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Neurobehavioral impact of sickle cell disease in early childhood

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Abstract

The physical effects of sickle cell disease (SCD) begin in infancy or early childhood, yet most behavioral studies have focused on school-age children. We evaluated the impact of higher *versus* lower neurologic risk on language, motor abilities, executive functions, and temperament in toddlers and early preschoolers with SCD. Thirty-nine children with higher risk SCD were compared to 22 children with lower risk SCD. Language and motor abilities were lower in older compared with younger children but were unrelated to sickle cell subgroups. Executive functions, particularly working memory, were poorer in children with higher risk SCD regardless of age. Parent-reported activity level was also lower in children with higher risk. Specific behavioral influences of SCD are evident early in childhood and include working memory decrements. Executive function deficits in SCD can emerge early in life and may be an important context for other areas of cognitive and behavioral development. (*JINS*, 2007, *13*, 933–943.)

Keywords: Child development, Chronic disease, Language development, Memory, Short-term, Neurologic manifestations, Temperament

INTRODUCTION

Sickle cell disease (SCD) is a genetic condition that results from inheriting genes for S-type hemoglobin. The homozygous HbSS type (sickle cell anemia) comprises approximately two-thirds of the population with sickle cell disease (Steinberg, 1984). Other major forms of SCD include S-type with C-type hemoglobin (HbSC), HbS-Beta-plus thalassemia (HbSβ^+), and HbS-Beta-zero thalassemia (HbSβ^0). Sickle cell genotypes differ in the degree of risk for neurologic disease and other morbidity. For example, the risk of childhood stroke is ~5% in children with HbSS, whereas with HbSC or HbSβ^+ the risk is ~1% (Ohene-Frempong et al., 1998). Silent cerebral infarction (i.e., cerebral infarction on neuroimaging without history of overt stroke) occurs in ~21% of children with HbSS or HbSβ^0, whereas less severe variants such as HbSC show a 6% to 8% prevalence rate (Pegelow et al., 2002; Wang et al., 2001). Cerebral infarction can occur at or before seven months of age (Wang et al., 1998). Approximately half of cases with silent cerebral infarction acquire the injury by age six years (Moser et al., 1996; Wang et al., 1998).

There are other physiological factors that may be important for child development in SCD other than stroke or silent cerebral infarction. In more severe subtypes hemolytic anemia is usually a persistent feature after the first months of life and creates lower blood oxygenation in the brain (Nahavandi et al., 2004). Sleep disordered breathing is more common in HbSS and may result in neurocognitive effects (Brooks et al., 1996; Hill et al., 2006; Kirkham et al., 2001a; Robertson et al., 1988; Wali et al., 2000). Increased metabolic needs and immune system compromise can lead to nutrition and antioxidant deficits that may impact brain health (Amer et al., 2006; Faraci, 2005; Sindel et al., 1990; Wood et al., 2005). Finally, autonomic reactivity differences have been described in school-age children. Children with SCD and a history of more severe complications also have greater autonomic nervous system reactivity to physical or mental stress than children with low morbidity (Pearson et al., 2005).

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Our current understanding of the early behavioral effects of SCD is limited. Data on behavioral outcomes has largely focused on school-age children and aggregated a wide age range into a single group. This literature indicates various effects related to the disease, including elevated rates of neurocognitive deficits (Armstrong et al., 1996; Schatz et al., 2002), academic or learning difficulties (Armstrong et al., 1996; Schatz et al., 2001, Schatz, 2004a), externalizing behavior disorders (Thompson et al., 2003) and depressive symptoms (Key et al., 2001). Specific cognitive deficits documented in middle childhood include sustained and selective attention, processing speed, working memory, and verbal ability (Bernaudin et al., 2000; Brandling-Bennett et al., 2003; Brown et al., 1993; Noll et al., 2001; Schatz et al., 2002, 2004b; Steen et al., 2005). There have been a few attempts to characterize the early development of children with SCD to better understand the pathways toward or away from these negative outcomes. An early cross-sectional study by Wang et al. (1993) reported on 344 children with SCD birth through 6 years of age. The rate of positive developmental screening increased after three years of age on the Denver Developmental Screening Test. Sickle cell genotype was unrelated to the likelihood of positive screenings. The low sensitivity of the original version of the Denver screening tool, however, limits the conclusions that can be drawn from this study (Greer et al., 1989; Meisels, 1989).

Thompson et al. (2002) conducted a longitudinal study of neurocognitive functioning in 89 children at 6 months ($n = 66$), 1 year ($n = 68$), 2 years ($n = 42$), and 3 years ($n = 26$) of age to examine relationships between disease severity and parent risk factors using the Bayley Scales of Infant Development (Bayley, 1993). There was a decline in Mental Development Index scores, but not Psychomotor Development Index scores, between one and two years of age compared with test norms. More severe disease subtypes were associated with poorer Mental Development Index scores at two years of age. No relationship was found between disease severity and cognitive development at six months or one year of age.

A recent study examining 14 infants with SCA and 14 demographic controls reported the number of SCA infants with moderate-high risk scores on the Bayley Infant Neurodevelopmental Screener (BINS; Aylward, 1995) increased between 3 and 9 months of age compared to controls (Hogan et al., 2006). Scores on the BINS also correlated with several physical markers of disease severity, such as hematocrit, by age 9 months. These data suggest an earlier onset of disease-related developmental effects than prior reports. A factor that could help account for a difference between the report by Hogan and that by Thompson is the use of domain-specific assessment measures with the BINS as opposed to the Mental Development Index. In older children disease-related cognitive effects are two to three times larger for measures of specific cognitive abilities than for general intelligence (Schatz et al., 2002).

The purpose of the present study was to characterize domain-specific behavioral patterns in early childhood associated with higher neurologic risk. Language skills, motor skills, executive skills, and temperament characteristics were examined at two cross-sectional ages (12–18 months, 32–40 months) and compared between children with higher risk (HbSS, HbSβ^0) *versus* those with less lower risk (HbSC, HbSβ^+) SCD. The two age ranges were selected because they correspond to period before and after the onset of disease-related cognitive deficits by Thompson et al. (2002). The lower risk SCD group provides a comparison group with a lower degree of neurodevelopmental risk, but similar ethnicity, socioeconomic features, and general health concerns. Characteristics of the child's primary caregiver and family context were assessed to consider the conjoint influence of biomedical and social risk factors on child outcomes. It was predicted that the higher risk SCD group (because of higher neurologic risk) and older age (due to progressive disease-related effects) would each be related to poorer developmental status for language and executive skills. We did not expect differences across SCD groups for motor skills due to the lack of differences found by Thompson et al. (2002) for psychomotor development.

Unlike neurocognitive functioning temperament characteristics have not been described in SCD. The report of increased autonomic nervous system reactivity to stress in children with sickle cell disease may have implications for temperament patterns (Blair et al., 2004; Calkins, 1997; Gunnar et al., 1995). We assessed temperament patterns based on the review of factor analytic studies by Sanson & Rothbart (1995). These authors indicated most temperament constructs could be linked to five major constructs, which they labeled: fear, irritability-anger, positive affect, activity level, and attention-persistence.

More recent work by Rothbart has described a temperament construct labeled effortful control that has been linked to attention regulation (Derryberry & Rothbart, 1997; Rothbart et al., 2003). Specifically, parent reports of emotional and behavioral regulation abilities in young children (termed effortful control) correlate with the child's ability to inhibit behavior on cognitively demanding selective attention tasks (Rothbart et al., 2003). Posner and Rothbart (1998) have proposed that effortful control is one manifestation of an integrated system that regulates intentionally sustaining and reallocating attention. In both infancy and early childhood a specific temperament feature termed low intensity pleasure has been the specific temperament feature most strongly related to effortful control (Gartstein & Rothbart, 2003; Rothbart et al., 2001). Low intensity pleasure refers to the young child's ability to enjoy activities that involve less intense stimulation from the environment. Reduced ability to enjoy activities under these environmental conditions presumably reflects poorer regulation of arousal and endogenous attention. Given prior reports of attention and executive function deficits in SCD we included a measure of low intensity pleasure as a potential behavioral marker of early executive function problems.

METHOD

Participants and Recruitment

Informed consent for research participation was obtained from a parent as approved by the Institutional Review Board. The 61 participants with SCD disease and a parent who was a primary caregiver were recruited at routine health maintenance visits at either the South Carolina Department of Health and Environmental Control Children's Rehabilitative Services Sickle Cell Clinics or the Center for Children's Cancer and Blood Disorders at Palmetto Health Richland. The participants were 61 of the first 64 children seen at the clinics for routine health maintenance visits. Fifty-seven of the primary caregivers were the mother of the child, one primary caregiver was the father, and three primary caregivers were female legal guardians other than the mother. Feedback regarding the child's developmental status and children's books were provided to participants.

Thirty-seven participants had HbSS, 12 had HbSC, 10 had HbSβ^+, and 2 had HbSβ^0. Both children with HbSβ^0 had hematocrit values from routine blood work consistently below 27%. These two cases were included with the HbSS group given their persistent anemia and the higher risk for neurologic complications in HbSβ^0. All participants were of African-American ethnicity according to medical records. Exclusionary criteria were a history of overt stroke or a major medical or psychiatric disorder unrelated to SCD. These criteria did not result in any participants being excluded. Neuroimaging exams were not available due to the young age of the participants and the need for sedation to obtain such exams at our institution. Descriptive data for the sample are provided in Table 1.

Procedures

The study procedures occurred in a single session and involved, in sequential order: behavioral testing of the child, a structured interview with a primary caregiver, parent questionnaires, and medical record review. Behavioral testing and interviews were completed by graduate-level psychometricians. Parent questionnaires were completed on a computer with written and auditory presentation of items to reduce literacy demands.

Descriptive Variables

The family's annual household income and family structure of the household was collected *via* questionnaires. The parent interview was used to determine pre- and perinatal birth history and neurologic history. Medical record review was also used to assess for neurologic history and other major medical conditions. Hematocrit data were collected from medical records for the closest routine blood lab to the date of testing, which was within one month of participation in all cases.

Cognitive and Motor Skills

Denver-II (Frankenburger et al., 1996)

The Language and Fine Motor scales of the Denver-II were completed as part of the child behavioral testing. We followed the testing the limits procedure as described in the test manual to obtain basal and ceiling levels. This allows for the computation of continuous scores rather than using the traditional screening criteria for the Denver-II, which are not domain-specific and have questionable validity (Glas-

Table 1. Descriptive data for the study sample

	12–18-month-olds		32–40-month-olds	
Variable	HbSS/HbSβ^0 $n = 20$	HbSC/HbSβ^+ $n = 9$	HbSS/HbSβ^0 $n = 19$	HbSC/HbSβ^+ $n = 13$
Age in months				
Mean (s.d.)	14.8_a (2.6)	15.9_a (2.1)	37.3_b (3.4)	36.1_b (2.5)
Gender (female : male)	11 : 9	4 : 5	7 : 12	5 : 8
Household income (n)				
$ 0–10,000	11	4	8	7
$10–20,000	4	3	4	0
$20–30,000	4	1	4	5
$30–40,000	1	0	2	0
>$40,000	0	1	1	1
Single-adult households (n)	6	2	6	4
Preterm birth (n)	5	0	3	4
Hospitalized in past year (n)	12	3	10	7
Hematocrit, Mean (s.d.)	26.2_a (4.6)	31.5_b (3.7)	25.4_a (3.9)	31.0_b (2.8)

Note. Values that do not share a subscript are significantly different based on t-tests ($p < .05$). Categorical values did not differ according to group based on χ^2 tests.

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coe et al., 1992). We have demonstrated convergent validity for computing age equivalencies and developmental quotients for the Language and Fine Motor scales of the Denver-II using this administration method (Schatz et al., in press). These Denver-II scales predict individual differences in language and fine motor skills independent of chronological age and generate comparable age-adjusted scores as the Vineland Adaptive Behavior Scales-survey form (Sparrow et al., 1984).

Vineland Adaptive Behavior Scales-survey form

The Communication domain and Motor domain of the VABS were administered as part of the parent interview according to the standard procedures in the test manual.

Expressive Vocabulary, MacArthur Communicative Development Inventory, short-form (CDI, Fenson et al., 2000; Dale et al., 2001)

The CDI is a parent-report questionnaire for language skills. The Level I version or the Level III version was used depending on the child's age. Percentile scores from age- and gender-based normative data were converted to standard scores using tables from the VABS manual to maintain a consistent metric across measures.

Delayed Response

Delayed Response is used in young children and nonhuman animals to assess working memory (Diamond, 1988; Diamond & Goldman-Rakic, 1989). Our materials and procedures were modeled after Espy et al. (1999a). A board with two wells is presented to the child. A sticker reward is shown to the child, placed in one of the two wells while the child watches, and the wells are covered with two identical covers. The board is then hidden under the table while the experimenter counts out loud for 10 seconds (5 seconds was used for 12–18 month-olds per Espy et al., 1999b). After revealing the board again, the child is verbally encouraged to find the sticker. The first well that the child reaches for is the behavioral response. After two consecutive correct responses the side is switched to the alternate well. Variables recorded were the number of correct responses and the number of perseverative errors (Espy et al., 1999a). Ten trials are administered.

Child Temperament Ratings

Parent questionnaires with Likert scale responses were used for all temperament ratings. The Emotionality-Activity-Sociability (EAS) Temperament Survey for Children: Parent Ratings assesses four constructs: emotionality, activity, sociability, and shyness as an elaboration of the original EAS temperament model (Buss & Plomin, 1984; Mathiesen & Tambs, 1999). These scales correspond to the constructs summarized by Sanson & Rothbart (1995) of in irritability-anger, activity level, positive affect, and fear, respectively (Mathiesen & Tambs, 1999). To assess the attention-perseverance factor we included the Attention Span-perseverance scale from the Colorado Childhood Temperament Scale (Rowe & Plomin, 1977). Finally, we constructed a scale to assess low intensity pleasure. Item content assessed the child's degree of enjoyment for activities such as being read to, hearing the sound of words, engaging in gentle rhythmic activities (e.g., rocking), and playing quietly with toys (Gartstein & Rothbart, 2003; Rothbart et al., 2001). Chronbach's alpha for these measures in the current sample was .72, .63, .60, .68, .63, and .71 for emotionality, activity, sociability, shyness, attention span-perseverance, and low intensity pleasure, respectively.

Caregiver Stress

Caregiver stress was measured with Cohen's Perceived Stress Scale (PSS; Cohen & Williamson 1987). This questionnaire assesses subjective stress over the past month. The measure correlates with the extent of psychological distress, physical symptoms of stress, and elevated stress in the absence of psychopathology symptoms (Cohen et al., 1983, Cohen, 1986, Cohen & Williamson, 1987). Chronbach's alpha for the current sample was .89.

Home Environment and Parenting Behavior

Home Screening Questionnaire-modified (HSQ-m; Coons et al., 1981)

The HSQ is a parent report questionnaire designed to predict scores on the Home Observation for Measurement of the Environment (HOME; Caldwell & Bradley, 1979). We adapted this measure into a structured parent interview to reduce literacy demands and simplify the response format for several complex items on the original scale. We used a 9-item version (items 5, 6, 9, 11, 15, 17, 20, 23, 31) that has shown internal consistency of .7 or higher. The nine items largely relate to the presence of developmentally stimulating materials in the home and parent support of a stimulating environment (e.g., the presence of books and developmentally appropriate toys, frequency of reading to the child, the range of play activities allowed by the parent). Chronbach's alpha for the current sample was .80.

Parenting Scale

This scale contained 12 items from two sources. Seven items were used from the Warmth/Involvement subscale of the Parent Practices Scale (McMahon et al., 1996; Strayhorn & Weidman, 1988). These items assessed the frequency of positive parenting behaviors between the caregiver and the child (e.g., plays one-on-one with child, praises child). In addition, the 5-item version of the Parenting Self-Agency Measure was administered to assess parenting self-efficacy

(Dumka et al., 1996). Chronbach's alpha for the Parenting Scale in the current sample was .74.

Statistical Methods

Descriptive Analyses

Univariate relationships among neurodevelopmental outcome measures and social environmental variables were evaluated via a correlation matrix to determine the most useful social environmental measures to include as covariates (see Table 2). Potential differences across the study groups in caregiver stress, parenting behavior, and family environment were also examined with analysis of variance (ANOVA) using Age Group (12–18 months, 32–40 months) and SCD Group (HbSS/HbSβ^0, HbSC/HbSβ^+) as independent variables. Results of these analyses failed to reveal effects of either factor or their interaction.

Primary Analyses

Analyses of cognitive and motor abilities were conducted at two levels of analysis: the domain level and the individual variable level. Each domain examined (language, motor, executive functions) had more than one indicator variable. These variables differ somewhat in content coverage within each domain as well as the source of the data (i.e., examiner observed child behavior *versus* parent report). Differences across the SCD subtype groups and/or age groups at the domain level would reflect patterns that are relatively consistent across narrower abilities within the domain as well as the methods of data collection. Differences across SCD subtype groups and age groups at the individual variable level can indicate which variables make the largest contribution to domain level effects and provide information about narrower abilities, but are also more prone to potential biases or error due to the specific source of the data.

Domain level analyses were conducted with three Multivariate Analysis of Covariance (MANCOVA) procedures. Age Group and SCD Group were the independent variables. Pillai's trace was used to compute the multivariate *F* statistic. Covariates for the MANCOVA's were chosen based on variables that showed a relationship with any of the study dependent variables based on the descriptive analyses detailed above, namely, the PSS, HSQ-m, and the Parenting Scale. The covariation helps increase the total explained variance in the analyses, which typically improves the statistical power. The covariation also allows a stronger inference about the specificity of the relationship between the outcome measures and the independent variables.

The first MANCOVA for language ability used Denver-II Language, VABS Communication, and CDI Vocabulary as the dependent variables. The second MANCOVA for motor ability used Denver-II Fine Motor and VABS Motor as the dependent variables. The third MANCOVA for executive functions used the number of correct responses on the delayed response task, the number of perseverative errors on the delayed response task, and parent ratings of low intensity pleasure as the dependent variables. The number of perseverative errors was transformed to 10 minus the number of perseverative errors so that higher scores indicated better executive functions on all three variables. An alpha level of .05 was used for statistical significance in these analyses, which were the focus of the primary study hypotheses.

Analyses at the individual variable level were conducted with Analysis of Covariance (ANCOVA) procedures. Age Group and SCD Group were the independent variables. Covariates were the same as described above for MANCOVA. The first series of ANCOVA's examined each of the

Table 2. Pearson correlation values among study dependent variables and social-environmental variables

Dependent variable	Household income	Single-adult household	Perceived Stress Scale	HSQ-modified	Parenting Scale
Denver-II Language	−.11	−.07	−.05	.29*	.00
VABS Communication	−.20	.21	−.05	−.02	.07
CDI Vocabulary	.04	−.05	−.03	.26*	.14
Denver II Fine Motor	.11	−.15	.16	.07	.10
VABS Motor	−.04	.02	.00	.08	.19
Delayed Response, correct	.13	−.01	−.02	.04	−.15
Delayed Response, P.E.	−.03	.17	−.14	−.25	.13
Low Intensity Pleasure	−.01	.05	−.44**	.06	.31*
Emotionality	−.11	−.03	.36**	−.40**	−.22
Activity	−.03	−.08	−.11	.03	.20
Sociability	−.19	.12	−.23	.13	.19
Shyness	.22	−.23	.02	−.01	−.04
Attention Span-persistence	−.04	.07	−.23	.00	.21

Note. VABS = Vineland Adaptive Behavior Scales; CDI = Communicative Development Inventory; P.E. = perseverative errors; * $p < .05$; ** $p < .01$.

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individual variables from the MANCOVA procedures described above. Each of the core temperament variables was also examined with ANCOVA. An alpha level of .05 was used for statistical significance in all ANCOVA's due to the largely exploratory nature of study. Effect size estimates (eta-squared) were generated for all MANCOVA and ANCOVA procedures to consider possible Type II errors.

RESULTS

Analyses of Cognitive and Motor Domains

Study dependent variables are listed in Table 3 according to age and SCD groups. Mean scores within each domain according to SCD Group, uncorrected for covariates, are shown in Fig. 1. The MANCOVA for the language domain showed a significant effect for Age Group, $F(3,52) = 3.45$, $p < .05$, $\eta^2 = .17$. Estimated marginal mean scores indicated the younger age group showed higher age-adjusted language scores than the older age group. Among the covariates HSQ-m was significantly related to language abilities, $F(3,52) = 4.12$, $p < .05$, $\eta^2 = .19$. The MANCOVA for the motor domain also showed a main effect for Age Group, $F(2,51) = 11.10$, $p < .01$, $\eta^2 = .30$. None of the covariates were related to motor abilities. Estimated marginal mean scores indicated that the younger age group showed higher age-adjusted motor scores than the older age group. The MANCOVA for the executive functions domain showed main effects for both Age Group, $F(3,52) = 7.67$, $p < .01$, $\eta^2 = .31$, and SCD Group, $F(3,52) = 3.34$, $p < .05$, $\eta^2 = .16$. Estimated marginal means indicated that the younger age group and the lower risk HbSC/HbSβ^+ group showed better executive functions (see Fig. 1). Among the covariates the PSS was significantly related to executive functions, $F(3,52) = 4.39$, $p < .01$, $\eta^2 = .20$. Nonsignificant effects all had η^2 values of less than .05 with the exception of the Age Group × SCD Group effect for the language domain ($\eta^2 = .09$).

Analyses of Individual Variables from Domain Analyses

For individual variables we report results for all ANCOVA procedures with η^2 values greater than .05. For Denver-II Language there was a significant effect for Age Group, $F(1,54) = 7.54$, $p < .01$, $\eta^2 = .12$. Estimated marginal means showed that the younger age group had higher scores than the older age group (102.6 *vs.* 89.9). HSQ-m was also a significant covariate for Denver-II Language, $F(1,54) = 6.15$, $p < .05$, $\eta^2 = .10$. For CDI Vocabulary the Age Group × SCD Group effect was significant, $F(1,54) = 4.30$, $p < .01$, $\eta^2 = .07$. The estimated marginal means showed a cross-over type interaction pattern similar to the uncorrected mean scores (see Table 3). *T*-tests run within each SCD Group for CDI scores, however, failed to show a statistically significant difference between age groups. HSQ-m was also a significant covariate for the CDI measure, $F(1,54) = 5.06$, $p < .05$, $\eta^2 = .09$.

For VABS-Motor there was a significant effect for Age Group, $F(1,54) = 19.72$, $p < .01$, $\eta^2 = .28$. Estimated

Table 3. Mean values (standard deviation) for study dependent variables

	12–18-month-olds		32–40-month-olds	
Variable	HbSS/HbSβ^0 $n = 20$	HbSC/HbSβ^+ $n = 9$	HbSS/HbSβ^0 $n = 19$	HbSC/HbSβ^+ $n = 13$
Language skills				
Denver-II Language D.Q.	105.5_a (17.0)	99.5_a (20.2)	85.8_b (12.1)	$94.4_{a,b}$ (21.8)
VABS Communication S.S.	100.2_a (12.2)	95.0_a (9.1)	92.9_a (10.5)	96.1_a (15.3)
CDI Vocabulary S.S.	87.2_a (12.8)	79.0_a (12.4)	83.3_a (12.3)	86.9_a (15.3)
Motor skills				
Denver II Fine Motor D.Q.	98.7_a (19.0)	$86.4_{a,b}$ (13.3)	85.8_b (13.8)	83.2_b (14.0)
VABS Motor S.S.	100.0_a (5.9)	101.1_a (4.3)	88.9_b (10.7)	86.6_b (14.9)
Executive functioning				
Delayed response # correct	4.4_a (2.4)	$5.6_{a,b}$ (2.4)	6.9_b (2.1)	8.4_c (.8)
Delayed response # P.E.	2.6_a (2.3)	1.7_a (1.3)	1.7_a (1.2)	1.4_a (1.0)
Low intensity pleasure	4.2_a (0.6)	4.7_b (0.4)	$4.2_{a,b}$ (.7)	$4.4_{a,b}$ (.5)
Core Temperament Ratings				
Emotionality	3.0_a (1.0)	2.7_a (.8)	2.5_a (1.0)	3.0_a (1.3)
Activity	4.4_a (.6)	4.9_b (.2)	4.4_a (.6)	4.5_a (.5)
Sociability	3.7_a (.7)	4.0_a (.5)	3.7_a (.5)	3.6_a (.7)
Shyness	2.2_a (.8)	2.2_a (1.0)	2.4_a (.8)	2.5_a (.9)
Attention span-persistence	3.3_a (.6)	3.0_a (.7)	3.2_a (.8)	3.1_a (.9)

Note. Scores without the same subscript differ according to t-tests ($p < .05$). D.Q. = Developmental Quotient; S.S. = Standard Score; VABS = Vineland Adaptive Behavior Scales; CDI = Communicative Development Inventory; P.E. = perseverative errors.

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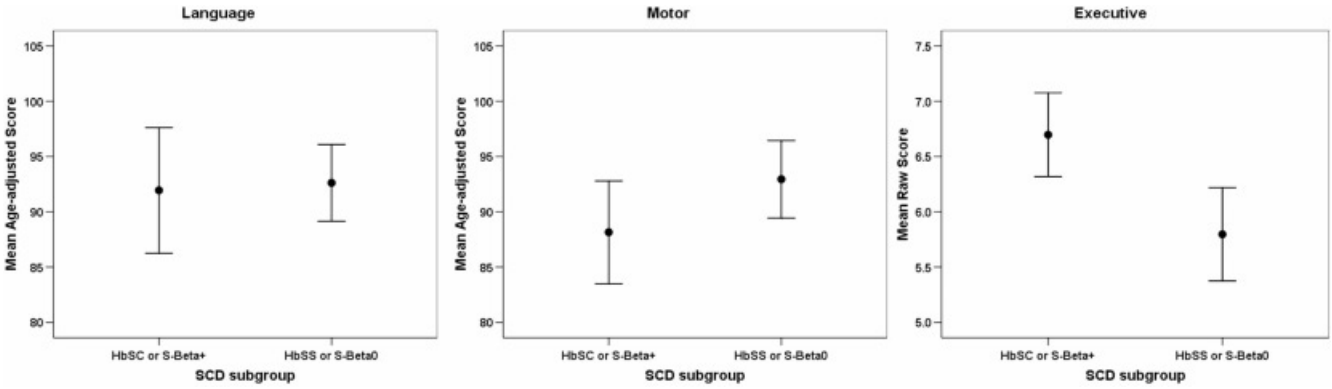

Fig. 1. Mean composite scores (95% confidence interval) for each of the three primary domains of analysis in lower risk (HbSC or HbSβ^+) and higher risk (HbSS or HbSβ^0) sickle cell groups. Composite scores were the arithmetic mean of each individual's scores for the domain (see Table 3). Perseverative errors on delayed response were transformed to ten minus the number of perseverative errors so that higher scores reflect higher ability for all component measures.

marginal means showed that the younger age group had higher scores than the older age group (100.3 *vs.* 88.0). For Denver-II Fine Motor the only notable result was a trend for the covariate Perceived Stress Scale, $F(1,54) = 5.06$, $p < .06$, $\eta^2 = .06$.

The number of correct responses on Delayed Response showed significant main effects for both Age Group, $F(1,54) = 21.89$, $p < .01$, $\eta^2 = .29$, and SCD Group, $F(1,54) = 5.69$, $p < .05$, $\eta^2 = .10$. Estimated marginal means showed that the younger age group had fewer correct responses than the older age group (5.0 *vs.* 7.6), and that the HbSS/HbSβ^0 group had fewer correct responses than the HbSC/HbSβ^+ group (5.6 *vs.* 7.0). The number of perseverative errors on Delayed Response also showed a significant main effect for Age Group, $F(1,54) = 4.54$, $p < .05$, $\eta^2 = .08$. Estimated marginal means showed that the younger age group had more perseverative errors than the older age group (2.6 *vs.* 1.5). For Low Intensity Pleasure there was a nonsignificant trend toward a difference according to SCD Group, $F(1,54) = 3.48$, $p < .07$, $\eta^2 = .06$, and the PSS was a significant covariate, $F(1,54) = 8.31$, $p < .01$, $\eta^2 = .13$. The trend was for the HbSS/HbSβ^0 group to have reduced low intensity pleasure on parent report compared to the HbSC/HbSβ^+ group.

Analyses of Core Temperament Variables

For the five core temperament variables we report results for all ANCOVA procedures with η^2 values greater than .05. The only significant independent variable in these analyses was for Activity, which showed an effect for SCD, $F(1,54) = 4.07$, $p < .05$, $\eta^2 = .07$. Estimated marginal means showed that the HbSS/HbSβ^0 group had lower parent ratings for Activity than the HbSC/HbSβ^+ group (4.4 *vs.* 4.7). There was a nonsignificant trend for Emotionality in the Age Group × SCD Group effect, $F(1,54) = 3.24$, $p < .08$, $\eta^2 = .06$, and both the HSQ-m, $F(1,54) = 7.47$, $p < .01$, $\eta^2 = .12$, and Perceived Stress Scale, $F(1,54) = 4.75$, $p < .05$, $\eta^2 = .08$, were significant covariates for Emotionality.

DISCUSSION

The present study examined domain-specific behavioral effects in SCD disease to characterize neurodevelopmental effects in early childhood. Two age points were used to examine potential progressive effects of SCD. Overall, the results of this study suggest benefits to examining a range of developmental domains in SCD during early childhood. In particular, the assessment of executive function abilities in early childhood may be important for understanding early disease-related effects. Consistent with our hypothesis, children at higher neurologic risk demonstrated poorer executive functions relative to the lower risk SCD group. This pattern was predominantly related to achieving fewer correct responses on the delayed response task, an indicator of poorer working memory. There was also a trend toward the higher risk SCD group to show reduced expression of low intensity pleasure per parent report. In early childhood reduced expression of low intensity pleasure has been associated with weaker executive control for regulating behavior and affect (a.k.a., effortful control; Rothbart et al., 2001, 2003). A more extensive evaluation of the effortful control temperament construct may have merit as a method of examining executive functions in SCD.

The finding for working memory performance is of potential interest for several reasons. First, this finding provides evidence of an early onset of specific cognitive decrements related to disease severity in SCD. Prior studies have used global measures of cognitive development or aggregated scores across specific domains (Hogan et al., 2006; Thompson et al., 2002; Wang et al., 1993). Prior findings therefore could have been the result of a generalized cognitive deficit. Second, working memory is a core cognitive function

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that can limit functioning in other areas, such as language comprehension and problem solving. Thus, a working memory deficit in early childhood could have implications for other areas of deficit that appear later in childhood. Specific deficits in early childhood could be related to early onset silent cerebral infarction or other effects of SCD. For example, localized deficits in brain function in SCD have been documented in the absence of structural injury using perfusion MRI (Kirkham et al., 2001b; Oguz et al., 2003). Additional studies will be needed to assess the causes of early cognitive deficits.

Our hypothesis of a relative increase in executive function difficulties with older age (due to progressive disease effects) was not supported in the present study. The lack of age-based norms for the executive function tasks and our difficulties in equating the delayed response task across ages weakened the test of this hypothesis. In addition to shortening the delay period for the younger children on the delayed response task, future work should incorporate the use of demographically-matched children without SCD to better understand age-related differences.

The results of this study indicated lower age-adjusted language and motor scores at 32–40 months of age compared with 12–18 months of age. These domain-level effects were largely caused by lower scores with older age on the Denver-II Language scale and the VABS Motor domain. Similar declines with increasing age as compared to test norms in sickle cell disease have been reported previously for the Bayley Mental Development Index (Thompson et al., 2002). In addition, in middle childhood a similar pattern has been reported for children with SCA and normal neuroimaging exams for the Wechsler Verbal IQ and Coding subtest (Wang et al., 2001). It is possible that these age-related effects are due mainly to the cumulative effect of social-environmental risk factors over time: prior longitudinal findings were based on test norms and did not show a relationship with neurologic risk (Wang et al., 2001). For example, children with socioeconomic disadvantage tend to show smaller gains in oral language and motor skills than less disadvantaged peers in longitudinal study (Bradley et al., 2001; Locke & Ginsborg, 2003). Consistent with this speculation, in the present study performance in the language domain was related to our measure of home environment.

Although our hypotheses about disease-related effects impacting the language domain were not supported, we do not believe the current study rules out a small to medium size impact of the disease on language development during early childhood. There was a noteworthy effect size for the interaction between age group and sickle cell group ($\eta^2 = .09$). It is possible that a disease-related effect on language development is subtle in this age range and we lacked statistical power to detect this effect. The observed pattern of data, however, may also be due to chance variations in the groups. The primary conclusion from our data regarding language development in SCD is that home environment probably accounts for more of the variability in development during early childhood than disease severity.

In general, temperament variables showed few differences with the exception of lower parent ratings for activity level in the higher risk SCD group. The finding for activity level requires replication due to the exploratory nature of these analyses. Lower activity levels in early childhood could be related to a behavioral adaptation to chronic hemolytic anemia. School age children with HbSS have higher resting metabolism than peers and partially compensate for this energy expenditure by reducing physical activity (Barden et al., 2000; Gray et al., 1992; Singhal et al., 1997, 2002).

There are several limitations to the methods used in this study that are worth considering. Several methodological factors increase the possibility of Type II errors. The sample size, though comparable to or larger than previous reports, is only large enough to detect medium to large size effects (Cohen, 1988). Also the internal consistency data for several of the temperament measures met only minimally adequate criteria for reliability (Clarke & Watson, 1995). Measurement error may have decreased the size of the observed effects, particularly for the temperament constructs with less reliable measurement. In addition, age differences were intended to make inferences about development, but the cross-sectional nature of the study limits the confidence in this inference. Finally, we attempted to equate the level of difficulty for the Delayed Response task across age groups based on prior studies. Given the extent of better performance for the older children, however, it would appear that task difficulty was not equated across age groups.

Efforts to prevent or reduce neurodevelopmental effects of SCD need to begin early in life. Identifying the specific causes of these effects, protective factors, and the most appropriate screening tools to identify at-risk children will be important for planning intervention efforts. Developmental assessment may be one such tool to identify children in most need of intervention. Assessment tools that focus on executive functioning in early childhood are not as well developed at this time, but may be of particular importance for SCD.

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