced degree. Since child age and parent education differed by sample, these variables were controlled for in subsequent analyses. As expected given the nature of the two study samples, there were significant differences between the groups' race or ethnicity. Consistent with the population primarily affected with SCD in the US, 85% of the children with SCD were African American or Black race and 9% were Hispanic or Latino ethnicity. In contrast, 19% of the community children were African American or Black and 50% were Hispanic or Latino.

For the children with SCD, diagnoses included 18 SCD-SS, 9 SCD-SC, 3 SCD-S β^+ Thalassemia and 3 SCD-S β^0 Thalassemia. Fourteen children (42%) were classified with severe disease--five of these (36%) had recurrent pain; two (14%) had recurrent acute chest syndrome; and 8 (57%) had had a mild stroke or were identified as at risk for stroke. Three children with severe disease (21%) were on hydroxyurea for the prevention of sickle-cell-related complications, while 6 (43%) were on chronic transfusion therapy for primary or secondary prevention of stroke. Nineteen children (58%) were classified as not having severe disease.

Autonomic Nervous System Responses

Descriptives and task means by group—Table 2 shows the RSA responses by domain for the children with SCD and the community sample. The community sample had significantly lower mean RSA scores, indicating greater parasympathetic withdrawal and thus higher ANS reactivity, in the social ($F(3, 59) = 5.56, p < .05$) and sensory domains ($F(3, 56) = 6.31, p < .05$) compared with the children with SCD, adjusted for child age and

parent education. The children with SCD and the community children did not differ in mean PEP scores in any domain or their domain responses overall (Table 3).

There were significant differences in RSA responses for the community children across the protocol ($F(6, 186) = 25.61, p < .05$), but not for the children with SCD (Figure 1). There were significant differences in PEP responses across the protocol for the community children and not the children with SCD. Specifically, there was a significant difference between responses to the social challenge compared to rest ($F(6, 174) = 3.04, p < .05$).

Group comparisons—The community sample had negative RSA difference scores, indicating parasympathetic withdrawal, and thus parasympathetic engagement to the challenges, in all but the emotion domain (Table 4). The children with SCD, in contrast, had positive difference scores in all domains, indicating that they exhibited parasympathetic activation in response to the challenges. There were significant RSA group differences for the social ($F(3, 59) = 7.57, p < .05$) and sensory ($F(3, 56) = 4.44, p < .05$) domains.

Both the children with SCD and the community children had positive PEP difference scores in every domain, indicating low sympathetic reactivity (Table 4). However, they showed a wide range of individual variability, with scores ranging from -12.28 to 9.35. The children with SCD obtained lower difference scores, compared with the community children in the cognitive domain ($F(3, 51) = 4.09, p < .05$), reflecting greater sympathetic activation and thus greater reactivity to the challenge task.

Distribution of individual responses— Percentages of children in each group who showed ANS reactivity, reflected in negative RSA and PEP difference scores, are shown in Table 5. There were significantly more community children with negative RSA challenge-specific difference scores in the social (chi-square [1 *df*] = 5.23, $p < .05$), and sensory domains (chi-square [1 *df*] = 6.13, $p < .05$) compared with the percentage of children with SCD showing negative RSA difference scores in these domains. More children with SCD showed negative PEP difference scores in the social domain, corresponding with sympathetic activation or high PEP reactivity, compared with the community children (chi-square [1 *df*] = 7.63, $p < .05$).

Post Hoc Analyses

To further explore the ANS responses within the sample of children with SCD, *post hoc* analyses were conducted to compare children with SCD with severe disease ($n = 14, 42\%$) with children without severe disease ($n = 19, 58\%$). There were no significant differences based on disease severity or complications.

Discussion

Children with SCD displayed a different pattern of ANS responses to laboratory challenges in some domains compared with children without SCD from the same community. The children without SCD consistently showed RSA changes across the protocol and RSA reactivity, reflecting parasympathetic withdrawal in response to the challenges, compared to the children with SCD. In contrast, PEP reactivity, reflecting sympathetic activation, was more prevalent for the children with SCD compared to the healthy children. These findings for RSA and PEP for the community children are comparable to other reactivity studies with healthy, similarly aged children (Alkon et al., 2003; Beauchaine, 2001; Salomon, Matthews, & Allen, 2000). At the same time, the range of individual differences in ANS responses for the children with SCD was comparable to these other reactivity studies. Thus, the reactivity protocol was a valid assessment of resting and challenging conditions for the children with SCD.

The findings provide some suggestion that the children with SCD exhibited a dampening of parasympathetic responses, particularly to social and sensory challenges, compared with community children without chronic physical conditions. It is possible that the diagnosis of SCD, accompanied by the stress of repeated pain experiences and medical procedures, may be associated with a dampening rather than heightening of parasympathetic responses and reactivity. Further study is needed to confirm these results with a larger sample and to investigate the implications of low parasympathetic reactivity over time for children with SCD.

The lack of responsivity from both groups of children to the emotion-provoking videos is consistent with previous findings that sustained attention requiring minimal physical or psychological effort--such as associated with viewing videos--can be calming, despite the content of the videos (Beauchaine, 2001). The findings contrast with the results of a study where adults with SCD showed a decrease in parasympathetic indices (and thus greater reactivity) when they were exposed to transient hypoxia, compared with healthy adults (Sangkatumvong et al., 2008). These researchers' use of a purely physical challenge makes these findings difficult to generalize to the current study that utilized varied, mild challenges. The different challenge domains used in the current protocol may differentiate the ANS response to specific outcomes. Further study is needed to determine if children with SCD who exhibit ANS reactivity to the social domain, for example, have more mental health problems compared to children reactive to the physical challenges.

While as a group, the children with SCD did not differ in mean parasympathetic responses from the community children in the cognitive domain or overall, over 40% of children with SCD in fact demonstrated RSA reactivity in these domains. Where group means for PEP reactivity for both samples were positive, suggesting less sympathetic reactivity, 32-50% of the children with SCD showed negative difference scores (stress reactivity) in the domains. Generally, it can be difficult to detect sympathetic responding given that often more extreme challenge conditions are required to elicit a response (Alkon et al., 2003). The findings might reflect a coupling of sympathetic dysregulation with the ongoing experience of pain in SCD (Chapman et al., 2008). Greater reactivity in the cognitive domain for the children with SCD is also consistent with the increased prevalence of a range of brain-related morbidities (Adams, Ohene-Frempong, & Wang, 2001) for the population. The results highlight the importance of examining individual differences as well as group means in ANS reactivity research, and of including measures of both the parasympathetic and sympathetic branches of the ANS.

Children vary in the degree they are affected by experiences or qualities of the environment they are exposed to, given that reactivity and regulation are governed by context, behavior, and biology (McEwen & Gianaros, 2010). It is critical to understand which children are most vulnerable due to their biological, temperamental, or behavior characteristics. Interventions can change reactivity at each of these levels. Future studies of ANS responses to challenge conditions may provide novel and important sources of information about individuals' biological sensitivity to their environment and guide nursing interventions that target these vulnerabilities.

Limitations

While new results were found in the field of ANS reactivity comparing two different samples of children, there were some threats to internal validity. Exclusion criteria for the community sample depended on parent report, so there may have been some children with chronic conditions included in the community sample. The health care record review for the children with SCD did not include identification of mental health symptoms that would be important factors potentially influencing psychobiological sensitivity of the children. The

samples were relatively small and measures of family and neighborhood stress were not included. Race or ethnicity could not be adjusted for because of confounding with group membership. Both groups of children were primarily from ethnic minority groups who encounter environmental and social stress related to experienced disparities (Paradies, 2006). However, it cannot be presumed that the stress levels for children from different minority groups are comparable. Income level was not found to differ between the two groups, and income level was not associated with measures of ANS responsivity, but there was missing data on the variable. There is no evidence that there was a systematic difference between families who reported income and those who did not.

The ANS reactivity protocols consisted of identical challenge tasks and beginning and ending rest periods. The protocols differed in the placement of neutral intertask periods, with one such period in the middle of the community protocol and four such periods following the challenge tasks in the SCD protocol. Over time, our stress reactivity protocol evolved, such that we considered it might be important to pair a neutral task with each challenge. Our lab began to use the revised protocol in 2003 (Obradovic, et al., 2010), so the children with SCD participated in this protocol. Scores for the children with SCD were calculated the same as for the community children (reactivity for each challenge task relative to resting Story 1) and by subtracting each neutral intertask period from its paired challenge task. Significant differences were not found in the scores for the children with SCD using these two methods (Obradovic et al., 2010).

In future research, examination should be included of the family and environmental context of support and stress, as well as immediate reactivity to challenge, when attempting to characterize levels of stress reactivity in samples of children. For example, if the present sample of children with SCD was experiencing moderate, chronic stress, while the community children were experiencing low stress, the results remain consistent with expectations based on the biological sensitivity to context theory. Future information on mental health and behavioral symptoms in relation to the stress reactivity protocol will also allow for inferences as to what patterns of responding are adaptive for children with SCD, whether the same or different than patterns found with physically healthy children.

Conclusions

The findings suggest that ANS reactivity may differ for children with SCD compared with a community sample of healthy children. Possibly, children with SCD may have developed a heightened sympathetic nervous system and dampened parasympathetic nervous system in response to their repeated experiences of pain and other stressors while living with SCD, compared to healthy children. The reactivity may offer a complementary approach for characterizing risk factors and vulnerabilities in the clinical expression of SCD. Nurses can help identify children at risk for difficulties with ANS regulation, within the context of challenging family environments, and can provide anticipatory guidance for parents to support their child and family's development and functioning. Further study of ANS reactivity appears warranted to determine if individuals with SCD differ in patterns of associations between ANS reactivity and health outcomes. Future studies of children with SCD and other chronic conditions are needed to identify the children at risk for poor physical and mental health outcomes.

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Figure 1. RSA and PEP Responding Across the ANS Reactivity Protocol

Respiratory sinus arrhythmia (RSA) and pre-ejection period (PEP) responding for the ANS reactivity protocol for the community children and the children with sickle cell disease (SCD). The community children showed significant changes across the protocol for RSA responding and between Resting Story 1 and the Social domain ($p < 0.05$) for PEP responding. The children with SCD did not show significant changes across the protocol for RSA or PEP responding.

Table 1

Demographics of Participants

	Study 1 Community Children without Sickle Cell Disease (<i>n</i> = 32)	Study 2 Children with Sickle Cell Disease (<i>n</i> = 33)
Child age, years [*] <i>M</i> (<i>SD</i>)	6.2 (0.6)	7.1 (1.1)
Average household size, <i>M</i> (<i>SD</i>)	4.1 (1.3)	4.4 (1.8)
Median annual household income (range)	\$35,000 - 49,999 (\$8,268 – 200,000)	\$25,000 – 39,999 (\$9,000 – 200,000)
Child gender – Female <i>n</i> (%)	21 (66)	18 (55)
Race or Ethnicity [*] <i>n</i> (%)		
Hispanic or Latino	16 (50)	3 (9)
Black or African American	6 (19)	28 (85)
White or Caucasian and Other	10 (31)	2 (6)
Primary caregiver living with a partner or married, <i>n</i> (%)	23 (72)	20 (61)
Primary caregiver employed outside of home, <i>n</i> (%)	23 (77%)	22 (67%)
Primary caregiver education, [*] <i>n</i> (%)		
High school or less	11 (35)	8 (25)
Some college or degree	9 (29)	21 (66)
Beyond college or advanced degree	11 (35)	3 (9)

Notes. Median annual household income reported by *n* = 27 parents of community children and *n* = 25 parents of children with SCD

^{*} *p* < .05, *p* values based on chi-square, Fisher's exact, or Student's *t* tests

Table 2
Parasympathetic (RSA) Resting and Challenge Responses by Domain Controlling for Child Age and Parent Education – Children with Sickle Cell Disease (SCD) and Community Sample

Domain	Study 1 Community Children (<i>n</i> = 32)			Study 2 Children with SCD (<i>n</i> = 33)		
		<i>M (SD)</i>	Range		<i>M (SD)</i>	Range
Rest	Story 1	6.29 (1.18)	3.72-8.27		6.70 (1.42)	3.82-9.89
Social *	Social interview	5.76 (1.07)	3.27-8.03		6.80 (1.41)	4.39-9.09
Cognitive	Number sequence recall	6.08 (1.16)	3.20-8.59		6.72 (1.40)	3.81-9.20
Sensory *	Lemon juice taste	5.48 (0.89)	3.24-7.88		6.72 (1.56)	2.90-9.17
Emotion	Fear movie	6.70 (1.30)	3.16-8.93		6.85 (1.55)	3.52-9.59
Rest	Story 2	6.40 (1.35)	2.57-8.39		6.64 (1.49)	3.30-8.91
	Domains Overall	6.00 (1.02)	3.49-8.24		6.80 (1.45)	3.84-9.23

Note. Domains Overall = the mean of the social cognitive, sensory and emotion domains

* $p < .05$

Sympathetic (PEP) Resting and Challenge Responses by Domain Controlling for Child Age and Parent Education – Children with Sickle Cell Disease (SCD) and Community Sample

Table 3

Domain	Study 1 Community Children (n = 32)			Study 2 Children with SCD (n = 33)		
	M (SD)	Range		M (SD)	Range	
Rest	80.00	65.00-101.00	79.67	51.15-97.48		
Social	81.60	64.00-102.00	80.04	50.85-98.30		
Cognitive	81.80	63.00-101.00	80.25	54.15-97.20		
Sensory	81.67	66.00-100.00	80.58	53.50-96.10		
Emotion	81.53	64.00-102.00	80.83	53.60-97.48		
Rest	80.97	63.00-101.00	80.88	54.05-97.20		
Domains Overall	81.65	65.00-101.25	80.70	53.02-97.27		

Notes: Domains Overall = the mean of the social cognitive, sensory and emotion domains

* p < .05

Table 4

RSA and PEP Difference Scores (Challenge Task Minus Rest) – Community Children and Children with Sickle Cell Disease (SCD)

	Study 1 Community Children (N = 32) Difference Scores		Study 2 Children with SCD (N = 33) Difference Scores	
RSA – Domain	<i>M(SD)</i>	Range	<i>M(SD)</i>	Range
Social [*]	-0.52 (0.73)	-2.13-1.1	0.21 (0.83)	-2.10-1.63
Cognitive	-0.20 (0.67)	-1.87-1.22	0.13 (0.65)	-0.95-1.52
Sensory [*]	-0.81 (1.08)	-3.65-1.32	0.07 (0.95)	-1.73-2.41
Emotion - Fear	0.41 (0.75)	-2.03-1.77	0.25 (0.47)	-0.48-1.18
Overall RSA Difference Scores	-0.28 (0.69)	-2.42-1.07	0.18 (0.63)	-1.00-1.58
PEP – Domain				
Social	1.60 (3.28)	-8.00-9.00	0.15 (3.96)	-12.28-9.35
Cognitive [*]	1.80 (3.30)	-6.00-8.00	.018 (2.69)	-6.88-8.53
Sensory	1.67 (3.20)	-4.00-9.00	0.44 (3.59)	-11.28-7.70
Emotion – Fear	1.53 z93.39)	-6.00-9.00	0.19 (3.50)	-9.63-4.40
Overall PEP Difference Scores	1.65 (2.88)	-6.00-7.00	0.24 (3.09)	-10.02-6.26

Note. Difference scores calculated as challenge task minus rest (Story 1) for each domain. Overall difference scores = mean of social, cognitive, sensory and emotion domains minus rest (Story 1).

*
 $p < 0.05$

Table 5

Distribution of Children Showing ANS Reactivity to Challenges by ANS Difference Scores – Community Children and Children with Sickle Cell Disease (SCD)

	Study 1 % of Community Children (<i>n</i> = 32)	Study 2 % of Children with SCD (<i>n</i> = 33)
Domain - RSA		
Social *	84	39
Cognitive	66	42
Sensory *	78	47
Emotion	22	37
Overall	59	45
Domain - PEP		
Social *	20	50
Cognitive	20	37
Sensory	27	32
Emotion	27	44
Overall	27	38

Notes. Overall difference scores = mean of social, cognitive, sensory and emotion domains minus rest (Story 1).

* $p < .05$, Values based on chi-square analyses