Neuropsychological functioning in preschool-aged children with sickle cell disease: The role of illness-related and psychosocial factors

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ABSTRACT

Neuropsychological functioning in preschool-aged children with sickle cell disease: The role of illness-related and psychosocial factors

Reem A. Tarazi

Lamia P. Barakat, Ph.D.

Objectives: The purpose of this study was to examine the association of illness-related and psychosocial factors with neuropsychological functioning in preschool-aged children with sickle cell disease (SCD). The following hypotheses were proposed: (1) children with SCD would perform less well than normative groups on neuropsychological measures, (2) they would perform relatively less well on measures of Memory/Attention as compared to other domains, and (3) psychosocial risk factors would predict variability in neuropsychological performance over and above that predicted by illness-related factors.

Methods: Participants were 22 children with SCD, ages 3-5 years, without overt stroke. The following neuropsychological domains were assessed: general intellectual functioning, language, memory/attention, visuospatial/visuoconstructional, and motor/visuomotor. Primary caregivers completed an information form, the Family Environment Scale, the Pediatric Inventory for Parents, and a questionnaire regarding home environment. Information about illness severity was gathered from medical charts and data collected as part of a longitudinal study from which all children were recruited.

Results: Mean standard scores across domains ranged from 87.7 to 94.9. The sample performed significantly lower than the normative sample on Full Scale IQ and several other domains. Although the sample performed statistically better on the Memory/Attention domain than other domains, these differences did not seem clinically meaningful. Correlation analyses indicated that disease severity was not significantly related to neuropsychological functioning. However, maternal education/family income was correlated with most neuropsychological domains and accounted for a large portion of the variance in regression analyses. Other

psychosocial variables of interest included the PIP difficulty total score, number of children living in the home, and hours per week in school/day care.

Conclusions: This study highlights the importance of identifying neuropsychological effects of SCD in preschool-aged children. Results of this study suggest that the disease process may not have a significant effect on neurological integrity in young children without overt stroke. At this age, psychosocial factors seem to be appropriate targets for intervention, with the goal of promoting cognitive development. Despite several limitations that may have affected the results, the study provides support for early identification of at-risk children in order to decrease neuropsychological morbidity in SCD.

CHAPTER 1: INTRODUCTION

Sickle cell disease (SCD) refers to a group of genetic disorders that is characterized by the presence of an abnormal variant of hemoglobin S, known as HbS, which affects those of African, Mediterranean, Indian, and Middle Eastern descent (Noll et al., 2001; Smith, 1999). Approximately one in 400 to 500 African-American newborns are affected with this disease (Desforges, Milner, Wethers, & Whitten, 1978). The expression of HbS results in an alteration of the shape of red blood cells into a "sickle" shape. In this case, red blood cells become less stable, do not bond oxygen properly, and die earlier than healthy red blood cells (Smith, 1999). These abnormally-shaped red blood cells become rigid and do not pass easily through vasculature. When sickled cells accumulate in the vessels, normal blood flow is blocked, which can prevent oxygen from being delivered to surrounding tissue (anemia) resulting in injury to organs within the body (Bonner, Gustafson, & Schumacher, 1999; Noll et al., 2001; Smith, 1999). Hemoglobin (Hgb) levels in children with SCD typically range between 5 and 9 g/dL; mean Hgb for children ages 2 to 6 is 12.5 g/dL (McMillan, DeAngelis, Feign, & Warshaw, 1999). SCD is classified by genotype. The most common is the homozygous condition, hemoglobin SS (HbSS); other types are hemoglobin SC (HbSC) and hemoglobin beta-thalassemia (HbSβ thalassemia). It has been found that children with HbSS have lower hemoglobin levels and they experience earlier, more frequent, and more severe symptoms than children with other forms of SCD (Bonner et al., 1999; Brown, Armstrong, & Eckman, 1993).

Children with SCD are at-risk for a number of physiological, neurological, and psychological problems. SCD is associated with early death (Kral, Brown & Hynd, 2001; Platt et al., 1994) and a number of medical problems, the most frequent being pain, fever, and infection (Bonner et al., 1999; Smith, 1999) which begin to appear early in life. Vascular involvement is related to a risk of stroke, silent infarcts, and chronic anemia, which can result in

neuropsychological deficits. Although the effects of overt stroke have been well established, the effects of silent infarcts and chronic anemia have been less clear (Kral et al., 2001; Steen, Xiong, Mulhern, Langston, & Wang, 1999).

It is essential for clinicians and researchers to understand the neurological and neuropsychological effects of SCD in order to develop ways to screen for evidence of early neurological involvement and to determine appropriate targets for early intervention. Although initially researchers attempted to define neuropsychological outcome in children with SCD by comparing them to various control groups (Fowler et al., 1988; Swift et al., 1989; Wasserman, Wilimas, Fairclough, Mulhern, & Wang, 1991), more recent studies have attempted to delineate the effects of overt stroke, silent stroke, and absence of neurological insult within groups of SCD patients (Armstrong et al., 1996; Bernaudin et al., 2000; Wang et al., 2001). There has also been an attempt to determine functioning across specific domains, rather than focusing on general neuropsychological functioning or individual tests (Noll et al., 2001; Schatz et al., 2001). There is now evidence that the disease process starts very early in life (Kwiatkowski et al., 2002), and children with SCD are at-risk for stroke at a young age (Thompson, Gustafson, Bonner, & Ware, 2002). As a response, researchers are beginning to determine educational readiness skills (Chua-Lim, Moore, McCleary, Shah, & Mankad, 1993; Steen, Hu, et al., 2002) and neuropsychological functioning (Best et al., 2002; Thompson et al., 2002) in very young children with SCD.

Continued examination of early neuropsychological effects of SCD is important, with a focus on determining a profile of functioning in order to identify specific areas of vulnerability. In addition, until very recently (Thompson et al., 2002), there has been inadequate focus on the contribution of psychosocial factors on neuropsychological functioning, not only in pediatric samples, but in studies assessing child development in general. There is evidence that parental intelligence and home environment affect academic and cognitive outcome in children (Burchinal, Campbell, Bryant, Wasik, & Ramey, 1997; Johnson et al., 1993;

Luster & McAdoo, 1994; Molfese & Molfese, 2002; Payne, Whithurst, & Angell, 1994; Sangwan, 2001). Although socioeconomic status (SES) has been found to be related to academic outcome in children with SCD (Brown, Buchanan, et al., 1993; Fowler et al., 1985), few studies have specifically addressed the role of psychosocial factors in neuropsychological outcome in these children.

The purpose of this study was to examine the effects of illness-related and psychosocial factors on neuropsychological functioning in preschool-aged children with SCD. Specific domains of neuropsychological functioning were examined in order to identify areas to be addressed through intervention and to identify potential areas to screen for evidence of early neurological involvement. Most published studies assess many aspects of disease severity retrospectively, without consistent and/or documented measurement of variables such hemoglobin levels and pain episodes. Children recruited for participation in the current study were drawn from participants in a longitudinal, prospective study, Attributes of Sickle Cell Pain in Infants and Young Children, assessing the patterns of SCD pain symptoms and analgesic response in young children over time, the relationship between age-related changes of biological markers and the sequence of pain episodes in infants and young children, and the use of pain diary in describing the daily life experiences and pain episodes or distress experienced by infants and young children. As part of several aims of this longitudinal, prospective study, children receive routine blood draws, monthly phone interviews, and/or complete a daily pain diary (Ely, Dampier, Gilday, O'Neal, & Brodecki, 2002).

The following introduction includes a detailed summary of SCD and its related morbidity, mortality, and current treatment, and a review of relevant review articles and empirical research regarding neuropsychological functioning of children with SCD, the impact of psychosocial factors on neuropsychological functioning, and psychological adjustment in children with SCD and their families. This is followed by a discussion of issues of neuropsychological

assessment in preschool children, a brief summary including limitations of previous studies, and an introduction to the current study.

1.1 Sickle Cell Disease: Morbidity, Mortality, and Treatment

1.1.1 Morbidity

Painful episodes, referred to as "crises," are common in SCD, and can be associated with dehydration, cold, injury, and/or infections. Other than pain crises, vascular obstruction can also cause acute chest syndrome (chest-pain, fever, and pneumonia-like symptoms), splenic sequestration crisis (enlarged spleen that may require surgical removal), cerebral infarct, sepsis, aplastic crisis, organ failure, gallstones, jaundice, and leg ulcers (Bonner et al., 1999; Brown, Armstrong, & Eckman, 1993; Kral et al., 2001; Smith, 1999). SCD is also associated with reduced exercise tolerance and delays in growth and sexual development, such that children with SCD appear smaller and less mature than same-age peers (Brown, Armstrong, & Eckman, 1993; Smith, 1999). The earliest symptoms of the disease usually appear in the first 2 years of life, a critical period for brain development (Smith, 1999). The cognitive and behavioral effects of the disease are variable, but these children have been found to be at-risk for learning problems (Brown, Armstrong, & Eckman, 1993). Although HbSS has been identified as the most severe form of the disease, children with other forms of the disease can have severe sequelae.

Miller et al. (2000) followed children with SCD from birth to 10 years of life in order to determine what factors are associated with increased complications of SCD in childhood. Seventy of the 392 total children had adverse outcomes that qualified their disease as severe: death, stroke, frequent pain crises (at least 2 events per year), or recurrent acute chest syndrome (at least one episode per year). The presence of dactylitis (pain in hands or feet) prior to age 1, steady-state hemoglobin level less than 7 g/dL, and leukocytosis without infection in early life were significant predictors of adverse outcome in later childhood. Although the rates and

severity of pain can vary considerably from patient to patient, several studies have outlined the rate of pain episodes, complications, and hospitalizations in children and adolescents (Gil et al., 1993; Hurtig & White, 1986; Shapiro et al., 1995). Hurtig and White (1986) found that 50 children and adolescents with SCD, ages 8 to 16 years, reported pain crises an average of one time every two weeks, with reduced hospitalizations (M = 2.3 at age 0-5, M = 1.2 at age 12-16) and ER visits (M = 3.0 at age 0-5, M = 1.5 at age 12-16) over time. In a sample of 18 children and adolescents with SCD, ages 7 to 17 years, who used a pain diary, pain was reported an average of 29.9% of the days in which they participated in the study (Shapiro et al., 1995). Pain episodes were reported once about every 6 weeks in 70 children and adolescents with SCD, ages 7 to 18 years, with an average duration of 3.3 days per episode (Gil et al., 1993). They reported an average of 0.25 acute events, 1.0 ER visit, 1.2 hospitalizations, and 2.1 visits/calls to the physician in a 9-month period.

Despite many medical advances, children with SCD are at-risk for physiological, neurological, and psychological effects. This disorder results in direct neurocognitive and indirect behavioral and psychological sequelae and can have a negative impact on school, social, and family functioning. Teachers and educators have been found to underestimate the rate of learning disabilities and emotional-behavioral problems in children with SCD, potentially leading to misattributions and misunderstandings about why a child may be having problems in school (Finke, Kellett, Schatz, & Robinson, 2002), affecting the ability of the child to receive appropriate support.

1.1.2 CNS involvement

The neurological and neuropsychological profiles seen in children with SCD are unique to this illness. Neurocognitive deficits and reduced academic competence result from complications of SCD including stroke, silent infarcts, and chronic anemia and poor oxygenation

to the brain. As much as 10% of children with SCD will have a stroke prior to age 15, and 16 to 22% present evidence of silent stroke (Thompson et al., 2002). Silent strokes refer to ischemic changes that appear on brain imaging with no obvious neurological signs or symptoms, and have been found to be associated with cognitive sequelae (Kral et al., 2001; Steen et al., 1999). In a review of all SCD patients imaged at a large children's hospital since 1993, it was found that at least half of the children had abnormal findings using current magnetic resonance methods, with vasculopathy, associated with anemia, being more prevalent than brain damage (Steen, Emudianughe, et al., 2002). When children with overt stroke were excluded, 35% of the sample had abnormal findings on conventional MRI. Although stroke can occur in anyone with SCD, it is most common in those with HbSS, and usually occurs within the first decade of life (Kral et al., 2001), with stroke incidence being highest in the 2-5-year-old age group (Kwiatkowski et al., 2002).

Cortical abnormalities in SCD may result from large vessel disease and distal small-vessel disease, or cerebral microinfarcts. In almost all of 22 patients who were found to have MRI abnormalities within a sample of patients with SCD, there was a tendency for lesions in the arterial borderzones between the major cerebral arteries, or watershed regions, and the adjacent deep white matter (Pavlakis et al., 1988). Furthermore, in a sample of 71 children with SCD who were found to have cerebral infarction, 36 had stroke due to large vessel disease and 35 had stroke due to small vessel disease, and stroke risk appeared to be related to specific alleles (Hoppe et al., 2002). Without treatment, which usually consists of chronic transfusion therapy, stroke can be recurrent. Considering that neurological damage can occur without a clinically apparent stroke, it is possible that damage may occur before it is even visible with MRI (Kral et al., 2001). Using EEG/ERP measurement, children with SCD and no cerebral infarction were found to have evidence of hypoxia-related changes in brain function as compared to age matched controls (Kellett & Schatz, 2002). Moreover, in a sample of 17 children ages 15-68 months, with

no history of neurological impairment, 6 had abnormal MRI or MRA findings, suggesting that the disease process leading to CNS pathology begins early in life (Kwiatkowski et al., 2002).

1.1.3 Mortality

Life expectancy of individuals with SCD is reduced. Although most children with SCD survive until at least 20 years of age and 50 percent of those diagnosed with SCD live past 50 years of age (Platt et al., 1994), the two main causes of mortality early in life are bacterial infection and stroke (Kral et al., 2001). Platt and colleagues (1994) followed 3,764 patients with SCD, ranging from infancy to middle adulthood to determine life expectancy. They found that the median age at death was 42 years for males and 48 years for females for those with HbSS. For those with HbSC, the median age at death was 60 years for males and 68 years for females. Most deaths were not due to overt organ failure; reduction in life expectancy was due to a number of factors, including acute chest syndrome, renal failure, seizures, stroke, high base-line white-cell count, and low fetal hemoglobin level. Those who died in childhood were most likely to die between the ages of 1 and 3 years, and death in childhood and adolescence was most often caused by pneumococcal sepsis. The life expectancy of people diagnosed with SCD has improved over the last several decades in response to improvements in treatment and clinical practice (Platt et al., 1994), which include pharmacological advances and improved screening measures.

1.1.4 Treatment for SCD

In 44 states (including Washington, D.C.), children are screened for sickle cell disease at birth (U.S. National Screening Status Report), and treatment is initiated at this time to reduce morbidity and mortality. Bonner and colleagues (1999) provide a summary of common treatment procedures for children with SCD. Due to the complexity of prophylactic treatment, the importance of early sickle cell education provided to families and caregivers has been stressed.

Early intervention usually occurs in the form of prophylactic antibiotic treatment, since early death can result from infection. Pain crises are managed at home with analgesics and hydration or, if severe enough, hospitalization may be necessary. Caregivers are also educated on how to address fever, check for splenic changes, and encouraged to comply with regular follow-up visits to assess hemoglobin levels. Regular blood transfusions reduce the percentage of hemoglobin S in the blood, and are typically started after a stroke occurs. The only cure for SCD is bone marrow transplantation. Chronic transfusion therapy and bone marrow transplantation are associated with risks such that only children identified as having significant enough stroke risk are eligible for these treatments (Kral et al., 2001). For example, chronic transfusion therapy can be associated with iron overload, infection, and transfusion reactions (Ris et al., 1996).

Currently, effort has been focused on the prevention and treatment of strokes (Bonner et al., 1999; Kral et al., 2001). One newer methodology being employed is Transcranial Doppler (TCD) ultrasonography, which assesses blood flow velocity in the brain, detecting vessel stenosis (Bonner et al., 1999; Kral et al., 2001). TCD is making it possible to detect which asymptomatic children are at-risk for cerebral infarction, such that those with elevated TCD readings are at increased risk for stroke (Adams et al., 1997). Adams and colleagues (1998) examined stroke outcome in 130 children with SCD, identified by TCD as having high stroke risk in at least two TCD examinations, who were assigned to receive either standard care ($N = 67$) or transfusion therapy ($N = 63$). In the group of children who received standard care, 10 sustained a cerebral infarction and 1 sustained an intracerebral hematoma. Only one child in the group of children receiving transfusion sustained an infarction. In the screening phase of this study, where children received at least two TCD examinations, 79 children who had normal results at the first screening subsequently had abnormal results, indicating the importance of routine screenings, although the optimal frequency of screenings is unknown.

Recent pharmacological advances include the drug hydroxyurea, which stimulates the production of fetal hemoglobin. Hydroxyurea has been found to be efficacious in adults (Charache et al., 1995), and clinical trials are currently being conducted with children. In a multicenter, double-blind, randomized clinical trial testing the efficacy of hydroxyurea in adults with SCD, Charache et al. (1995) found that those receiving hydroxyurea ($N = 152$) had less painful crises, fewer had episodes of chest syndrome, and fewer required transfusions as compared to controls ($N = 147$).

1.2 Neuropsychological Functioning of Children with SCD

In an early study, Chodorkoff and Whitten (1963) found no significant differences in intellectual functioning in 19 children with SCD with no overt stroke as compared to sibling controls. It took some time for researchers to re-examine the question of neurocognitive functioning in children with SCD with and without overt stroke. Recent research has highlighted that both children with and without major neurological complications are at-risk for broad neuropsychological sequelae. The following sections will summarize relevant literature that examines the effect of overt stroke on neuropsychological outcome and the role of silent infarcts and anemia on neuropsychological outcome, and introduce results of research with very young children with SCD. Some inconsistencies in the results of various investigations are related to inclusion of children with various levels of cerebrovascular complications, the use of different measures with or without identification of constructs, and differences in strategies used to control group differences on demographic variables.

1.2.1 Children with overt stroke

The pathology of stroke in children with SCD is most often cerebral infarction. Considering that by age 10, more the 20% of children with SCD have positive findings on MRI, it

is important to understand the effects of these infarctions. In children who sustain stroke from SCD, there is heterogeneity of lesion size, location, and chronicity, making generalizations about effects on neuropsychological functioning difficult and leading to masking of differences in studies with a heterogeneous sample (Ris et al., 1996). Children with SCD who have had even one stroke, followed by transfusion therapy, have been found to have significant cognitive impairments, and recurrent strokes occur frequently after an initial stroke in children without treatment. In a recent study with a large sample of 222 children with SCD (150 with HbSS and 72 with HbSC), children with overt stroke had IQ scores that were, on average, 14.4 points lower than that of children with normal MRIs (Thompson et al., 2003). Performance following both left and right hemisphere strokes in children with SCD mimicked that of adult stroke patients, with various etiologies (Cohen, Branch, McKie, & Adams, 1994). When compared to 8 matched controls, 16 children and adolescents with SCD, who had sustained an overt stroke between the ages of 2 and 12 years, had delays in reading and writing skills on the Peabody Individual Achievement Test-Revised (Markwardt, 1989), although receptive and expressive vocabulary on the Comprehensive Receptive Expressive Vocabulary Test (Wallace & Hammill, 1994) was similar for the two groups (Sanders et al., 1997).

In another study, Hariman, Griffith, Hurtig, and Keehn (1991) compared physical and cognitive functioning of 14 children with SCD (11 HbSS, 2 HbSβ, 1 HbSC), ages 5 to 18 years, who had sustained 1 to 3 strokes to that of matched children with SCD who had not had strokes. The children with history of stroke had few limitations in activities of daily living or evidence of motoric dysfunction. However, when compared to the comparison group, most patients performed more poorly on measures of intellectual functioning and exhibited impaired language functions and problems in adjustment. Eleven of these children had Full Scale IQ scores (based on abbreviated WISC-R; Kaufman, 1976) and 10 had expressive and receptive language functions (based on The Test of Language Development; Newcomer & Hammill, 1982) in the

borderline to retarded range. In general, the authors concluded that children had intact gross motor and physical functioning following stroke, however cognitive functioning was impaired.

Although these described studies identified general effects of stroke, they did not address the heterogeneity of lesion size and location. In an examination of 28 children and adolescents with SCD HbSS, ages 7 to 21 years, with a history positive for cerebral infarction, location and size of cerebral infarct was related to kind and extent of cognitive sequelae (Schatz et al., 1999). These children were identified as having infarcted tissue anterior to the central sulcus or infarcted tissue in both anterior and posterior regions and were compared to 17 sibling controls. Poor performance on the Tower of Hanoi test (Klahr & Robinson, 1981) and the Test of Variables of Attention (TOVA; McCarney & Greenberg, 1990), tests of attention and executive functions, was associated with anterior lesions, with or without posterior lesions. Children with more diffuse injuries also presented with deficits in visual spatial skills on a variety of discrimination, orientation, and construction tasks. Although lesion volume was not associated with attentional or executive deficits, it was related to spatial and language functions.

Since sequelae of stroke can be variable, study samples are often heterogeneous, and neuropsychological outcome can depend on lesion location and size, case studies are important in delineating specific effects of cerebral infarct. In a case study, Ris et al. (1996) reported MRI and neuropsychological test results of an 11-year-old female with SCD HbSS before and after she suffered a right hemisphere stroke. Five weeks prior to the stroke, the patient's performance on neuropsychological test measures of general intelligence, achievement, memory and learning, and attention was generally within normal limits, with many scores above average. Three weeks following her stroke, although psychometric intelligence was generally conserved, arithmetic abilities were significantly reduced, short-term memory with nonverbal information decreased slightly, the patient made increased errors and had an increased reaction-time on a test of attention, and there was evidence of left neglect. MRI results showed an infarction in the right

anterior temporal lobe and central parietal lobe in areas perfused by the middle cerebral artery. The results of this case study highlight the importance of examining performance patterns or profiles within individual patients to determine areas of relative strengths and weaknesses that can be affected by stroke.

In general, there is consistent support for the idea that overt stroke in children with SCD results in neuropsychological impairment. Empirical studies have found evidence of academic and cognitive impairment, particularly in areas of language and attention/executive functions, yet have not found evidence of long-term motor deficits. Effects are partly dependent on lesion location, with anterior lesions found to be associated with poorer performance on tests of attention and executive functions, and deficits in visual spatial skills accompanying more diffuse injuries. The importance of case study research is highlighted to address heterogeneity of outcome following stroke. The neuropsychological effects of SCD in the absence of overt stroke are less clear and have been an area of recent focus in the literature.

1.2.2 Evidence for neurological changes in the absence of overt stroke

Brain damage from SCD occurs in relation to chronic hypoxia or vaso-occlusion in cranial circulation, and ischemic change in brain tissue can result even if there is no evidence of clinical stroke (Kral et al., 2001; Steen, Xiong, Mulhern, Langston, & Wang, 1999). Brown, Armstrong, and Eckman (1993) outlined four potential neurological mechanisms to explain the relationship between disease process in SCD and neurocognitive functioning in children without clinically detectable stroke: (1) numerous microinfarctions in minor CNS vessels can lead to subtle neurocognitive effects with no overt neurological deficits, (2) anemia could lead to decreased oxygen in the brain during critical developmental periods, (3) nutritional deficiencies caused by severe hemolytic anemia could result in compromised brain development, and

(4) ischemia could result from anemia. Information processing and complex cognitive abilities may be compromised as a result of silent stroke, even without evidence of overt stroke.

Neuroimaging studies have functioned to highlight evidence of neurological abnormalities in SCD in the absence of overt stroke, providing evidence for the effect of the disease process. Wang et al. (1998) used MRI and magnetic resonance angiography (MRA) to determine the presence of CNS abnormalities in 39 young children with HbSS, ages 7-48 months, who had no evidence of clinical stroke (3 subjects had history of seizures). Findings showed that 11% of the 36 asymptomatic patients had CNS abnormality; 1 had a silent infarct on MRI and a stenotic lesion on MRA, and 3 had stenotic lesions on MRA. Of the 21 patients in this sample who had developmental testing, only one had evidence of developmental delay. These results indicate that, in neurologically asymptomatic children with SCD, lesions of vascular stenosis and brain ischemia may occur in the first few years of life. In another study, Steen et al. (1999) compared quantitative MRI results from 50 children with SCD (34 HbSS, 14 HbSC, 2 other), ages 4-17 years, who did not have evidence of stroke, to those of 52 unrelated, healthy children of hospital personnel. They examined spin-lattice reaction time (T1), which is sensitive to subtle structural changes at the cellular level. When compared to the control group, quantitative MRI findings indicated that patients showed a pattern of subtle T1 abnormality in every gray matter structure measured, with no abnormalities in any white matter structures. In fact, several measurements reached significance by the age of 4 years.

These neuroimaging studies provide evidence for neurological changes, such as stenotic lesions and cellular changes in gray matter structures, in the absence of clinical stroke in children with SCD. Early intervention with treatment commonly used after children incur stroke may be appropriate for children who are identified to be at-risk based on neuroimaging results.

1.2.3 Neuropsychological effects in the absence of stroke

Although it is well established that stroke in children with SCD impacts cognitive functioning, there is less agreement on the cognitive effects of SCD when no cerebral vascular injuries have occurred. Although there have been inconsistent findings in studies examining neuropsychological functioning in children with SCD without overt stroke, which is described in more detail below, in a meta-analysis of studies of cognition in children with SCD with no evidence of cerebral infarction, Schatz, Finke, Kellet, and Kramer (2002) found an IQ difference of 4.3 standard score points in a comparison of 631 children with SCD and no cerebral infarcts and 446 comparison children (either siblings or matched peers). The effect size, though small, was within the range of that expected with other disorders with known neuropsychological effects, such as phenylketonuria and bacterial meningitis. Many studies used in the meta-analysis used neurological history in the absence of MRI data to exclude children with cerebral infarction. Due to the small number of children within a large group who would be expected to have silent infarcts (about 15%), the authors concluded that the inclusion of these children would not have a significant overall effect on group differences in IQ scores. Finally, the meta-analysis indicated a possible age effect over middle childhood, such that cognitive effects increase with age.

Some early studies (Fowler et al., 1988; Swift et al., 1989; Wasserman et al., 1991) found neuropsychological deficits in children with SCD and no overt stroke as compared to control groups. However, these studies did not clearly differentiate children with SCD and silent strokes from those with no CNS abnormality. Fowler and colleagues (1988) examined neurocognitive functioning in 28 children with SCD and no overt stroke (HbSS) and 28 matched controls and found that, though groups did not differ on global measures of intelligence, children with SCD performed more poorly on reading and spelling and older children with SCD performed significantly less well on reading, visual-motor, and attention tasks. These findings were not accounted for by disease severity.

In a similar study, 43 children and adolescents with SCD (41 with HbSS) and no overt stroke, ages 8 to 16 years, had lower scores on Full Scale and Performance IQ scores on the Wechsler Intelligence Scale for Children-Revised (WISC-R; Wechsler, 1974) as compared to 30 sibling controls (Wasserman et al., 1991). Despite missing more school, children with SCD did not differ in terms of academic achievement as measured by the Wide Range Achievement Test-Revised (WRAT-R; Jastak & Jastak, 1978) or the need for special education. In this study, younger children were actually found to perform more poorly on several cognitive domains of the Luria-Nebraska Neuropsychological Battery-Children's Revision (LNNB-C; Golden, 1987), such as expressive speech, memory, visual functioning, writing, and arithmetic. The authors hypothesized that these young children may have silent infarcts, whereas older children who may have performed less well on the LNNB (Golden, Hammeke, & Purisch, 1982) had more opportunity to incur stroke which would exclude them from the study, or that the effects are related to a transient ischemic episode that is more common in younger children.

Finally, when compared to 21 sibling controls, 21 children and adolescents, ages 7 to 16 years, with SCD (HbSS) and no identified neurological disease, had lower scores on WISC-R Full Scale IQ and tests of perceptual organization, attention, memory, and academic achievement, though there was no identifiable pattern of functioning (Swift et al., 1989). Only 4 children with SCD had IQ scores lower than 70, but the SCD group collectively scored approximately 1 SD below the control group on most measures. This impairment, which was not associated with disease severity or age, was present by the age of 7 and tended to stabilize after this point.

In the Steen et al. (1999) study, a subset of 27 of the children with SCD were administered the Wechsler Intelligence Scale for Children –Third Edition (WISC-III; Wechsler, 1991). Based on the results, 9 had a Full Scale IQ in the mildly mentally retarded range and 11 had evidence of mild cognitive impairment. Patients with HbSS had significantly lower Full Scale IQ than those with HbSC, accounted for by a difference in the perceptual organization

index score. Low hematocrit (Hct; volume of packed red blood cells) was associated with impairment in WISC-III Full Scale IQ; more specifically, Hct was positively correlated with the verbal comprehension, perceptual organization, and freedom from distractibility indices. The psychometric results were not significantly correlated with age, such that deficits were apparent at an early age and did not necessarily worsen over time. Because cognitive deficits were present even in the youngest children of the sample and did not worsen with age, the authors hypothesized that cognitive deficits were not likely related to school absences or poor access to education. Several patients in this sample had cognitive deficits in psychometric testing in the absence of any MRI abnormality, indicating that neuropsychological testing may be more sensitive to neurological damage than MRI scanning. The authors concluded that T1 reduction in gray matter and psychometric deficits both result from hypoxic damage, since Hct levels are related to both outcomes.

A more recent study (Noll et al., 2001) also found deficits in neuropsychological functioning of children with SCD without overt stroke, and attempted to determine a specific profile of functioning by formally defining specific measures and subtests that would reflect specific domains of functioning. In a comparison of 31 children with SCD, ages 9 to 16 years, with no overt stroke (half with HbSS) and 31 matched peers without a chronic illness, the authors found that the children with SCD had significantly lower scores on total neuropsychological functioning, verbal abilities, and Memory/Attention constructs. Constructs were built that would provide a score for each of 5 domains comprised of total or subtest scores of various neuropsychological measures: WISC-R, WRAT-R, The Beery Developmental Test of Visual-Motor Integration (VMI; Beery, 1989), the Kagan Matching Familiar Figures Test (MFFT; Kagan, 1966), the Wide Range Achievement Test of Memory and Learning (WRAML; Sheslow & Adams, 1990), and the Purdue Pegboard Test (Tiffin, 1948). The five domains were 1) verbal, 2) spatial/constructional, 3) achievement, 4) attention/memory, and 5) fine motor, as well as total

performance. Although not all significant, children with SCD performed more poorly on every construct score and standardized test score. From the domain scores, a pattern of performance was developed to determine discrepancies between domains. The patterns of performance were similar between the two groups. The fact that children with SCD performed more poorly across domains may indicate that physiological processes associated with SCD, for example hypoxia, may be related to subsequent problems, but it is also important to consider that children with silent strokes may have been included in the study, affecting performance of the SCD group. Age was not significantly correlated with performance, indicating that deficits in children with SCD occur early in development in key cognitive domains.

The described studies provide evidence for the effects of SCD on neuropsychological functioning in the absence of overt stroke when children are compared to matched control groups, indicating lower IQ scores, and poorer performance on measures of academic functioning, attention, memory, visuomotor skills, and perceptual organization in children with SCD without overt stroke. However, these studies do not formally distinguish between children with evidence of silent strokes and those with no evidence of neurological involvement, so it is difficult to identify the role of silent infarcts in these studies. Noll and colleagues (2001) provide a useful model for assessing neuropsychological profiles in children with SCD to determine areas of specific dysfunction.

1.2.4. Silent infarcts and neuropsychological functioning

In the Thompson et al. (2003) study, children with silent infarcts were found to have IQ scores on average 3.8 points lower than those of children with normal MRIs, and the sample at large had Full Scale IQ decreases of 1.2 points per year with age. Two issues that remain unresolved are the specific causes of cognitive effects in SCD in the absence of stroke and the functional meaning of these cognitive effects.

With a growing interest in the effect of silent infarcts, researchers have begun to attempt to examine differences in outcome depending on specific levels of neurological involvement. Neuroimaging has been used to diagnose patients with silent infarcts and determine sequelae specific to these neurological changes (Armstrong et al., 1996; Bernaudin et al., 2000; Wang et al., 2001). Armstrong and colleagues (1996) compared the cognitive functioning of 194 children with SCD, ages 6 to 12 years, based on presence of MRI abnormality. Analyses were conducted only with children with HbSS, who were most likely to have history of cerebrovascular accident (CVA) or silent infarct. The groups were comprised of children with history of CVA ($N = 9$), MRI abnormality showing silent infarcts with no clinical history of CVA (silent stroke; $N = 21$), and those with no MRI abnormality ($N = 105$). Children with a history of CVA had significantly lower scores on the WISC-R Full Scale IQ and Performance Scale IQ when compared to the silent stroke group and additionally lower scores on Verbal Scale IQ and math achievement when compared to children with normal MRIs. In fact, global intellectual functioning was often within the borderline range or below in children with a history of CVA. Children with silent infarcts had significantly lower Verbal Scale IQ scores as compared to children with no abnormalities. When subtest scores were examined, children with CVA performed significantly poorer than the other children on tests of verbal knowledge and language abilities, and visual-motor and spatial organization and integration, and lower than children with no abnormalities on visual-motor speed and sequential memory. Children with silent strokes performed less well on tests of arithmetic, vocabulary, and visual motor speed and coordination when compared to children with no abnormalities. The authors concluded that children with history of CVA are at greatest risk for global neuropsychological abnormalities and that children with silent strokes also have specific areas of diminished function, although outcome is less severe. They highlighted the use of test batteries that include evaluation of processing speed, visual-motor skills, arithmetic, memory, and attention-concentration skills.

Wang and colleagues (2001) conducted a long-term study of 373 children with SCD (255 with HbSS, 118 with HbSC) in which children, who were 6 to 12 years old at the time of their first evaluation, received serial neuropsychological evaluation and MRI testing every 2-3 years for a total of 1 to 4 assessments (the Cooperative Study of Sickle Cell Disease). Based on MRI results, 27 children were found to have overt strokes and 62 had evidence of silent infarcts. Because only 10 children with HbSC had evidence of silent infarcts, only children with HbSS were included in the study analyses. Children with silent infarcts had lower scores on the WISC-III Full Scale and Verbal IQs, the Digit Span subtest, and the Woodcock-Johnson Math and Reading subtests as compared to children with normal MRI findings. Interestingly, there was no significant difference between children with overt and silent strokes on the WISC-III. The rate of change in scores over time was not different for children with silent strokes when compared to children with normal MRIs, nor was it different between HbSS and HbSC children with normal MRIs. There was no relationship between number and length of hospitalizations and neuropsychometric tests results.

As part of a longitudinal, multicenter study, 173 children with SCD (155 with HbSS, 11 with Hb Sβ thalassemia, 7 with HbSC), ages 5 to 15, received blood screening, TCD ultrasonography (*N*=143), MRI (*N*=144), and neuropsychological evaluation (*N*=156) (Bernaudin et al., 2000). Seventy-six sibling controls were also given a neuropsychological evaluation. Twelve children (6.9%) had a history of overt stroke, 8.4% had abnormal TCD findings, and 15% had evidence of silent stroke. Children with overt strokes performed significantly lower on WISC-III/WPPSI-R Full Scale, Verbal, and Performance IQ scores when compared to siblings. After exclusion of stroke patients, there were no differences between children with normal or abnormal TCD findings. Children with a history of stroke had lower Performance and Full Scale IQ scores when compared to those without stroke, and children with silent infarcts were impaired in Similarities, Vocabulary, and Verbal Comprehension. In addition to abnormal MRI results,

hematocrit and platelet levels also contributed to deficits in cognitive functioning. In fact, isolated silent strokes, unless associated with severe anemia or thrombocytosis, did not appear to compromise cognitive functioning.

Findings across studies examining the neuropsychological effects of SCD with no overt stroke have been inconsistent. Some early studies did not separate children with silent infarcts from those with no neurological involvement. While some studies differentiate children with SCD into various groups, other studies employ control groups. With improvements in neuroimaging and measurement techniques, more recent studies have investigated the neurological and neuropsychological effects of silent infarcts. Results seem to indicate that children with SCD and silent infarcts are at-risk for neuropsychological deficits, including lower overall IQ scores and poorer performance on tests of academic achievement. Although the sample sizes for both groups were small, Wang and colleagues (2001) found similar performance in children with overt and silent strokes in a longitudinal study, suggesting that performance in children with overt neurological disease may actually reflect effects of multiple silent infarcts. Recently, more interest has been focused on performances within individual cognitive domains. Several of the studies reviewed indicate deficits in areas of attention. The following section reviews evidence for frontal lobe involvement in the disease process of SCD and neuropsychological outcome, suggesting frontal lobe deficits.

1.2.5 Evidence for frontal lobe involvement

The frontal systems appear to be vulnerable to SCD pathology. Adults with SCD and no overt stroke have been found to perform less well than matched "nearest-relatives" without SCD on timed tests associated with attention, namely, cancellation time on a cancellation task (Sano et al., 1996). A series of studies investigating neuropsychological sequelae of SCD in children have also identified deficits specific to frontal lobe functioning, such as attention and executive

functions (Brown et al., 2000; Brown, Buchanan, et al., 1993; DeBaun et al., 1998; Kral & Brown, 2002; Schatz, Brown, Pascual, Hsu, & DeBaun, 2001; Watkins et al., 1998). In fact, Schatz and colleagues (2001) found that most children with SCD in their sample (79%) sustained lesions involving the frontal lobe or white matter underlying the frontal lobes. This would indicate that complex cognitive functions involving attention and executive functions are specifically at-risk, which, in turn, can compromise other domains of functioning. When specific cognitive domains were considered in a meta-analysis (Schatz et al., 2002), most studies that were examined (8/10) showed deficits on measures of attention and executive skills with a likely medium effect size, whereas 4 of 10 studies found differences in language functioning, and 3 of 10 found differences in memory functioning.

A behaviorally-based examination of attention and executive deficits in children with SCD found that more than half of the 28 children with SCD, ages 3 to 18 years, (12 with cerebrovascular complications) exhibited evidence of attentional difficulties as measured by the Behavior Rating Inventory of Executive Functioning (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000) and the Behavior Assessment System for Children (BASC; Reynolds & Kamphaus, 1992), paper-and-pencil measures completed by parents (Brouwers et al., 2002). Symptoms of inattention were more prevalent than those of hyperactivity, and were most common in children with cerebrovascular complications. In a study using the same measures, teachers and parents reported more executive dysfunction in children with HbSS with abnormal TCD readings in the absence of CVA as compared to those with normal TCD readings, specifically in areas of inhibitory control, problem-solving flexibility, modulation of emotional responses, working memory, planning and organizing, and self-monitoring (Kral & Brown, 2002). Despite these reported problems in executive control, those with abnormal TCD readings did not exhibit more internalizing, externalizing, or adaptive behavior problems as compared to children with normal TCD readings.

Lesions involving the prefrontal cortex that do not result in hemiparesis, may go undetected, highlighting the importance of identifying and screening for cognitive correlates of such lesions. Watkins and colleagues (1998) examined cognitive correlates of frontal lobe infarctions (determined by MRI) in 41 children with SCD (32 with HbSS, 5 with HbSC, and 4 with HbSβ thalassemia), ages 6 to 16 years. A control group of 15 siblings without SCD was used. Out of 10 patients with evidence of infarction, 9 were found to have infarctions of frontal lobe tissue; 5 had history of overt stroke and damage extending to the prefrontal cortex and possibly to the white matter underlying the prefrontal cortex. The symptomatic group (large infarctions and symptoms of stroke) had significantly lower Verbal, Performance, and Full Scale WISC-III IQ scores and were more impaired on tests of learning and memory as compared to the asymptomatic (small to medium infarctions with no symptoms of stroke) and normal (normal scans) groups and the sibling control group. The symptomatic group also had more perseverative responses on the Wisconsin Card Sorting Test (WCST; Heaton, 1981), a measure of prefrontal functioning. A trend toward lower scores was noted with the asymptomatic group as compared to the sibling group. The children with SCD and normal MRIs had a mean IQ that was 6 points lower than the sibling group; though not significant, the authors suggest that this difference could indicate increased risk for learning difficulties in this population, even without the presence of infarct. The use of MRI to detect covert cerebral infarction may be helpful in detecting risk for later clinical stroke.

Other empirical studies have also highlighted the sensitivity of measures of attention in identifying children with SCD with neurological involvement. In a comparison of children and adolescents, ages 7 to 21 years, with SCD HbSS and no overt stroke ($N = 7$), with SCD HbSS and overt stroke ($N = 21$), and normal sibling controls ($N = 17$), the TOVA was most sensitive (86%) and specific (81%) in identifying children with silent infarcts and distinguishing them from children without stroke (DeBaun et al., 1998) when compared to other tests of attention and

executive functioning, such as the WCST, and 12 other subtests used to measure aspects of spatial and motor functioning, language, and memory. Due to the safety, inconvenience, and cost of yearly MRI examinations, these authors conclude that measures of attention can be useful in screening for the presence of silent infarcts.

Brown, Buchanan, et al. (1993) compared cognitive and academic functioning in 70 children with SCD and no history of CVA, ages 2 to 17 years, to 18 sibling controls. Despite normal intelligence, children with SCD were more impaired than their siblings in areas of attention as measured by the MFFT and in reading decoding. Similarly, in an extension of Armstong et al. (1996), Brown and colleagues (2000) examined neurocognitive functioning of children, ages 6 to 17 years, with SCD and either clinical stroke ($N = 22$), silent infarct ($N = 11$), or no MRI abnormalities ($N = 30$), adding measures of attention, executive functions, language, and behavior and adaptive functioning. Children with HbSS (76.2% of sample) had lower hemoglobin levels and more overall symptoms than children with HbSC (23.8% of sample). Children with overt strokes had more SCD-related symptoms over their lifetime and lower hemoglobin levels than those with no CNS abnormalities. Those with silent strokes had more symptoms over their lifetime than did those without CNS abnormalities. Performance on the MFFT, a task of sustained attention, was poorest in the children with overt and silent strokes, when compared to children with no abnormalities on MRI. No statistically significant differences were found on measures of global intelligence, academic achievement, or visual-motor functioning, although children with overt strokes performed more poorly than children in the other groups. However, the children with no CNS abnormalities in this study were referred based on a history of academic problems, and they performed less well than similar groups in other studies. These findings support the use of measures of attention and concentration to identify children with possible cerebral infarcts and suggest frontal lobe involvement in the pathophysiology of SCD.

Academic concerns have also been highlighted in children with frontal lobe impairments, stressing the need for intervention to address these deficits. In their study, Schatz and colleagues (2001) compared academic and neuropsychological functioning in 19 children with HbSS and silent infarcts, 45 children with SCD and no evidence of infarcts, and 18 siblings without SCD. As mentioned, most children in the sample sustained frontal lesions. Fifty-eight percent of children with silent infarcts, as compared to 27% of those with SCD without silent infarcts and 6% of sibling controls, were retained in school or required special education services. In addition, a larger percentage of children with silent infarcts (37%) had problems with academic achievement when compared to children with no infarcts (27%) and the sibling group (6%). Finally, the children with silent infarcts had evidence of deficits in other cognitive domains, particularly in attention and executive functioning (53%). The authors suggest that, due to the high occurrence of lesions in the frontal lobes in children with SCD and deficits in performance on tests of attention and executive functioning, interventions focused on treating impulsivity, inattention, and executive skills deficits are appropriate. In addition, tests of attention and executive functioning can serve to screen for silent infarcts in children with no history of CVA.

Despite evidence for frontal lobe deficits in children with SCD, a study conducted by Goonan, Goonan, Brown, Buchanan, and Eckman (1994) did not support this conclusion and highlights the need for research focusing on specific frontal lobe functions. These authors used a computerized vigilance task and the MFFT to examine the capacity for sustained attention and inhibitory control in 24 children and adolescents, ages 4 to 15 years, with SCD and no history of overt stroke, as compared to 11 healthy siblings, ages 7 to 15 years, in order to determine the presence and level of attentional difficulties in children with SCD that may be related to frontal lobe dysfunction. Although there appeared to be differences between the groups, with the SCD children showing evidence of difficulty sustaining attention and inhibiting impulsivity, these differences disappeared when age was considered. That is, older children performed better on

these tasks across the board and both children with SCD and siblings improved as expected with age. Results of this study supported the idea that the development of attention and inhibitory control proceeds similarly in children with SCD as it does in normally developing children.

Although the sample of the Goonan et al. (1994) study was small and may not have included any children with silent stroke, indicating that children with no neurological involvement do not have attentional deficits, it does highlight the importance of considering age when assessing functions that normally develop throughout childhood and into adolescence, specifically attentional and executive functions. Although other studies have not specifically considered the role of age, research with adults and studies differentiating SCD children based on level of cerebrovascular involvement has suggested that children with overt or silent stroke are at-risk for frontal lobe infarct, which can result in specific problems in the development of skills related to attention and executive functioning. A developmental perspective in the assessment of these skills is essential.

Most of the research examining neuropsychological and cognitive functioning in children with SCD has relied on samples of school-aged children and adolescents. Little is known about the neurological and neuropsychological effects of SCD in younger children, and researchers have begun to examine the early neuropsychological effects of the disease process to determine when deficits first appear.

1.2.6 Neuropsychological functioning of very young children with SCD

The presence of structural brain changes in very young children with SCD indicates that cognitive impairment may also occur at a very young age, affecting cognitive and behavioral functioning before a child even begins school (Steen, Hu, et al., 2002). Assessment of young children with SCD is important in order to determine when deficits initially emerge and to identify the factors that may account for these deficits, as well as to provide targets for early

intervention. Several studies have assessed school readiness skills in children with SCD as they prepare to begin formal schooling (Chua-Lim et al., 1993; Steen, Hu, et al., 2002). Early educational experience impacts later academic competence or problems in school, and by determining problems in school readiness at the preschool level, early intervention can be provided (Chua-Lim et al., 1993). Steen, Hu, et al. (2002) examined kindergarten readiness skills in children with SCD tested by the Memphis City School system, where incoming kindergarteners have been routinely tested since 1995 using a teacher-administered checklist which measures pre-reading skills, arithmetic skills, and writing concepts and was designed to identify children who need early educational support or intervention. Data from 34 children with SCD (22 with HbSS, 8 with HbSC, and 4 with HbSβ thalassemia) without history of stroke and data from 68 matched controls were compared. They found that children with SCD had significantly lower scores in the area of auditory discrimination. This difference was significant even when only children with HbSS were included. Auditory discrimination refers to the ability to discriminate between similar and dissimilar sounds, assumed to be skills necessary for reading acquisition. These results may indicate problems with hearing, auditory processing, or deficits in attention or short-term memory.

In another study, 10 children with HbSS, ages 4 to 6 years and without history of CVA, were compared to 10 matched controls to determine school readiness skills (Chua-Lim et al., 1993). Children with SCD were functioning within the normal range on a test of general cognitive abilities, the McCarthy Scales of Children's Abilities (McCarthy, 1972). However, they scored significantly lower than normal controls in all categories except somatesthetic input on a specific measure of visual input, verbal output, and short-term memory. Fifty to seventy percent of children with SCD were found to have deficiencies in the areas of visual input, sequential input, short-term memory, experimental acquisition, fine motor output, and motor sequential output. The three children with the poorest performances did not show any

abnormalities on MRI. However, the children with SCD were found to be functioning within the normal range of intelligence as measured by the McCarthy Scales of Children's Abilities. Therefore, even though young children with SCD may fall within the normal range on general intellectual tests, they are functioning below the level of matched controls and there is evidence of deficits in specific areas of functioning, such as attention and motor functioning. Problems in these areas may affect school readiness skills in these children, such that they begin formal schooling already a step behind their healthy peers. These studies used matched controls, which supports the idea that functioning in these areas may be related specifically to the disease process.

Recently, researchers have begun to focus on neurocognitive functioning of very young children with SCD in order to determine the early effects of the disease (Best et al., 2002; Thompson et al., 2002). In a longitudinal study, Thompson and colleagues (2002) extended the assessment of neurocognitive functioning of children with SCD to infancy and toddlerhood and examined the effects of biomedical risk and parenting risk. These researchers assessed 89 children with HbSS ($N = 55$), HbSC ($N = 27$) or other types of SCD ($N = 7$) and their caregivers at 6, 12, 24, and 36 months of age (only 19% completed all 4 assessments). Based on the Bayley Scales of Infant Development II (Bayley, 1993), there was a significant decline in cognitive, but not psychomotor, functioning over the first 3 years of life, with a significant decline occurring between 12 and 24 months. This pattern was consistent with that of African-American children without chronic illness from low-income families, who have been found to have average cognitive functioning in infancy and gradual declines in early childhood (Burchinal et al., 1997), highlighting the importance of considering the role of factors such as race, SES, and psychosocial functioning when examining neuropsychological functioning and development in children with SCD. Best and colleagues (2002) examined neuropsychological and developmental functioning in 18 infants (mean age 19 months) and young children (mean age 54 months) with SCD and no clinical neurological abnormalities. Infants were assessed with the Mullen Scales of Early

Learning (Mullen, 1995) and young children completed various tests to assess verbal skills, visual skills, fine motor skills, memory and attention. Performance of children in both groups fell in the average range across most measures; however, there was a significant decline in memory performance with age and a trend towards declines in visual attention and verbal comprehension with age.

Although there is evidence of early cognitive and academic deficits in children with SCD, there were no identified studies that examined specific neuropsychological functions in preschool-aged children. Similarly, there has not been an investigation of the integrity of frontal lobe functioning in very young children with SCD. Methodological and theoretical limitations may make it difficult to assess neuropsychological functioning in this group of children, particularly attentional skills. Although there is evidence that illness-related factors of SCD affect cognitive development, the role of demographic and psychosocial factors should be considered.

1.3 The Impact of Demographic and Psychosocial Factors on Neuropsychological Functioning

1.3.1 The effects of parental intelligence and home environment

There is strong evidence that parental intelligence and home environment impact cognitive functioning in children without chronic illness at various stages of development. For example, parental education, occupation, and family income positively correlated with child IQ in children falling in various intelligence categories (Sangwan, 2001). The total amount of family risk has been found to be more important than the pattern of risk. In a longitudinal study (Sameroff, Seifer, Baldwin, & Baldwin, 1993), one-third to one-half of the variance in intelligence scores of 152 children of varied SES and race, assessed at ages 4 to 13 years, was explained by multiple risk scores, representing the number of high-risk conditions (mother's behavior, mother's developmental beliefs, mother's anxiety, mother's mental health, mother's

educational attainment, family social support, family size, major stressful life events, occupation of head of household, and disadvantaged minority status). Although general cognitive development in an African-American infant sample was not affected by a Cumulative Risk Index (poverty status, maternal education less than high school, household size, unmarried mother, stressful life events, depressed maternal affect, mother-infant interactions, maternal IQ, quality of home environment, quality of day care environment), this score was associated with language outcomes (Hooper, Burchinal, Roberts, Zeisel, & Neebe, 1998), such that environmental factors may affect outcome in some specific cognitive domains, even in the presence of normal overall cognitive functioning.

More specifically, language development seems to be affected by SES, parental IQ, parenting practices, and family activities (Molfese & Molfese, 2002). Home literacy environment also affects language development (Payne et al., 1994) and kindergarten school readiness (Christian, Morrison, & Bryant, 1998). Payne and colleagues (1994) defined the home literacy environment as frequency, age of onset, and duration of shared picture book reading; number of picture books in the home; frequency of child's requests to engage in shared reading, child's private play with books, shared trips to the library, and caregiver's private reading; and caregiver's enjoyment of private reading. Lending further support, a sample of 87 African-American children, ages 18-30 months, were more likely to have larger vocabularies, use more irregular nouns and verbs, and use longer utterances if they came from more stimulating and responsive homes (Roberts, Burchinal, & Durham, 1999) as assessed by the Home Observation for Measurement of the Environment (HOME; Caldwell & Bradley, 1994), a widely used measure of home environment.

Home environment has been identified as an important factor in other studies with at-risk children, including low-birth-weight children and children from African-American and/or low-income families. In addition to variability accounted for by biological risk, in premature,

low-birth-weight children, factors such as parental intelligence, income, and home environment were found to be related to cognitive development and intellectual outcome in children, either directly or indirectly (Bacharach & Baumeister, 1998; Bohm, Katz-Salamon, Smedler, Lagercrantz, & Forssberg, 2002; Bradley et al., 1993; Thompson, Goldstein, et al., 1994). In fact, in a comparison of healthy infants and those requiring neonatal intensive care treatment at birth, biomedical birth risk factors were not significant predictors of intelligence at ages 3 to 8 years once home environment and SES were accounted for (Molfese, DiLalla, & Bunce, 1997). Low-income children are found to benefit from supportive and stimulating early environments, often in the form of formal child-care environments. More favorable cognitive and social-emotional outcomes in 378 African-American children, ages 6 to 9 years, was related to higher maternal intelligence, relatively supportive home environment as assessed by a short form of the HOME, and fewer siblings (Luster & McAdoo, 1994). In 161 children from low-income African-American families, cognitive development from 6 months to 8 years of age was supported by intensive early educational child care, responsive stimulating care at home, and higher maternal IQ (Burchinal et al., 1997). In this study, maternal IQ directly and indirectly affected outcome through its influence on family environment. Presence in child-care seems to promote school readiness in children with less educated mothers (Christian, Morrison, & Bryant, 1998).

The literature is inconsistent regarding whether or not home environment predicts variability in outcome over and above that predicted by income or SES, particularly for African-American children. In a longitudinal study assessing intellectual growth patterns in 122 Caucasian children between the ages of 3 and 6 years, both scores on the HOME and SES influenced the intelligence scores, with each variable having a differential effect on the intellectual growth patterns (Espy, Molfese, & DiLalla, 2001). The effects of home environment and maternal intelligence were comparable in their effects on receptive language of 1,336 children ages 3 to 5 years, although maternal intelligence was a stronger predictor than home

environment in the 6-8-year-old age group (Luster & Dubow, 1992). However, using the HOME, home environment was not found to add to the prediction of intelligence above that provided by SES for a group of African-American children (Johnson et al., 1993). Also, in the Luster and Dubow (1992) study, the percentage of variance in receptive language scores accounted for by maternal intelligence and home environment was considerably less for minority children, particularly for the African-American subsample, in the 3-5-year-old group only. Bradley, Corwyn, Pipes-McAdoo, and Garcia-Coll (2001) found that ethnic group differences on the short form of the HOME were accounted for by poverty status. Similarly, in a comparison of different income groups on the HOME, 41% of the variance in each sample was accounted for by income alone (Lotas, Penticuff, Medoff-Cooper, Brooten, & Brown, 1992).

Psychosocial variables, such as home environment, income, and SES should be considered when examining neuropsychological and academic outcome in any group. SCD generally affects urban-dwelling, African-American children of lower SES who are at-risk for psychosocial stressors in addition to living with a chronic illness. Results of studies examining neuropsychological outcomes should be interpreted with caution if demographic and psychosocial factors are not explicitly considered. Though the research is limited, the following section reviews information related to the effect of such variables on intellectual, cognitive, and academic outcomes in children with SCD.

1.3.2 Factors impacting outcome in children with SCD

Considering the effects of demographic and psychosocial factors on cognitive development in at-risk children, it is difficult for researchers to tease apart the role of illness-related and psychosocial factors on cognitive functioning in children with SCD. In addition to factors related to disease process, cognitive and academic performance in children with SCD can be affected by psychosocial factors such as socioeconomic status, opportunities for learning,

cultural issues, physical ability, increased family stress, frequent hospitalization, and the general impact of living with chronic illness (Brown, Armstrong, & Eckman, 1993). Highlighting the importance of considering such factors in cognitive outcome even in illnesses that impact the CNS, in children with HIV-1 infection, measures of home environment mediated the association between SES and child IQ (Coscia et al., 2001).

Research examining psychological and academic adjustment in children with SCD has been inconsistent, and may be related to problems with the identification of comparison groups and the strategies used to control group differences on demographic variables. In an attempt to address these limitations, Richard and Burlew (1997) compared academic performance of 42 children with SCD, ages 7 to 11 years, to 26 African-American children with no chronic illness who were similar on age, sex, and socioeconomic indicators, determined to be an appropriate comparison group. There was no significant difference between groups in terms of grades on mathematics or reading, scores on standardized tests, or grade retention. Both groups had high rates of absenteeism, had mean percentiles in math and reading that were below the national average, and had high rates of grade retention. These authors suggest that matching on age, sex, race, and socioeconomic status is the minimum criteria for selecting a comparison group; in this case it seems that these factors play a larger role in academic problems than the presence of SCD itself. The importance of selecting adequate comparison groups when assessing cognitive functioning is highlighted by Brooks-Gunn, Klebanov, and Duncan (1996), who found that differences in IQ scores between Black and White children were generally eliminated when economic and social differences (poverty, maternal education) were accounted for.

Some recent research has attempted to determine associations between various disease-related and psychosocial variables on cognitive outcome. In the Brown, Buchanan, et al. (1993) study, SES was moderately related to most neuropsychological and achievement measures and, when SES was controlled for, hemoglobin level was predictive of intellectual functioning, fine-

motor skills, and academic achievement. School absenteeism was not related to these outcomes. Thompson and colleagues (2002) assessed neurocognitive functioning in infants and toddlers with SCD and found that at 24 months of age, genotype accounted for 20% of the variance in cognitive functioning. The authors examined the effects of parenting risk, measured by the Hassles Scale (Kanner, Koyne, Schaefer, & Lazarus, 1981), the Knowledge of Infant Development Inventory (MacPhee, 1981), and the Brief Symptom Inventory (Derogatis & Melisaratos, 1983) and biomedical risk (SCD genotype and percentage hematocrit) on developmental outcome. When parenting risk was combined with biomedical risk, 42% of the variance in cognitive functioning was explained. This study highlights the individual and combined effects of biomedical and psychosocial factors on cognitive outcome in children with SCD.

Although the role of school absenteeism is not specifically relevant in a study assessing preschool-aged children, the fact that school absenteeism, which is associated with other indicators of disease severity (Shapiro et al., 1995), has not been found to be related to neuropsychological and academic outcome in children with SCD (Brown, Armstrong, & Eckman, 1993; Fowler, Johnson, & Atkinson, 1985; Knight, Singhal, Thomas, & Serjeant, 1995; Nettles, 1994) further supports the role of other psychosocial factors on functioning in these areas. For example, in a number of studies, socioeconomic factors have been found to have more of an impact on neuropsychological and academic outcome than did school absenteeism (Brown, Buchanan, et al., 1993; Fowler et al., 1985; Nettles, 1994).

Research with children with SCD is consistent with that examining cognitive and academic outcome in healthy children with demographic and psychosocial risk factors. The importance of accounting for these variables is highlighted. In addition, in order to determine needs for early intervention, it is essential to examine more specifically the role of these factors in the cognitive development of children with SCD in addition to the effects expected based on CNS

involvement. Thompson and colleagues (2002) provide a helpful model for examining the role of illness-related and psychosocial risk factors on cognitive development in these children.

Both children with SCD and their families are at-risk for difficulties with psychological adjustment related to dealing with chronic illness. Psychological adjustment of these children and families must be considered as a component of psychosocial risk factors that can affect academic, cognitive, and behavioral outcome. Results of the research outlined in the following section suggest an indirect impact of maternal adjustment on outcome in children with SCD.

1.4 Psychological Adjustment and SCD

1.4.1 Psychological effects of chronic illness

As a result of improved diagnostic procedures and better medical treatment, the prevalence of chronic illness in children is increasing; 10 to 20 percent of children are affected by chronic illness (Midence, 1994). A chronic illness is differentiated from acute illness in that chronic illness has a duration of 3 months or more, the diagnostic process is no longer of primary importance, it is managed over months to years, and parents and children assume significant responsibility for the management of the illness (Fritz & McQuaid, 2000). Children and their families adapt to and cope with this stress in different ways, and some illnesses impose disease-specific difficulties. There is a variable impact of chronic illness on adjustment in children and adolescents. The role of psychosocial factors appears to significantly contribute to adjustment beyond what is expected based on illness factors in children with SCD. In addition to the direct impact of a chronic illness on a child's adjustment, its impact on the psychological well-being of the family can further affect the adjustment of the ill child. Despite these risks, most children with chronic illness and their families appear to adjust to and cope effectively with the illness and related factors, indicating the importance of identifying a framework of resilience within families (Barakat & Kazak, 1999; Midence, 1994). Until recently, little attention has been focused on the

psychological adjustment of children with SCD and their families. However, illnesses that cause disability and/or affect the CNS place children at increased risk for problems (Midence, 1994). Cognitive impairments or poor developmental competencies may be risk factors in the adjustment of children with SCD (Casey, Brown, & Bakeman, 2000).

Chronic illness can impact psychological development in children and adolescents and can present a risk factor for psychopathology and adjustment problems (Cadman, Boyle, Szatmari, & Offord, 1987; Fritz & McQuaid, 2000). Models have been developed that attempt to account for illness specific parameters and common parameters that exist across illnesses. The most recent and most popular models of child and family adjustment to illness are based on the integration of child factors and social-ecological factors within a stress and coping framework of adaptation to illness (Barakat & Kazak, 1999; Kazak, 1997; Thompson, Gustafson, et al., 1999; Wallander & Varni, 1998). For example, Wood (1993) proposed a multilevel systems model of childhood illness that considers the interaction among these three sets of processes, with a focus on the bi-directional pathway by which family patterns and disease factors influence each other. Many studies that examine psychosocial adjustment in children with SCD and their families focus on developmentally-based psychosocial models that incorporate biological, environmental, and developmental factors.

The link between physical illness and behavioral functioning in childhood and adolescence is complicated by developmental issues; children at different stages of development have varied goals, expectations, and needs (Fritz & McQuaid, 2000). Failure to successfully achieve critical developmental milestones and address critical developmental needs can in turn affect adjustment later in development. Psychosocial factors associated with chronic illness can impact successful development of trust, social relationships, social competence, academic goals, autonomy, self-image, and romantic relationships.

1.4.1 Adjustment of children with SCD

The role of psychosocial factors, as opposed to factors related to disease severity, have been identified as playing a significant role in adjustment of children with SCD (Casey et al., 2000; Hurtig, Koepke, & Parks, 1989; Lemanek, Moore, Gresham, Williamson, & Kelley, 1986; Lutz, Barakat, Smith-Whitley, & Ohene-Frempong, 2003). A literature review of research examining the effects of psychosocial factors on adjustment and development of children and adolescents with SCD further supported the idea that variation in functioning does not appear to be related to illness severity (Telfair, 1994). Social variables, such as family demographics and resources, family structure, school environment, peer relationships, and the level of support and integration in the community have been found to affect adjustment in these children and their family members (Barakat & Kazak, 1999; Telfair, 1994).

Children with SCD are at-risk for problems in psychological adjustment, although there is evidence that many of these children are resilient in the face of risk factors (Lemanek et al., 1986; Lutz et al., 2003). In a comparison of psychosocial adjustment of children with SCD and cystic fibrosis (CF), Thompson, Gustafson, Gil, Godfrey, and Murphy (1998) found that anxiety disorders were the most frequently reported disorders for both sets of children, with a rate of 27.5% in children with SCD. Children with SCD were less likely to exhibit externalizing behaviors, although they reported higher levels of stress as compared to children with CF. A large portion of the variance in behavioral symptoms in children with SCD was accounted for by perceived stress and lower levels of self-worth. In an examination of data from 289 children with SCD (196 with HbSS and 93 with HbSC), ages 5 to 15 years, enrolled in the Cooperative Study of Sickle Cell Disease, Thompson, Armstrong, et al. (1999) found that 30% of the sample had at least one behavior problem as reported by the mother on the Child Behavior Checklist (CBCL; Achenbach & Edelbrock, 1983); 22% had reported internalizing behavior problems and 18% had

externalizing behavior problems. No significant differences were found on the CBCL in terms of gender, MRI status, or genotype.

As part of a larger study concerned with determining the interaction of medical, health, environmental, and adjustment variables, Hurtig and White (1986) examined the role of stress on adjustment in 50 children and adolescents with SCD, ages 8 to 16 years. Using multiple methods, results indicated that children have increasing adjustment problems as they get older, with boys more affected than girls and social adjustment more affected than personal adjustment. Due to the importance of determining children at-risk for adjustment difficulties, in a follow-up study, Hurtig, Koepke, and Parks (1989) attempted to determine the relationship between illness severity and adjustment in 70 children and adolescents with sickle cell disease, ages 8 to 16 years. The results of this study provided little support for the hypothesis that disease severity in children and adolescents would significantly predict psychosocial adjustment. Pain frequency was found to significantly predict school performance, but not intellectual functioning, and, consistent with previously discussed findings, SS hemoglobinopathy was related to reduced intellectual functioning. It should be noted that children with overt stroke were included in the sample. Factors such as gender and age appeared to have more of an impact on adjustment overall than did disease severity.

Lemanek and colleagues (1986) concluded that psychosocial factors, such as socioeconomic status, likely had more of an impact on adjustment in children with SCD than did illness factors. These authors looked at psychological adjustment in 30 children with SCD, ages 6 to 16 years, as compared to a group of 30 healthy controls. Although illness factors differed between the two groups, they had similar rates of psychological and behavioral problems, with both groups reporting more difficulties at home, in school, and with peers than the normative sample. Since SES was similar between groups, these authors hypothesized that this factor may play a larger role in psychological outcome than the presence of chronic illness, with ultimate

adjustment outcome resulting from an interaction between medical and environmental factors. All of these studies (Hurtig et al., 1989; Hurtig & White, 1986; Lemanek et al., 1986) included children with various types of SCD.

In terms of social adjustment, based on the reports of parents, teachers, and clinic staff members, and self-report measures, young children with SCD have been found to be as socially competent as healthy peers and their own perceptions of competence and acceptance were similar to that of healthy peers (Lemanek, Horwitz, & Ohene-Frempong, 1994). However, Boni, Brown, Davis, Hsu, and Hopkins (2001) found evidence that children with HbSS and history of CVA had deficits in social information processing which could lead to difficulties comprehending subtle and implicit cues that are inherent to social interaction. Rating scales completed by caregivers, teachers, and children indicated that the children in all groups had normal social and emotional functioning, indicating that subtle effects of problems in social information processing may not be noticed by others.

Although social adjustment is not significantly affected in children with SCD, there is variation in other aspects of psychological adjustment. Internalizing problems are the most common type of behavioral sequelae in children with SCD. SES has been identified as a factor that affects psychological adjustment in these children, while illness severity does not seem to account for the variation in adjustment. The next section will highlight the complex interaction between parental adjustment, family functioning, and child adjustment in families affected by SCD.

1.4.3 Role of maternal adjustment and family functioning

In addition to the effects of chronic illness on a child's functioning, many members within a family may be at-risk for problems in psychological functioning, and the functioning of the family can in turn impact the child's and family's adjustment to the illness

(Barakat & Kazak, 1999). Adaptational processes linked to adjustment include cognitive processes, coping methods, and family functioning. Several studies have aimed to identify types of adjustment problems in children with chronic illness and their mothers, identify adaptational processes associated with successful or problematic adjustment, and determine how adjustment and adaptation changes over time (Thompson, Gil, et al., 1994; Thompson et al., 2003; Thompson, Gustafson, Gil, Kinney, & Spock, 1999). Thompson, Gil, et al. (1994) followed 60 children with SCD, ages 7 to 17 years, and their mothers over 2 assessment periods, which were 8-16 months apart. The rate of poor maternal adjustment decreased from 37% to 28% and most mothers (55%) met criteria for good adjustment at both time periods. Those with stable poor adjustment had higher levels of daily stress and illness-related stress, used more palliative coping methods (emotion-focused, avoidance, wishful thinking, and self-blame factors), and had lower levels of family supportiveness as compared to mothers with stable good adjustment. Hierarchical regression analyses revealed that the variance in maternal adjustment at follow-up was accounted for by initial adjustment (47%), demographic factors (8%), and perceptions of daily stress (15%). For families of children with SCD, neither child adjustment nor illness severity significantly impacted maternal adjustment. This study highlighted the role of perceived daily stress on maternal adjustment in childhood chronic illness.

Thompson, Gustafson, et al. (1999) studied adjustment in 50 children with SCD (54% with HbSS), ages 7 to 16 years, and their mothers. The number of children with SCD that reported symptoms that met criteria for a DSM-III diagnosis declined over the 2-year assessment period from 56% to 42%. Internalizing disorders were the most frequently reported at each of three assessment points. Based on mothers' reports, the number of children with SCD with behavioral problems decreased from 72% to 59% over the three assessment periods. Psychological distress for mothers in the SCD group did not decline over time (increased from 30% to 41%). There was a substantial amount of variability in adjustment over time for both

children and mothers. Favorable maternal adjustment was related to lower levels of daily stress, less use of palliative coping, and lower illness-related stress. For children with SCD, demographic factors and poorer coping strategies was related to more self-reported behavioral symptoms, but no hypothesized adaptational processes at the initial assessment were related to adjustment at follow-up above that accounted for by demographic variables.

Family functioning, which is not necessarily stable over time, has been found to affect child and parental adjustment over the course of chronic illness (Barakat & Kazak, 1997). Thompson, Gil, et al. (1999) attempted to determine the contribution of family functioning and neurocognitive functioning to psychological adjustment in children with SCD. In a hierarchical multiple regression analysis, demographic and biomedical factors accounted for only 2-6% in total, internalizing, and externalizing behavior problem scores of the CBCL. MRI status and neuropsychological test results did not account for a significant portion of the variance of any of the composite scales. Conflicted family functioning accounted for 19% more of the variance in total behavior problems scores, 11% in internalizing behavior problems scores, and 20% in externalizing behavior problems scores. The contribution of family functioning could explain why the rates of internalizing and externalizing problems were similar in this sample, considering that children with chronic illness tend to present with more internalizing problems.

In a related study, Thompson and colleagues (2003) attempted to determine the role that intellectual functioning and family functioning had on psychological adjustment and level of behavior problems over 2 years in 222 children (150 with HbSS and 72 with HbSC), ages 5 to 15 years at the time of initial evaluation, who were part of the Cooperative Study of Sickle Cell Disease. These authors found that 9% of the children in the sample had consistent behavior problems over assessment periods as measured by the CBCL, a rate similar to that found in the normative group. Fifty-one percent of the sample was described as having consistently good adjustment over assessment periods. There were no significant changes in behavior functioning

and family functioning over the 2-year assessment period, and the risk of consistent behavior problems was higher in children with a higher baseline level of family conflict and lower in children with a higher baseline IQ score. These authors did not examine the relationship between family functioning and changes in IQ scores.

Despite potential difficulties in psychological adjustment, families have been found to be resilient in the face of many psychosocial barriers. For example, even though more than 90% of 85 patients with SCD were found to be living at or below the poverty level, with associated violence, transportation, and occupational concerns, 85% of the families attended every clinic appointment, were adhering to a prophylactic penicillin regimen, were complying with preventative care, and were appropriately using the ER for emergency visits (Basemore, Lewis, Chanda, & Fleming, 2002). The authors emphasized the importance of case management activities and support through care coordination in helping families remain compliant.

There is a complex interaction among presence of chronic illness, parental psychological adjustment, family functioning, child psychological adjustment, and demographic variables. Psychosocial factors, such as SES and family functioning, appear to affect outcome in children with SCD beyond what is explained by illness-related factors. Families and caregivers are at-risk for problems with psychological adjustment, which can in turn affect child outcomes. With support, families can be resilient in the face of psychosocial stress.

1.5 Summary

SCD is a genetic disorder that most commonly affects African-American children. Improvements in treatment and clinical care have extended the life span of children diagnosed with SCD. However, the disease is related to a large number of physiological, neuropsychological, and psychological risk factors. Compromised neuropsychological functioning can result from small and/or large vessel disease causing overt stroke, silent stroke,

and chronic anemia resulting in reduced oxygenation to the brain. The most common areas affected by SCD are the arterial borderzones (Pavlakis et al., 1988) and the frontal lobes or associated white matter (Schatz et al., 2001).

Most research examining neuropsychological outcome has been conducted with school-aged children and adolescents. Early studies only distinguished patients with and without overt stroke, without accounting for children with silent strokes. The finding of neuropsychological impairment in children with a history of overt stroke is consistent. These children have deficits and delays in various measures of language functioning (Cohen et al., 1994; Hariman et al., 1991) and general intellectual functioning (Hariman et al., 1991), with little evidence of motor dysfunction. Effects are partly dependent on lesion location. Children who have sustained anterior strokes have evidence of problems in attention and executive functions, while those with diffuse injuries have additional problems in visual spatial skills (Schatz et al., 1999).

The neuropsychological effects of SCD in the absence of overt stroke are not as well understood. Many physiological mechanisms can explain the risk for neuropsychological problems in the absence of overt stroke, including the presence of silent infracts, which do not correlate with measurable neurological changes but are apparent on neuroimaging. Positive neurological findings have been found in a subset of children without stroke in several studies (Steen et al., 1999; Wang et al., 1998). In a review, Schatz and colleagues (2002) found that children with SCD without overt stroke have IQ scores on average 4.3 points lower than comparison children, with cognitive effects increasing with age. Independent studies have also revealed that children with overt stroke have lower general intellectual functioning and deficits across multiple domains as compared to children with SCD and no overt stroke (Armstrong et al., 1996) or to healthy sibling controls (Bernaudin et al., 2000).

Although there have been a large number of studies examining neuropsychological outcomes in children with SCD without overt stroke, the studies employ various methodologies,

inclusion ages, and control groups. Although some studies have found that children with SCD have lower general intelligence scores (Swift et al., 1989; Wasserman et al., 1991), others have not found such a difference (Brown, Buchanan, et al., 1993; Fowler et al., 1988; Goonan et al., 1994). Children with SCD have been found to have lower scores on tests of achievement (Brown, Buchanan, et al., 1993; Fowler et al., 1988; Swift et al., 1989), measures of visual spatial or visuoconstructional skills (Fowler et al., 1988), and measures of attention or memory (Brown, Buchanan, et al., 1993; Fowler et al., 1988; Swift et al., 1989). Several studies have attempted to formally examine functioning in different neuropsychological domains, finding that children with SCD score more poorly across areas as compared to control children (Noll et al., 2001; Schatz et al., 2001). In the examination of sequelae associated with the presence of diagnosed silent infarcts, children with silent strokes perform more poorly on tests of general intellectual functioning (Wang et al., 2001), achievement (Armstrong et al., 1996; Wang et al., 2001), motor functions (Armstrong et al., 1996), attention (Wang et al., 2001), and individual verbal subtests (Armstrong et al., 1996; Bernaudin et al., 2000). Despite the lack of consistency across studies, there is evidence of common frontal lobe involvement and related deficits in attention and executive functions (Brown et al., 2000; DeBaun et al., 1998; Kral & Brown, 2002; Schatz et al., 2001; Watkins et al., 1998), a pattern similar to that found in adults (Sano et al., 1996). Children with SCD have also been described to have deficits in attention and executive functions on behavioral rating scales, with a prevalence of inattentive symptoms (Brouwers et al., 2002). Measures specific for these functions can be used to screen for the presence of neurological involvement.

Neuropsychological effects of SCD early in life are not well-understood. Few studies have examined neuropsychological and academic functioning in infants, toddlers, and preschoolers with SCD, despite evidence that structural brain changes are evident very early in life (Steen, Emudianughe, et al., 2002), and stroke is most common in 2-5-year-old children

(Kwiatkowski, 2002). There is evidence of early cognitive decline within the first 3 years of life in children with SCD (Best et al., 2002; Thompson et al., 2002), problems with auditory discrimination (Steen, Hu, et al., 2002), and problems with school readiness (Chua-Lim et al., 1993).

The lack of consistency regarding deficits across studies indicates the importance of considering factors that can mediate the relationship between SCD and neuropsychological functioning. In children without chronic illness, factors such as parental intelligence, socioeconomic status, and quality of home environment impact cognitive development in children in the areas of language (Hooper et al., 1998; Luster & Dubow, 1992; Molfese & Molfese, 2002; Payne et al., 1994), school readiness (Christian et al., 1998), and IQ (Espy et al., 2001; Sangwan, 2001). Family income seems to be a strong predictor of cognitive outcome (Lotas et al., 1992), although number of risk factors has been found to be more important than pattern of risk factors (Sameroff et al., 1993) in intellectual outcome. Appropriate child-care environments can positively affect outcome in at-risk children (Burchinal et al., 1997; Christian et al., 1998). The specific role of home environment in cognitive outcome seems less clear for African-American children (Johnson et al., 1993; Luster & Dubow, 1992), though vocabulary and grammatical development in African-American children has been found to be related to stimulating and responsive environments (Roberts et al., 1999). Factors such as maternal stress, parental education, income, and home environment also affect intelligence and early cognitive development in low-birth-weight children (Bacharach & Baumeister, 1998; Bohm et al., 2002; Bradley et al., 1993; Thompson, Goldstein et al., 1994), those requiring neonatal intensive care (Molfese et al., 1997), and children with HIV-1 (Coscia et al., 2001).

Considering the importance of psychosocial factors in cognitive outcome in many samples of children, it is essential to consider the role of these factors when assessing neuropsychological outcome in children with SCD. The rate of school absenteeism, which is

high in children with SCD due to pain episodes and infections, has not been found to be related to cognitive functioning (Brown, Armstrong, & Eckman, 1993; Fowler et al., 1985; Knight et al., 1995; Nettles, 1994). Although socioeconomic factors and other measures of disease severity have been found to be related to academic and cognitive outcomes (Brown, Buchanan, et al., 1993; Fowler et al., 1985) in children with SCD, others have not found support for the role of disease severity (Knight et al., 1995; Nettles, 1994). More studies that examine the individual and combined effects of illness-related and psychosocial risk factors are needed (Thompson et al., 2002).

One other area of concern appears to be the psychological adjustment of children with SCD and their families, although there is clear indication that many individuals are resilient to such problems (Midence, 1994; Thompson, Gil, et al., 1994; Thompson et al., 2003). Children with SCD appear to have few problems in social functioning (Boni et al., 2001; Lemanek et al., 1994). However, they are at-risk for adjustment problems, particularly internalizing behaviors (Thompson et al., 1998; Thompson, Gustafson, et al., 1999), which may be related to CNS involvement (Midence, 1994) and cognitive impairments (Casey et al., 2002). Illness severity has not been found to be an essential predictor of psychological adjustment in these children (Hurtig et al., 1989; Telfair, 1994; Thompson, Armstrong, et al., 1999), but SES has been found to be related to psychological adjustment (Lemanek et al., 1986). Models of adjustment that account for the interaction among biological, psychological and ecological factors are essential (Wood, 1993). Family members and caregivers of children with SCD are also at-risk for adjustment problems, and several studies have found that the quality of family functioning (Thompson, Armstrong, et al., 1999; Thompson et al., 2003) and daily stress (Thompson, Armstrong, et al., 1999; Thompson, Gustafson, et al., 1999) affects psychological adjustment. Higher levels of intellectual functioning were found to be associated with lower levels of behavior problems in a

prospective study of the impact of intellectual functioning and family functioning on psychological adjustment in children with SCD (Thompson et al., 2003).

The complex interaction of illness-related and psychosocial factors in SCD must be considered in the examination of all outcome measures. Due to compromise of the CNS in SCD, and evidence for early CNS involvement, it is important to determine early neuropsychological outcomes in SCD and to examine factors that affect such outcome. By identifying early processes of the disease, intervention programs can be implemented and measures can be developed to screen for risk of neurological complications. Since children with SCD can have neuropsychological dysfunction in the absence of MRI abnormality, it has been suggested that neuropsychological measures may be able to provide evidence for neurological involvement. However, the role of psychosocial factors, including psychological adjustment, in neuropsychological outcome, must be considered.

1.6 Current study

Currently, there is little research on neuropsychological functioning in very young children with SCD, and no published study that appropriately assesses functioning across specific domains in preschool-aged children with SCD. In addition, few studies that describe neuropsychological functioning in these children sufficiently account for the role of psychosocial risk factors on cognitive development. Although some researchers address the role of SES and parental IQ, the role of the quality of home environment has been largely ignored in this population.

One of the difficulties with examining neuropsychological functioning in preschool-aged children is the lack of available and valid measurements for particular skills. For example, studies of intellectual functioning in preschoolers are scarce, and many of the early tests developed were adapted from those designed for older children (Bracken & Walker, 1997). In

developing an assessment battery for preschool-aged children, it has been recommended that measures should be developmentally appropriate, have satisfactory normative data, and provide some degree of redundancy to account for variations in effort and attention (Hooper, 2000). Hooper (2000) described the development of a number of clinical and empirical neuropsychological assessment models that define relevant constructs for preschool children. In general, the models provide evidence for constructs that include skills related to motor and sensory functions, language, visual processing, memory and abstract thinking. None of the models describe a specific construct tapping components of attention. However, Gioia, Isquith, and Guy (2001) recommend a neuropsychological assessment battery with preschool children that assesses the following domains: general intellectual functioning, attention, language and language-related processing, visual/nonverbal processing, learning and memory, motor and sensory functions, academic skills, and social/emotional/behavioral functioning.

Although there is evidence of frontal lobe impairment in children with SCD, there are few established measures of attention and executive functions in young children, in part because there are few adequate theories of the early development of these skills and poor construct definition. Executive functions have been defined as an "umbrella construct for a collection of interrelated functions responsible for purposeful, goal-directed, problem-solving behavior" (Gioia et al., 2001, p. 320). Early theories indicated that executive skills did not become available until puberty, but recent studies have shown that even young children demonstrate the use of what we consider to be executive skills, although these skills are less differentiated and less sophisticated (Espy & Kaufmann, 2002; Gioia et al., 2001). Findings relating lesions to executive functions in children have mimicked findings in adult patients. For example, children ages 4 to 17 years with damage to the dorsolateral prefrontal cortex were more impaired on the WCST than children with damage to other areas of the frontal lobes, children with diffuse cerebral injuries, and children

with psychiatric illness, although there was no difference between groups on WISC-III performance (Filley, Young, Reardon, & Wilkening, 1999).

Although some researchers have assessed "executive functions" in young children using the Tower of Hanoi, Finger Sequencing Task, and the Tapping Test (Harvey, O'Callaghan, & Mahoy, 1999) and in infants using A-not-B and delayed response tasks (Espy & Kaufmann, 2002), there are few available, well-normed measures of executive functions in children under 5 years. Considering evidence for involvement of the frontal lobes in the pathophysiological effects of SCD, it is important to assess the development of skills such as attention and executive functions from early childhood. These developing skills, however, should be considered in terms of the "age-relevant functions with which they are intimately associated" (Gioia et al., 2001, p. 323), which indicates that executive control functions in early childhood would look behaviorally different than those in later childhood or adulthood.

Children with SCD are at-risk for neurocognitive and academic deficits associated with both complications related to the disease itself, and with demographic and psychosocial risk factors. It is important for clinicians and researchers to understand the neurological and neuropsychological effects of SCD in order to develop ways to screen for evidence of early neurological involvement and to determine appropriate targets for early intervention. Emphasis on pattern of functioning within groups of children with SCD would help to identify specific areas of vulnerability. Although SES has been found to be related to academic outcome in children with SCD, few studies have specifically addressed the role of psychosocial factors, especially home environment, in neuropsychological outcome in children with SCD.

The purpose of this study was to examine the effects of illness-related and psychosocial factors on neuropsychological functioning in preschool-aged children with SCD without overt stroke in order to identify risk factors and potential targets for preventive interventions. The goals of the study were to identify the presence of specific areas of neuropsychological deficits in

these young children and to determine the contributions of illness-related and demographic/ psychosocial risk factors to neuropsychological functioning. The following domains of neuropsychological functioning were examined: general intellectual functioning, language, memory/attention, visuospatial/visuoconstructional, and motor/visuomotor. Since attention and executive skills in young children are not well-defined resulting in few available measures of these functions in preschoolers, and to address the overlap of skills necessary for several groups of subtests, some skill areas were combined into a single domain.

The measure of disease severity is an important component in all studies assessing outcome in children with SCD. Usually, information about disease severity is collected retrospectively through the child's medical chart and/or interview with the child's parents. If a family does not comply with routine clinic visits, or if a family does not have a way of recording pain episodes that do not require hospitalization, these measurements are likely to be inconsistent or inaccurate. Children recruited for participation in the current study were drawn from participants in the Attributes of Sickle Cell Pain in Infants and Young Children study, a longitudinal, prospective grant-funded investigation. As part of several aims of this project, children receive routine blood draws, monthly phone interviews, and/or complete a daily pain diary (Ely et al., 2002). In this way, information about disease severity was systematically available for all study participants, often for several years prior to participation in the current study, allowing the use of prospective data to provide information used to predict current functioning.

There were three major hypotheses for this study. *Hypothesis 1:* Based on results of previous research (Best et al., 2002; Brown, Buchanan, et al., 1993; Fowler et al., 1988; Noll et al., 2001; Swift et al., 1989; Thompson et al., 2002; Wasserman et al., 1991), it was expected that the study sample would perform less well than normative groups on all measures of neuropsychological functioning.

Hypothesis 2: Based on findings from previous studies that children with SCD have problems with measures of attention and that frontal lobes are specifically vulnerable to the pathophysiological changes associated with SCD (Brown et al., 2000; Brown, Armstrong, & Eckman, 1993; DeBaun et al., 1998; Fowler et al., 1993; Kral & Brown, 2002; Schatz et al., 2001; Swift et al., 1989; Watkins et al., 1998), as well as findings that children with SCD and no overt stroke do less well on measures of Memory/Attention when compared to comparison children (Fowler et al., 1988; Noll et al., 2001) or siblings (Brown, Buchanan, et al., 1993; Swift et al., 1989), and that memory functioning decreases with age in young children (Best et al., 2002), it was expected that the study sample would have lower scores in the Memory/Attention domain as compared to scores in other cognitive domains.

Hypothesis 3: Based on inconsistent findings that cognitive outcome in children with SCD is related to disease severity in older children (Knight et al., 1995; Nettles, 1994) and literature that highlights the role of psychosocial factors in cognitive outcome in children with SCD (Brown, Armstrong, & Eckman, 1993; Fowler et al., 1985; Richard & Burlew, 1997) even in early life (Thompson et al., 2002), it was expected that psychosocial risk factors would significantly predict variability in neuropsychological performance over and above that predicted by illness-related risk factors.

CHAPTER 2: METHOD

2.1 Participants

Participants were recruited from patients enrolled in research studies associated with the NIH-funded Center Grant, Attributes of Sickle Cell Pain in Infants and Young Children, being conducted at the Marian Anderson Comprehensive Sickle Cell Center at St. Christopher's Hospital for Children in Philadelphia, PA. Initial recruitment for studies comprising this investigation occurred in 1998, when eligible children with SCD aged 4 years or younger were recruited, and ongoing recruitment occurs with families of children with SCD during the second or third teaching visit after the initial infant screening, or with families of children aged 4 years or younger who are new to the clinic. All information about the study is provided at regular clinic visits and data are collected at these visits, which occur every 3 months for children age 2 or younger, and every 4 months for children over 2.

Families of children between the ages of 3:0 and 5:11 who were enrolled in a study within this longitudinal grant-funded investigation were invited to participate in the proposed study. Children who met any of the following conditions based on file review and/or communication with clinic staff were excluded: history of overt stroke, documented mental retardation or other developmental delay, presence of acquired or congenital CNS insult (e.g. traumatic brain injury, tumor, epilepsy), presence of another major chronic illness in addition to SCD (e.g. cancer, diabetes), or non-English speaking parents.

Letters describing the study were sent to the parent or guardian of each eligible child. This letter included information about the purpose and design of the study, as well as informed families that they would receive a phone call regarding their participation in the study. A follow-up phone call was placed one to two weeks after the letter was sent, at which time the study was described in more detail. If a family was interested in participating in the study, an appointment to complete the study protocol was scheduled.

In all, letters were sent to 27 families. Twenty-five of these families were reached by phone. The other 2 families could not be contacted by phone or follow-up letter, and no up-to-date contact information was available. Of the 25 families that were contacted, all 25 were interested in participating. Twenty-three were deemed eligible and completed the study requirements. Of the two that were considered ineligible, one child was in foster care and the other did not speak or understand English. Participation rate of families that were contacted about the study was 92.6%. One child who participated in the study was unable to complete the Verbal subtests on the WPPSI-III and six additional tasks (Visual Attention, Phonological Processing, Sentence Repetition, Narrative Memory, Verbal Comprehension, Recognition of Pictures) due to severe speech and language delay and inability to persist with the testing. This child was unable to comprehend many instructions or to provide verbal responses longer than one word. The data for this child are not included in the sample description or investigation of hypotheses.

2.2 Measures

The following demographic information was collected from a parent: age and gender of the child, parental age, marital status, parental education, family income, parental occupation, number of primary caregivers, and number of children living within the home. All additional measures and associated variables are outlined in Table 1.

2.2.1 Illness-related risk factors

The following indicators of SCD severity were determined from the child's research file associated with studies in which they were already enrolled: SCD genotype, documented number of visits to hospital/ER in last 12 months, average of last 3 Hgb levels, documented number of pain episodes in last 12 months, and documented days of pain in the last 12 months. A severity

summary score was calculated as follows: (difference between 12.5 g/dL and average of last 3 Hgb levels) + (number of pain episodes in the last 12 months) + (number of visits to hospital/ER in last 12 months).

2.2.2 Psychosocial risk factors

The Family Environment Scale (Moos & Moos, 1981) was used to determine characteristics of family functioning. This scale consists of 90 true-false questions. Research has revealed that the items cluster into three empirically-derived factors in families of children with chronic illness and those specifically with SCD: Supportive, Conflicted, and Controlling (Kronenberger & Thompson, 1990; Thompson, Gustafson, et al., 1999). Although these subscales were calculated, in order to increase power and reduce risk of Type 1 error, an FES total score was calculated using a summary score discussed by Perrin, Ayoub, and Willett (1993). Their sample consisted of 187 children from 5 health status groups (including healthy, seizure disorders, cerebral palsy, and visible conditions like spina bifida or muscular dystrophy). The summary score was calculated as follows: (cohesion + expressiveness + active/recreational orientation + organization – conflict – control). Due to small sample size, factor analysis could not be conducted with the FES data in order to determine the reliability of this summary score. However, the FES is a widely used measure of family functioning.

The Pediatric Inventory for Parents (PIP; Streisand, Braniecki, Tercyak, & Kazak, 2001) was developed specifically as a measure of parenting stress related to caring for a child with a chronic illness. Although there is no research using this measure with parents of children with SCD, it has been found to be reliable and valid with a pediatric cancer population and is suggested to be broadly applicable to pediatric chronic illness (Streisand et al., 2001). Considering that parents of children with SCD are at-risk for problems in psychological adjustment and increased stress, and that illness-related stress in these parents can in turn affect

adjustment in both the parent and child, the PIP may be a useful measure in this population. This measure includes 42 items grouped together into the following scales: communication (e.g. speaking with doctor), emotional functioning (e.g. learning upsetting news), medical care (e.g. helping child with medical procedure), and role function (e.g. being unable to work/hold a job). Each item is rated by parents on a 5-point Likert-type scale as to the frequency of its occurrence and the level of difficulty associated with it. The frequency and difficulty scores were summed for each domain. The scale was considered to be reliable based on results of reliability analyses. Specifically, the Cronbach's alphas for the frequency subscales ranged from .69 to .85. The Cronbach's alphas for the difficulty subscales ranged from .66 to .86. A total frequency score and total difficulty score were calculated and used in the analyses.

In order to assess aspects of the home environment, a paper-and-pencil Home Environment Questionnaire was developed for the purposes of this study (see Appendix A). This questionnaire was based on the Home Observation for Measurement of the Environment (HOME; Caldwell & Bradley, 1984), one of the most widely used broad-scale measures of home environment. The HOME is an observation-based assessment designed to be conducted within the family's home. This scale has been validated for use with medically fragile infants and those with neurological impairment (Holditch-Davis, Tesh, David-Goldman, Miles, & D'Auria, 2000). Bradley and colleagues (1994) found that the factor structure of the Early Childhood HOME was similar for African-American and Caucasian families. Since home observations were not part of this current study, the Home Environment Questionnaire consisted of 11 questions translated from the interview items of the HOME-Short Form, plus 1 question asking about how often the parent reads him/herself for pleasure. Although not included in the score for the questionnaire, parents were also asked about family history of learning or reading problems. Aspects of parental responsiveness and physical environment included in the observation measure were not assessed, since this requires direct observation within the home. Reliability analyses revealed that the

internal reliability of the 12 items comprising the total score was .59. This suggested a moderate but acceptable level of reliability between items on this modified scale.

2.2.3 Neuropsychological outcome measures

All of the neuropsychological measures used are widely available, have been developed for use with preschool-aged children, and are up-to-date with fairly recent normative data available. Few studies have been published that describe neuropsychological functioning specifically in preschool-aged children with SCD. The neuropsychological measures used in this study were chosen because they assess similar areas of functioning as those assessed with older children with SCD, and normative data are available for children ages 3 to 5 years. As the performance of preschool children was compared across domains, an attempt was made to limit the tests used in the battery so as to limit the number of normative data against which these participants would be compared, and to keep the length of the battery sufficiently short as appropriate for preschoolers. The whole battery took 75-95 minutes to administer with the 3-year-old participants and 85-105 minutes to administer with the 4-5-year-old participants. Although few studies have developed constructs to assess specific neurocognitive domains to determine patterns of performance, more recent researchers have been utilizing these methods (Noll et al., 2002) and the examination of such domains have been recommended by others (Gioia et al., 2001). Therefore, the following domains were assessed in this study: general intellectual functioning, language, memory/attention, visuospatial/visuoconstructional, motor/visuomotor.

The Wechsler Preschool and Primary Scale of Intelligence – Third Edition (WPPSI-III; Wechsler, 2002) was used to evaluate the child's general intelligence. The standardization sample of the WPPSI-III included 1,700 children divided into 9 age groups, consisting of an equal number of male and female children in each age group. Five parent education levels were represented, ranging from 8 years or less to at least 16 years of education. In terms of diversity of

race and ethnicity, the proportion of each group was based on the US population according to the 2000 Census data; approximately 15% of the total standardization sample was African-American. Four core subtests were used with the 3-year-old children (Receptive Vocabulary, Information, Block Design, Object Assembly), which most children complete in 30-35 minutes. Seven core subtests were used with 4- to 5-year old children (Information, Vocabulary, Word Reasoning, Block Design, Matrix Reasoning, Picture Concepts, and Coding), which most children complete in 40-50 minutes.

The remaining domains were comprised of scores from a combination of subtests from the WPPSI-III, the NEPSY (Korkman, Kirk, & Kemp, 1988), and the Differential Abilities Scales (DAS; Elliott, 1990), as well as the Purdue Pegboard Test (Tiffin, 1968). The NEPSY is one of the first neuropsychological batteries developed for children (ages 3:0 through 12 years) based on a neurodevelopmental theoretical framework, which is well-normed, well-standardized, and has adequate reliability (Hooper, 2000). The standardization sample of the NEPSY included 1,000 children divided into 10 age groups, consisting of an equal number of male and female children in each age group. The sample represented 3 parent education levels, ranging from less than 12 years to at least 16 years of education. In terms of diversity of race and ethnicity, the proportion of each group was based on the US population according to the 1995 Census data; 15% of the total standardization sample was African-American. The NEPSY is comprised of various subtests that assess five major domains (attention/executive, language, sensorimotor, visuospatial, and memory and learning). It is designed to allow for use of individual subtests. The subtests used for this study, and the NEPSY domains in which they are included, were: Phonological Processing (language), Sentence Repetition (memory and learning), Narrative Memory (memory and learning), Visual Attention (attention/executive), Design Copying (visuospatial processing), and Visuomotor Precision (sensorimotor).

The DAS consists of a variety of tasks to assess cognitive and academic functioning in children and adolescents (ages 30 months through 17 years). The standardization sample of the DAS included 3,475 children and adolescents, which closely matched US Census data of 1985. The sample represented 4 parent education levels, ranging from less than 12 years to more than 16 years of education. In terms of diversity of race and ethnicity, the proportion of each group was based on the US population according to the 1985 Census data; 15.2% of the total standardization sample was African-American. Although few studies have examined its utility in use with preschool children, it seems to include valid measures of verbal and nonverbal functioning for preschool-aged children (Hooper, 2000) and the subtests have at least moderate reliability and adequate floors (Bracken & Walker, 1997). The subtests used for this study were Verbal Comprehension and Recognition of Pictures.

2.2.4 Order of administration

Each child was given the NEPSY Design Copying subtest first, followed by the WPPSI-III. In order to account for the effect of fatigue and length of the assessment on performance, the eight remaining subtests were divided and counterbalanced. This resulted in two different versions of the order in which the tasks were presented, which can be seen in Table 2. Each child was randomly given one of the two orders of presentation of assessment tasks.

2.2.5 Proposed neuropsychological domains

The proposed neuropsychological domains can be seen in Table 1. The proposed Language domain was comprised of scores from the Picture Naming subtest of the WPPSI-III and the Phonological Processing and Verbal Comprehension of the DAS. The proposed Memory/Attention domain was comprised of scores from the Sentence Repetition, Narrative Memory, and Visual Attention subtests of the NEPSY and the Recognition of Pictures subtest of

the DAS. The proposed Visuospatial/Visuoconstructional domain was comprised of scores from the Design Copying subtest of the NEPSY and the Block Design subtest of the WPPSI-III. The proposed Motor/Visuomotor domain was comprised of the Visuomotor Precision subtest of the NEPSY and the Purdue Pegboard Test.

2.2.6 Revised domain composition

Results of Cronbach's alpha reliability analyses shown in Table 3 suggested the need for alteration in the way that the proposed neuropsychological domains were comprised. Based on the differences between composite scores required for statistical significance at the p = .05 level presented by Wechsler (2002), 12 participants had statistically significant differences between their WPPSI-III Verbal and Performance Scale scores. In order to give more consideration to these IQ scores, as opposed to only the Full Scale IQ, the Verbal IQ and the Performance IQ were included as variables within the domain scores.

Correlation analyses revealed that the Phonological Processing subtest was not significantly correlated with the other measures included in the proposed Language domain. Theoretically, phonological processing skills, which are related to the development of reading and spelling skills, are not necessarily related to other aspects of expressive and receptive language. In addition, many children appeared to have difficulty with this task, possibly because the directions require a fairly sophisticated level of verbal comprehension that these young children had not yet acquired. Based on these factors, this subtest was not included in subsequent analyses. In addition, because the Verbal IQ score was correlated with Verbal Comprehension (r = .42, p = .056) and Picture Naming (r = .60, p = .007) and is comprised of language-related tasks, it was considered as a variable for the Language domain. When Verbal IQ was substituted for Phonological Processing, the Cronbach's coefficient alpha increased from -.22 to .65.

Because 4 children in the study were unable to adequately complete the Visual Attention task, it was dropped from the Memory/Attention domain, increasing the Cronbach's coefficient alpha for this domain from .51 to .66. Although some of the youngest children achieved a raw score of 0 on the Narrative Memory task, overall this measure appeared to be valid and was retained as part of the Memory/Attention domain.

The proposed Visuospatial/Visuoconstructional domain was comprised of the NEPSY Design Copying and WPPSI-III Block Design subtests. Children that had difficulty on the Design Copying subtest appeared to have problems holding and manipulating the pencil to draw. Problems did not seem to be visual-perceptual or spatial in nature, but motor and graphomotor. Because of this, the Design Copying subtest appeared to fit more appropriately with the Motor/Visuomotor domain, which is discussed below. The Block Design subtest alone was not considered to be an adequate representation of different aspects of visuospatial and visuoconstructional functioning. The Performance IQ score encompasses the Block Design score and other tasks that measure spatial processing, nonverbal reasoning, visual-motor integration (Wechsler, 2002), and integration and synthesis of visual information. Also, there were no other tasks included in the assessment battery that assessed these skills. Therefore, the Performance IQ was substituted as a representation of the Visuospatial/Visuoconstructional domain.

As mentioned above, the Design Copying subtest was considered as part of the Motor/Visuomotor domain. When this task was added to Visuomotor Precision and the 3 trials of the Purdue Pegboard Test, the Cronbach's coefficient alpha generally remained the same (.70 to.72), suggesting that the Design Copying task was related in some way to the other tasks in this domain. All three trials of the Purdue Pegboard Test were included due to variability within participants across trials. Despite variability within subjects, this test appeared to be valid and, when all trials were considered, it appropriately loaded with other motor tasks. In addition, the trial using both hands was significantly correlated with Full Scale IQ ($r = .59$, $p = .004$).

2.3 Procedures

An examiner met with the child and family in the child's home or at the outpatient clinic or inpatient unit at St. Christopher's Hospital for Children. At that time, the consent form was reviewed with the parent and any questions answered. In addition, the examiner explained to the child what he/she could expect from the testing session. Following the signing of the consent form, the evaluation was completed. If the child had difficulty separating from his/her parent, the parent was invited to sit in with the child during the neuropsychological testing. Each child was given a colorful sticker map during the evaluation on which he/she placed stickers of his/her choice at the completion of each task. The child kept this sticker map. Also, at the end of the evaluation, the child was allowed to choose from among several small, inexpensive prizes (e.g. crayons, PlayDough, reading books, and small toys).

Following completion of each evaluation, a short summary of the results was reviewed with a supervising pediatric neuropsychologist. The parent was provided feedback over the phone regarding these results and a written summary was sent to each family within 2-3 months of the assessment. All parents were encouraged to share this information with clinic staff. At the patient's next visit to the clinic, if the parent gave written permission, a copy of the evaluation results was placed in the medical chart.

2.4 Data Analyses

Preliminary descriptive analyses were conducted to examine the data for normal distributions and outliers. For all analyses, a p-value of .05 was used. Descriptive analyses were conducted in order to describe the study sample on demographic variables and illness-related risk factors.

To determine performance within neuropsychological constructs other than general intellectual functioning, each variable was represented by a standard score ($M = 100$, $SD = 15$).

The variables within each construct were summed and divided by the number of subtests in each domain, to yield one standard score per domain. General intellectual functioning was represented by the Full Scale IQ.

To test *Hypothesis 1*, that the study sample would perform less well than normative groups on measures of neuropsychological functioning, standard scores were compared with one-sample t-tests to a test value of 100, which represents the normative sample standard score mean. Standard scores of 90 to 110 were considered to be in the average range. Bonferroni correction was used in order to reduce the likelihood of Type 1 error. Z-score equivalents were used to represent how many standard deviations away from the mean each domain fell.

To test *Hypothesis 2*, that the study sample would have lower scores on the Memory/ Attention domain as compared to scores on other cognitive domains, the mean standard scores across domains were compared using one-sample t-tests. Bonferroni correction was used in order to reduce the likelihood of Type 1 error.

To test *Hypothesis 3*, that psychosocial risk factors would significantly predict variance in neuropsychological performance over and above that predicted by illness-related risk factors, preliminary bivariate correlation analyses were conducted to determine variables to include in subsequent analyses. In order to reduce the number of variables entered into the regression analyses and therefore reduce the likelihood of Type 1 errors in a small sample, only those variables that were significantly correlated with the neuropsychological domain standard scores were considered for the regression analyses. Two additional correlation analyses were conducted with the following variables representing (A) demographics and family structure and (B) parental/family functioning: (A) the total score of the Home Environment Questionnaire, parental marital status, maternal education, family income, number of primary caregivers, number of children living within the home, number of hours per week in day care/school, and history of reading/learning problems in family (Home Environment Questionnaire #13); (B) PIP frequency

score, PIP difficulty score, FES total score. In order to decrease multicolinearity and increase power, the variable(s) that was(were) most strongly representative of the factors within each correlation and/or the variables that were not correlated with the others were considered for entry into the regression analyses. Based on findings of previous studies (Johnson et al., 1993; Lotas et al., 1992), it was expected that the Home Environment Questionnaire would be highly correlated with demographic factors, particularly variables representing SES. If so, since psychosocial factors represented by the Home Environment Questionnaire can be targets for early intervention, it was to be included in the regression analyses.

Following preliminary correlational analyses, forced-entry hierarchical regression analyses were conducted for each domain. Since the aim of these analyses was to determine how much of the variance in neuropsychological functioning was accounted for by psychosocial variables above and beyond that accounted for by disease severity, disease severity was entered first into the regression, if applicable. Variable(s) from group (A) were entered next, as variables related to SES and home environment have been found to be strongly associated with neuropsychological outcome. Variables(s) from group (B) were entered last, as they were expected to have the least relative impact on neuropsychological outcome in these children.

CHAPTER 3: RESULTS

3.1 Description of Sample

3.1.1 Demographic characteristics

Table 4 lists the demographic characteristics of the study sample. The average age of the participants was 51.3 months (*SD* = 9.4, *range* = 40-70). Most of these children were male (72.7%), African-American (90.9%), and right-handed (81.8%). Fifty-five percent of the female guardians in the sample were married or partnered; 86.4% of the participants lived in a home with 2 or more adults. The specific role of the other adult(s) was not assessed. The mother or female guardian completed the forms in all but 2 cases (90.9%); fathers completed the forms in the other 2 cases. In the cases where fathers completed the forms, they were part of a 2-parent household where the mother was an active caregiver. Since only one female was not the mother of the participant (she was a grandmother), for the remainder of this discussion, "mothers" will include all female guardians. Because data on fathers and other secondary caregivers were not available for most participants, only maternal demographic data were considered in subsequent analyses. Mean maternal age was 31 years (*SD* = 7.7, *range* = 20-48). Most mothers (59.1%) completed some or all of high school. About 41% completed college or post-graduate work. Four participants (18.2%) had a yearly household income of less than $9,999. Most (40.9%) had a yearly household income of $20,000-$39,999. Only six (27.2%) had a household income of $40,000 or more; three of these (13.6%) had an income of $60,000 or more. Seventy-seven percent of the children attended a day care or preschool program outside of the home, for an average of 33.6 hours per week (*SD* = 11.1, *range* = 8-50). According to parent's report, most children in the study (85.7%) did not have a documented family history of learning or reading problems.

3.1.2 Illness-related characteristics

As shown in Table 5, about half of the participants (*n* = 12) had a genotype of HbSS. The others had a genotype of HbSC (*n* = 9) or Hbß$^{+}$Thal (*n* = 1). For group comparisons based on genotype, the child with Hbß$^{+}$Thal was included with those with HbSC, since disease severity for Hbß$^{+}$Thal is more similar to that of HbSC than HbSS (Bonner et al., 1999). Only five children (22.7%) had either a TCD or MRI test completed. These tests are not routinely conducted with very young children at the center from which these children were recruited. Older children were more likely to have had an MRI or TCD than younger children, as very young children often require sedation. Based on chart review, the results of the scans were unremarkable for all five children. Overall, the average of the last 3 hemoglobin levels for the sample was 9.56 g/dL (*SD* = 1.5, *range* = 6.8-11.8). The average number of hospitalizations in the past year was 1.50 (*SD* = 1.9, *range* = 0-7). Pain episodes were counted as the number of episodes documented in the form of monthly pain diaries or through a daily pager system. In general, this sample had an average of 3.2 pain episodes within 1 year of participating in the study (*SD* = 4.6, *range* = 0-14) with an average of 10.3 days of pain (*SD* = 15.3, *range* = 0-46). Undocumented pain episodes were not included, which likely led to an underestimation of pain episodes and days of pain.

The severity summary score was defined as the sum of the difference between 12.5 g/dL and the average of last 3 Hgb levels, the number of pain episodes in the last 12 months, and the number of visits to the hospital/ER in last 12 months. Although the Cronbach's alpha for these variables was only .15, it may be that these factors represent different aspects of the disease process. Since these variables are used in some combination in the literature to represent SCD severity (Boni et al., 2001; Brown, Buchanan, et al., 1993; Knight et al., 1995; Thompson et al., 2002; Thompson et al., 2003), the severity summary score was used as proposed.

A comparison of illness-related factors for the HbSS and HbSC/Hbß$^{+}$Thal groups is shown in Table 6. Children with HbSS had significantly lower hemoglobin levels ($F(1,20) = 3.77$, $p = <.001$), significantly more hospitalizations in the year prior to participation ($F(1,20) = 4.29$, $p = .020$), and a significantly higher summary severity score ($F(1,20) = .17$, $p = .032$) than the children with HbSC/ Hbß$^{+}$Thal. This was consistent with the expectation that SCD would be more severe in children with the HbSS genotype.

3.1.3 Psychosocial functioning

Table 7 shows summary scores for the psychosocial questionnaires. The mean total FES score for this sample was 119.4 (*SD* = 24.9, *range* = 74-164). The range was more limited than that reported by Perrin and colleagues (1993), which was 6 to 192. Although not considered in subsequent analyses, the mean Supportive, Conflicted, and Controlling summary scores were 262.1 (*SD* = 26.3, *range* = 223-321), -70.8 (*SD* = 17.2, *range* = -101- -36), and 125.8 (*SD* = 19.3, *range* = 86-157), respectively. The means for the Supportive and Controlling scores were fairly comparable to those reported by Kronenberger and Thompson (1990) from a sample of chronically ill children, which were 248.4 (*SD* = 42.9) and 116.5 (*SD* = 24.4), respectively. However, scores on the Conflicted scale suggested lower conflict in the current sample than that reported by Kronenberger and Thompson (*M* = 55.3, *SD* = 29.1). The FES total score and factors structures referred to here were developed based on chronically ill children. In regard to the subscales used to calculate the FES total score, this sample reported slightly more cohesion and organization and slight less conflict and active-reactive orientation than that reported by an African-American and Latino adult normative group (Moos & Moos, 1981). The reported levels of expressiveness and control appeared similar.

The PIP frequency total for this sample was 99.6 (*SD* = 21.9, *range* = 52-145) and the difficulty total was 86.0 (*SD* = 22.7, *range* = 43-135). In a pediatric oncology sample, Streisand

et al. (2001) reported a reverse relationship between frequency and difficulty, reporting a frequency total of 94 (33.3) and a difficulty total of 112.4 (35.1). There is no normative data for the PIP, as many items on the scale are specific to illness-related events. The average score on the Home Environment Questionnaire was 25.0 (*SD* = 5.8, *range* = 15-38). As this questionnaire was developed for this study, no comparison could be made with other published data.

3.1.4 Sample representativeness

There were 34 additional preschool-aged children, being treated at the Marian Anderson Sickle Cell Center, who were not enrolled in this study. Some of these 34 children were not eligible and/or not enrolled in the longitudinal grant-funded research study from which this sample was recruited. One was the twin sibling of a child whose data were used for this study, and therefore was not formally included in this study. When gender and genotype information for these 34 children was added to that of the 22 children described above, 36 of the total population were male (64%) and 34 had HbSS (61%). This study sample had a relatively higher male:female ratio and a lower HbSS:HbSC ratio when compared to the general preschool-aged population treated at the clinic from which these children were identified. No formal data were available regarding maternal education and income of those children not enrolled in this study (E. Ely, Ph.D., personal communication, February 2004).

3.1.5 Neuropsychological functioning

The scores for the neuropsychological measures were converted to standard scores (*M* = 100, *SD* = 15). Table 8 describes the results of neuropsychological assessment, including Full Scale IQ and domain scores, as well as Verbal and Performance IQs and individual subtest scores. Although the NEPSY Phonological Processing and Visual Attention tasks were not included in the domain scores, data for these subtests are also presented. Mean Full Scale IQ was

89.6 (*SD* = 9.1, *range* = 74-105). The mean standard scores for the Language, Memory/ Attention, Visuospatial/Visuoconstructional, and Motor/Visuomotor domains were 88.1 (*SD* = 9.3, *range* = 70-105.7), 94.9 (*SD* = 10.3, *range* = 75-108.7), 89.7 (*SD* = 10.6, *range* = 70-105), and 87.7 (*SD* = 8.9, *range* = 72.2-105.6), respectively.

Children who completed version A of the presentation order of test measures had significantly lower scores on the Visuospatial/Visuoconstructional domain ($F(1,18) = .15$, $p = .039$). However, the WPPSI-III was given at the same time in the beginning of the assessment to all children. Therefore, the difference in the scores representing the Visuospatial/ Visuoconstructional domain, which was represented by WPPSI-III Performance IQ, was not due to assessment order. Order of assessment was not considered in subsequent analyses.

3.1.6 Testing environment

Fifteen of the participants (68.2%) were assessed solely in their home. Four participants completed the assessment in the outpatient clinic and one while an inpatient in the hospital. The latter was hospitalized two days prior to the assessment for fever and acute chest syndrome; at the time of the evaluation, he was deemed able to participate. The remaining two participants were assessed on two separate occasions; one session occurred in the outpatient clinic and testing was completed on another day in their homes. In this case, quality of testing environment was rated as "average" in both environments. Ten of the participants were given version A and eleven were given version B of the assessment orders. The remaining participant was not presented tasks in either specific order. He was assessed over two sessions and, due to fatigue, the assessment order was altered. The quality of the testing environment was measured using a scale comprised of the following descriptions: optimal, good, average, poor, or detrimental. The testing environment was deemed optimal in 22.7 percent of cases and average/good in 77.3 percent of cases. Since most participants were tested within their homes, the quality of the testing environment was

generally affected by the presence of other family members near the location in which testing occurred, or by telephone calls. Validity of testing was not considered to be compromised by the testing environment in any of the cases, as testing was paused, as necessary, if interruption occurred.

3.1.7 Missing data

Eighteen children (82%) validly completed all tasks presented to them. Three of these children were not given the Picture Naming subtest because of examiner error. The 5 remaining children (23%) did not complete at least one test measure. The children who had difficulty completing one or more tasks were among the youngest in the sample (age = 40-44 months). Individual tasks were considered invalid if it appeared that the child was not sufficiently attending to the task or if he/she could not comprehend the instructions in a way that would allow him/her to appropriately approach the task. One child could not complete the Narrative Memory task because of speech/language difficulties. Two children were not able to adequately understand and follow instructions for the Visual Attention task; one of them also could not complete the Visuomotor Precision task for the same reason. One child did not complete four tasks (Visuomotor Precision, Visual Attention, Verbal Comprehension, Recognition of Pictures) because of very poor attention and waning persistence with testing and a Block Design score could not be calculated because of examiner error. As discussed in section 2.2.6, the Visual Attention task was dropped from the Memory/Attention domain score.

Based on data analyses conducted in June 2003 for the Center Grant study regarding compliance over time with pain data collection methods, there was 91% compliance with 49 participants over 22 months for the monthly phone calls (E. Ely, Ph.D., personal communication, February 5, 2004). Pain data for this study were determined mostly from monthly phone calls. Compliance for the paper diary and electronic pager system as of June 2003, 86.25% and 95%

respectively, was also acceptable. There were no or minimal missing data for the 22 children enrolled in this study. However, for one participant, who had not been seen at the clinic for over 1 year and who did not participate consistently in the pain data collection, no pain data were available.

3.2 Preliminary Analyses

T-tests and correlation analyses were conducted in order to determine which demographic, illness-related, and psychosocial variables were related to neuropsychological functioning and would be considered for entry in regression analyses.

T-tests were conducted to compare performance on neuropsychological domains between groups represented by categorical variables. These analyses revealed that performance on neuropsychological measures was not related to genotype, gender, whether or not MRI or TCD was performed, marital status (married/partnered vs. single/divorced), or whether or not children attended school/day care. Those with a family history of learning or reading problems had significantly better scores on the Memory/Attention domain (M = 102.1, SD = 2.0) than those with no family history (M = 93.8, SD = 11.0; $t(1,17) = 2.80$, p = .012). However, the group with a family history was very small and the variances between groups were unequal, so interpretation of these results is cautioned.

Correlation coefficients were computed to examine which demographic, illness-related, and psychosocial variables were significantly correlated with neuropsychological outcome measures and would be included in the regression analyses. Since mother's education and family income were so highly correlated with one another (r = .70, p = <.001), a composite score representing the sum of the scores for maternal education and family income was used in the subsequent correlation analyses. The variables used in the correlation analyses were as follows: 1) Neuropsychological measures: Full Scale IQ, Language score, Memory/Attention score,

Visuospatial/Visuoconstructional score, Motor/Visuomotor score, 2) Illness-related factors: severity summary score, and 3) Demographic and Psychosocial factors: education/income composite, child age, maternal age, number of adults living in home, number of children living in home, number of hours per week in school or day care, FES Total score, PIP frequency total, PIP difficulty total, Home Environment Questionnaire total score.

The severity summary score was not significantly correlated with any of the neuropsychological summary measures (see Table 9). Table 10 shows the correlation coefficients for the examination of the relationships among neuropsychological measures and psychosocial factors. Maternal education/income was significantly correlated with Full Scale IQ (r = .66, p = .001) and the Language (r = .66, p = .003) and Visuospatial/Visuoconstructional (r = .58, p = .005) domain scores. Number of children living in the home was significantly negatively correlated with the Motor/Visuomotor domain score (r = -.77, p = <.001). Number of hours per week in school or day care was significantly correlated with the Language domain score (r = .55, p = .022). The PIP total difficulty score was significantly negatively correlated with the Visuospatial/Visuoconstructional (r = -.47, p = .034) and the Motor/Visuomotor (r = -.47, p = .035) domains. Trends were noted in the relationship between maternal education/income and the Memory/Attention domain (r = .56, p = .011) and in the negative relationship between number of children living in the home and Full Scale IQ (r = -.39, p = .069). In addition, the correlation coefficients representing the relationships between the PIP total difficulty score and Full Scale IQ (r = -.41, p = .057) and the Language domain (r = -.44, p = .065) suggested trends. The following variables were not significantly correlated with any of the neuropsychological domain scores: child age, maternal age, number of adults living in the home, total FES score, PIP frequency total, and the Home Environment Questionnaire total score. Based on the results of these correlation analyses, the following variables were considered for examination of Hypothesis 3: maternal

education/income composite score, number of children living in the home, hours per week in day care or school, and PIP difficulty total score.

Table 11 shows the correlation coefficients for the variables related to family structure and demographics (Group A). None of the variables were significantly correlated with the neuropsychological outcome measures. However, the Home Environment Questionnaire was significantly correlated with maternal education/income, such that families with higher maternal education/income had better home environments (r = .45, p = .043). In order to determine whether mediation analyses were indicated, a partial correlation analyses was conducted to assess the relationship between maternal education/income and the neuropsychological measures while controlling for the Home Environment Questionnaire total score. Maternal education/income was still significantly correlated with Full Scale IQ (r = .78, p = .001), the Language domain score (r = .75, p = .001), and the Visuospatial/Visuoconstructional domain score (r = .59, p = .022) when controlling for the contribution of the Home Environment Questionnaire total score. A trend was noted in the relationship between maternal education/income and the Memory/Attention domain score (r = .49, p = .061). Therefore, the maternal education/income composite score was considered independently in subsequent regression analyses and mediation was not considered.

The measures assessing parental distress (PIP) and family functioning (FES) were not significantly correlated with each other (see Table 12). Although there was a significant relationship between the PIP Frequency and PIP Difficulty scores (r = .77, p = <.001), only the PIP Difficulty score was significantly correlated with some of the neuropsychological outcome measures and was included in subsequent regression analyses.

3.3 Hypothesis 1

Hypothesis 1 stated that the study sample would perform less well than normative groups on measures of neuropsychological functioning. In order to decrease the likelihood of

capitalizing on chance, a Bonferroni procedure was used; therefore, findings were considered significant if $p < .01$ (.05/5). Although all scores were below the normative sample mean of 100 (See Table 8), scores for the Full Scale IQ, the Memory/Attention domain, and the Visuospatial/ Visuoconstructional domain fell within the average range and within .70 standard deviations of the normative mean. Scores for the Language domain and the Motor/Visuomotor domain were in the low average range; z-scores were -.73 for both domains. One-sample t-tests using 100 as the test value indicated that the sample performed significantly lower than the normative sample mean on Full Scale IQ ($t[21] = -5.32$, $p < .001$) and the Language ($t[17] = -5.44$, $p < .001$), Visuospatial/Visuoconstructional ($t[20] = -4.46$, $p < .001$), and Motor/Visuomotor ($t[19] = -6.18$, $p < .001$) domains. Although not statistically significant, a trend was noted with the Memory/Attention domain ($t[19] = -2.23$, $p = .038$). Hypothesis 1 was supported.

3.4 Hypothesis 2

Hypothesis 2 stated that the study sample would have lower scores in the Memory/ Attention domain as compared to scores in other cognitive domains. A Bonferroni procedure was used; therefore, findings were considered significant if $p < .01$ (.05/5). Contrary to this hypothesis, the sample performed best on tasks comprising the Memory/Attention domain as compared to performance in other domains. One-sample t-tests comparing the mean score of the Memory/Attention domain to the mean scores of all other domains indicated that the sample scored significantly better on the Memory/Attention domain than on the Language ($t[17] = -3.11$, $p = .006$) and Motor/Visuomotor ($t[19] = -3.61$, $p = .002$) domains. In addition, although not statistically significant, the differences between the Memory/Attention domain score and the Full Scale IQ ($t[21] = -2.70$, $p = .013$) and Visuospatial/Visuoconstructional domain score ($t[20] = -2.26$, $p = .035$) suggested trends. Hypothesis 2 was not supported.

3.5 Hypothesis 3

To test Hypothesis 3, that psychosocial risk factors would significantly predict variability in neuropsychological performance in addition to that predicted by illness-related risk factors, four forced-entry hierarchical regression analyses were conducted. Variables that were not significant based on correlational analyses, but suggested trends, were also included in the regression analyses. Since so few variables were included in the regression analyses, each variable was entered in an individual step. Because only one examined variable, maternal education/income composite score, was correlated with the Memory/Attention domain score, no regression analysis was conducted for this domain. As noted previously, the correlation coefficient representing the relationship between maternal education/income and the Memory/Attention score was .56 (p = .011).

Tables 13-16 show the results of regression analyses for Full Scale IQ, Language, Visuospatial/Visuoconstructional, and Motor/Visuomotor domains, respectively. A p-value of 0.05 was used to represent significance. Based on the results of correlation analyses described above, the following variables were entered into a forced-entry hierarchical regression analysis for Full Scale IQ: (step 1) maternal education/income composite score; (step 2) number of children living in the home; (step 3) PIP difficulty total score. The regression model was significant (R^2 = .51, F(3,18) = 6.15, p = .005). Only maternal education/income, which accounted for 43% of the variance in Full Scale IQ, contributed significantly to the model (B = .55, p = .007). Number of children living in the home (B = -.24, p = .193) and the PIP difficulty total score (B = -.13, p = .503) did not contribute significantly to the model.

The following variables were entered into a forced-entry hierarchical regression analysis for the Language domain score: (step 1) maternal education/income composite score; (step 2)

hours per week in day care or school; (step 3) PIP difficulty total score. The overall regression model was significant (R^2 = .51, F(3,13) = 4.47, p = .023). Although maternal education/income accounted for 44% of the variance in the Language domain score, once all variables were entered, neither maternal education/income (B = .27, p = .451), hours per week in day care/school (B = .30, p = .260), nor PIP difficulty total score (B = .29, p = .343) contributed significantly to the model. When only maternal education/income was entered (step 1), it contributed significantly (B = .66, p = .001). When hours per week in day care or school was added (step 2), maternal education/income no longer contributed significantly to the model (B = .52, p = .054). Based on the decrease in beta for maternal education/income after number of hours per week in day care/school was added to the equation, a mediational role was considered. However, the relationship between maternal education/income and number of hours per week in day care/school (r = .21, p = .369) was not significant. In addition, although the beta for maternal education/income further decreased when the PIP difficulty total score was added to the equation, the PIP difficulty total score was not significantly correlated with maternal education/income (r = -.40, p = .062) or hours per week in day care/school (r = -.31, p = .166). Therefore, the conditions to test for mediation were not met (Holmbeck, 2002).

The following variables were entered into a forced-entry hierarchical regression analysis for the Visuospatial/Visuoconstructional domain score: (step 1) maternal education/income composite score; (step 2) PIP difficulty total score. The regression model was significant (R^2 = .38, F(2,18) = 5.60, p = .013). Only maternal education/income, which accounted for 34% of the variance in the Visuospatial/Visuoconstructional domain score, contributed significantly to the model (B = .47, p = .040). The PIP difficulty score did not contribute significantly to the regression model (B = -.24, p = .280).

Finally, the following variables were entered into a forced-entry hierarchical regression analysis for the Motor/Visuomotor domain score: (step 1) number of children living in the home;

(step 2) PIP difficulty total score. The regression model was significant (R^2 = .66, F(3,16) = 16.77, p = <.001). Only number of children living in the home (B = -.69, p = <.001), which accounted for 59% of the variance, contributed significantly to the model. The PIP difficulty total score (B = -.29, p = .062) did not contribute significantly to this regression model.

3.6 Follow-up Analyses: Further Examination of the PIP

As reported, the PIP difficulty total score was significantly correlated with performance on the Visuospatial/Visuoconstructional and Motor/Visuomotor domains. In order to reduce the number of analyses conducted and to increase power, specific subscale scores were not considered in the primary analyses. Follow-up analyses were conducted in order to examine the relationship between specific PIP subscales and neuropsychological outcome measures. Such analyses could provide important information when considering implications of study results. Follow-up correlation analyses examining the relationship between PIP difficulty scores on individual subscales and neuropsychological measures indicated that the Communication scale difficulty score was significantly correlated with Full Scale IQ (r = -.43, p = .049), and the Language (r = -.50, p = .034) and Visuospatial/Visuoconstructional (r = -.52, p = .016) domain scores. The relationship between the PIP Communication scale difficulty score and the Motor/Visuomotor domain score suggested a trend (r = -.44, p = .051). None of the other difficulty subscales were significantly correlated with the neuropsychological outcome measures.

CHAPTER 4: DISCUSSION

In 1993, Brown, Armstrong, and Eckman recommended that "future studies need to obtain psychometrically sound, clinically and educationally relevant data on the cognitive and neuropsychologic processing of children with SCD from preschool through adolescence" (p. 42). Until this time, there has been limited investigation of neuropsychological functioning in very young children with SCD. Even today, few studies examining neuropsychological sequelae of SCD systematically account for the role of psychosocial factors. The goal of this study was to describe functioning across a number of cognitive domains in preschool-aged children with SCD. This study also aimed to examine the contributions of illness severity factors as well as psychosocial factors to neuropsychological functioning. In sum, the children in this study performed less well across measures of intellectual and neuropsychological functioning as compared to normative samples, with relatively consistent functioning across domains. Psychosocial factors, particularly maternal education and family income, appeared to play a more significant role in predicting variance in neuropsychological performance than did disease-related factors. These findings, which will be discussed in detail below, highlight the difficulties in conducting research with this population, the challenges associated with assessing very young children, the need for more appropriately defined neuropsychological constructs with a developmental perspective, and the need for further investigation regarding the effects of sickle cell disease process on early brain development. Most importantly, the results of this study provide support for early and ongoing neuropsychological assessment in this population and intervention programs that address the role of environmental factors on development.

4.1 Review of Results

4.1.1 Hypothesis 1

The literature describing neuropsychological functioning in children with SCD, which has mostly been conducted with school-aged children, suggests deficits and delays in neuropsychological functioning, often related to stroke status (Armstrong et al., 1996; Bernaudin et al., 2000; Brown, Buchanan, et al., 1993; Cohen et al., 1994; Fowler et al., 1988; Hariman et al., 1991; Schatz et al., 1999; Schatz et al., 2002; Steen et al., 1999; Swift et al., 1989; Wang et al., 1998; Wang et al., 2001; Wasserman et al., 1991). Deficits have also been found in very young children with SCD (Best et al., 2002; Chua-Lim et al., 1993; Steen, Hu, et al., 2002; Thompson et al., 2002). Based on the extant literature, it was expected that neuropsychological functioning of the current sample would be significantly below that of normative samples. Compared to a mean standard score of 100, which was assumed to represent average functioning in a group of typically developing children, general intellectual functioning and performance across all domain scores fell significantly below this normative sample mean. However, scores fell within the average to low average range. Specifically, scores for the Full Scale IQ, the Memory/Attention domain, and the Visuospatial/Visuoconstructional domain were within the average range. The mean scores for the Language and Motor/Visuomotor domains fell in the low average range, and were .73 standard deviations below the normative sample mean.

Although the current study did not include a comparison group, the performance of children in this sample can be compared to that published in the literature examining neuropsychological functioning in children with SCD without overt stroke. For example, in a meta-analysis, Schatz and colleagues (2002) found that school-aged children (mean age = 9.2 – 12.4 years) and adolescents (15 – 18 years) with SCD without overt stroke had IQ scores, on average, 4.3 points lower than comparison children, with cognitive effects increasing with age. The weighted grand mean IQ in the studies included in this meta-analysis was 86.4 for children

with SCD and 90.7 for comparison children. The effect size was considered to be small. Therefore, an equivalent 4-point difference would not be considered significant in an individual study without a very large sample and it is not clear how clinically meaningful this difference is. The mean Full Scale IQ of 89.6 that was achieved in the current study is more comparable to the comparison group described by Schatz et al. than the SCD group, although it was only several IQ points different than the mean score of the SCD groups. Maternal education of this study sample was higher than that found in other described SCD samples (Thompson et al., 2002; Thompson et al., 2003). Although maternal education was similar to that described by Brown et al. (2000), the income of this study sample was higher. These differences may play a role in terms of the higher IQ found in this study as compared to that described by Schatz and colleagues. In a large sample of children participating in the Cooperative Study of SCD with parental education similar to that described in the current study, children without MRI abnormality had an average IQ consistent with that found in the current study (Armstrong et al., 1996; Thompson et al., 2003).

The suggestion that neuropsychological functioning of children in the current study is more consistent with that of control groups than school-aged children with SCD may be related to the age of the sample. That is, disease-specific effects on general intellectual functioning in the absence of stroke may not be apparent at this young age, such that other factors account for below-average performance. Another factor that may account for higher than expected scores is that other studies are comprised of samples that include more children with SS than SC (Brown, Buchanan, et al., 1993; Brown et al., 2002; Steen et al., 2001; Thompson et al., 2002), and therefore may include children with more severe disease. In fact, studies examining school readiness in very young children with SCD only included children with SS (Chua-Lim et al., 1993; Steen, Hu, et al., 2002), and therefore may have been more likely to find disease-related problems.

The extent of neurological abnormality in this study sample could not be determined, as most of the children have not had neuroimaging studies. However, neuropsychological performance in this sample was consistent with that demonstrated by the children without MRI abnormality described by Armstrong et al. (1996). This, in addition to the lack of significant relationships between disease severity measures and neuropsychological outcome, may suggest that this sample had little measurable disease-related neurological changes.

Although it is possible that disease-related effects are not apparent in preschoolers with SCD, other factors and study limitations, such as sample size, representativeness, and measures used, may have affected the ability to detect true disease-related deficits. These limitations will be discussed in more detail below. In addition, the difference described by Schatz et al. (2002) is small and, although statistically significant, it may not be very clinically meaningful. However, similarities between IQ scores of this sample and control groups highlights the fact that the below-average performance in this study is consistent with performance achieved by other African-American populations without SCD. For example, in an examination of 5-year-old African-American children, Brooks-Gunn, Klebanov and Duncan (1996) found that black children perform about .75 to 1 standard deviations lower than white children on tests of cognitive functioning and school readiness. Although their sample consisted of premature, low birthweight children, their findings suggested that family income and environmental factors were predictive, such that performance was consistent with that expected in a similar sample of normal birthweight children. The relative role of environmental factors on neuropsychological functioning in this sample will be discussed below in a review of the findings of Hypothesis 3.

4.1.2 Hypothesis 2

Like several other published research studies (Brown, Buchanan, et al., 1993; Brown et al., 2000; Noll et al., 2001; Schatz et al., 1999; Schatz et al., 2001; Wasserman et al., 1991), the

current study attempted to formally define and examine functioning within different neuropsychological domains in children with SCD. Of these reviewed studies, only Noll and colleagues (2001) report Cronbach's alpha, item-total correlations, and results of factor analyses in determining the neuropsychological constructs that they used. Although the sample size in the current study was not large enough to allow for factor analyses, reliability analyses were conducted and these results were used to modify the variables representing proposed domains. The initially proposed domains, which were discussed with two pediatric neuropsychologists, were developed based on the constructs thought to be measured by specific tests.

The literature suggests that the frontal lobes are specifically vulnerable to the effects of SCD, leading to relatively poor performance on tasks associated with frontal lobe functioning (Brown et al., 2000; Brown, Armstrong, & Eckman, 1993; Brown, Buchanan, et al., 1993; DeBaun et al., 1998; Fowler et al., 1988; Fowler et al., 1993; Kral & Brown, 2002; Noll et al., 2001; Schatz et al., 2001; Swift et al., 1989; Watkins et al., 1998). In addition, there is some suggestion that young children with SCD have decreases in performance on memory tasks over time (Best et al., 2002). The hypothesis that participants would perform relatively less well on the Memory/Attention domain as compared to the other domains was not supported. In fact, performance on the Memory/Attention domain was significantly higher than that achieved in the other domains. Although these differences were statistically significant, they did not seem to be clinically meaningful. That is, despite the large number of participants that had a significant split between Verbal and Performance IQ suggesting variability in performance within subjects, there was little meaningful difference between mean scores across neuropsychological domains. Raw mean standard scores across domains ranged from 87.7 to 94.9.

The lack of support for Hypothesis 2 may be related to problems in the way the neuropsychological constructs were defined. The changes made based on results of reliability analyses highlight an ongoing dilemma in the field of neuropsychology. Namely, do

neuropsychological measures assess pure skill areas and, since individual skills within a particular construct are dissociable, is important information lost when one examines constructs instead of subtest scores? Results of reliability analyses suggested that some of the measures thought to fit within certain domains did not hold together as expected. For example, a test of phonological processing did not seem to fit with other measures of expressive and receptive language skills. However, reliability analyses also supported the idea that certain tasks measure, in some sense, similar skills. These results were specific to this sample, and may not hold for other samples. As neuropsychologists, we are essentially more interested in an overall picture and pattern of functioning than performance on individual tests. Therefore, it makes sense to group together tests that measure similar areas of functioning in a meaningful way. When a score within a particular construct is discrepant from what is expected, then unique skills assessed with that measure could be considered more carefully. In the case of the current study, data analysis supported the clustering of various measures. However, the issue regarding whether or not frontal lobe functioning was adequately assessed must be considered.

The tests included in the battery may not have been appropriate or sensitive enough to identify deficits in areas associated with frontal lobe functioning. Because the nature of executive functioning in very young children is not well understood and because there are few readily available and well-normed tests available to assess "executive functioning" in very young children, tasks of immediate attention and memory were used. The NEPSY Visual Attention task was dropped from the Memory/Attention domain because several children had difficulty completing the task. But it could be that the difficulties observed were representative of executive functioning deficits. For example, these children expressed a tendency to get stuck and to not "remember" task instructions. However, this explanation is not likely since only the youngest children in the sample had difficulty completing the task. Consideration of the use of different tests to assess this domain will be discussed later.

It may be that attentional and executive skills found to be affected in SCD populations have not yet developed in a preschool-aged sample. If this were the case, then the lack of relative difficulties would not be related to problems with the measures used. Rather, consistent with conclusions from the pediatric traumatic brain injury literature, the effects of damage to the frontal lobes may not appear until these children develop skills expected to appear as the frontal lobes develop (Ylvisaker & Feeney, 1998).

Finally, the disease process that has been assumed to affect frontal lobe functioning in children with SCD may not be a factor at this young age, such that results actually reflect a lack of disease-related frontal lobe involvement. During the course of SCD, abnormally-shaped red blood cells become rigid and do not pass easily through vasculature, blocking normal blood flow and causing decreased tissue perfusion (Bonner, Gustafson, & Schumacher, 1999; Smith, 1999). Frontal lobe tissue appears to be particularly vulnerable to SCD-related infarction (Watkins et al., 1998). Brown and colleagues (2000) found relative problems in attention and executive functioning in children who had sustained strokes or silent infarcts. It is unknown how many children in the current study had measurable neurological changes, since most did not have an MRI or TCD conducted. Those that had either an MRI or TCD had unremarkable findings. Since preschool-aged children are at-risk for stroke, it seems unlikely that this group would have no or little neurological vulnerability. However, unlike older children and adults, the frontal lobes may not be differentially affected at this age compared to other areas.

4.1.3 Hypothesis 3

Correlation analyses indicated that the disease severity factors examined as part of this study were not significantly related to Full Scale IQ or any of the neuropsychological domains. In addition, there was no difference in neuropsychological functioning based on genotype. However, various psychosocial factors were correlated with neuropsychological outcome

measures. Specifically, at $p < .01$, maternal education/income was significantly correlated with Full Scale IQ, Language, and Visuospatial/Visuoconstructional scores. At a significance level of $p < .05$, maternal education/income was also correlated with the Memory/Attention domain score. Number of children living in the home was significantly correlated with the Motor/Visuomotor score. Hours per week in school or day care was correlated with the Language domain score. The PIP difficulty score was correlated with the Visuospatial/Visuoconstructional and Motor/ Visuomotor domain scores. Results of hierarchical regression analyses revealed that maternal education/income accounted for 43% of the variance in Full Scale IQ, 44% of the variance in the Language domain score, and 34% of the variance in the Visuospatial/Visuoconstructional domain score. Although the regression model for the Language domain was not significant due to entry of other variables, the total variance explained by maternal education/income remained constant at each step. Although conditions for mediation were not met, further examination of the relationship among the variables correlated with the Language domain score, namely maternal education/income, number of hours in day care/school, and the PIP difficulty total score, is indicated. Most of the variance in the Motor/Visuomotor domain (59%) was accounted for by number of children living in the home.

The lack of findings related to genotype or disease severity was surprising. The literature examining the role of SCD severity in cognitive outcome is inconsistent (Knight et al., 1995; Nettles, 1994). However, in a longitudinal study examining children ages 0 to 36 months, Thompson and colleagues (2002) found subtle effects of biomedical risk by 24 months of age, such that genotype accounted for 15% of the variance in psychomotor functioning and 20% in mental functioning. It is unclear why disease severity was not significantly correlated with any outcome variables in this study. Perhaps small sample size and low power made it difficult to pick up real effects. Also, disease-related neurological effects may be too subtle in preschool-aged children without stroke such that neuropsychological testing would not be sensitive in

identifying children with these effects. If effects exist but are nonspecific, then averaging performance across a sample may mask intra-individual variability that is associated with disease-related neurological changes. In addition, controversy regarding the development of executive functioning in very young children may suggest that skills sensitive to neurological effects of SCD may not yet be developed in very young children such that deficits would not be apparent until later in life. Or, the lack of well-normed tests to assess executive functioning in preschoolers may have limited the ability of this study to identify problems in executive functioning. Finally, many problems with the measures used to represent disease severity in this group have been outlined (Barakat, Lash, Lutz, & Nicolaou, in press), and are considered in more detail in the following section.

The relationship between psychosocial factors and cognitive functioning in children with SCD has been highlighted (Fowler et al., 1985; Richard & Burlew, 1997; Thompson et al., 2002) and Brown, Armstrong, and Eckman (1993) stressed the importance of considering the role of socioeconomic status on neuropsychological functioning in this population. Maternal education/ income, which represented SES in this study, was significantly related to most neuropsychological domain scores. These findings are consistent with the literature, which highlights the relationships between SES and outcome on cognitive tests (Brown, Buchanan, et al., 1993). Thompson et al. (2002) reported that the decline in mental development scores in their sample of SCD children followed from birth to 36 months of age, was consistent with that seen in poor African-American children without chronic illness.

The effects of lower socioeconomic status on cognitive development in children may be indirect. For example, these families may not be able to provide the level of experiences or amount of equipment in and out of the home that may promote learning. Also, these environments may be less literacy-rich, with less opportunity for reading and less exposure to language. The association between race and cognitive functioning seems to be mediated by

poverty (Brooks-Gunn, Klebanov, & Duncan, 1996). Even if not poor, black children are more likely to live in poor neighborhoods, reside in single parent families, have parents with lower education and lower literacy scores, and have younger parents than white children (Brooks-Gunn, Klebanov, & Duncan, 1996). They also tend to live in households with fewer cognitive enrichment opportunities, including less access to books and reading, and more hours of television watching (Evans, 2004). Poverty and these associated cofactors have been linked to child outcomes. Evans argues that these factors are important, as genes do not account completely for childhood outcomes. However, an interaction between genetic and environmental factors is likely. Genetic factors may limit the likelihood that those "born" with lower intelligence will attain as much education as those "born" with higher levels of intelligence. This may, in turn, affect the eligibility for jobs and potential earning power in people with lower intelligence, leading to lower SES and other poverty factors that are associated with it.

Aspects of cognitive development have been linked to family size, such that larger family size and more siblings are related to poorer functioning in some areas of cognition. For example, problems with speech development (Evans, Maxwell, & Hart, 1999) and lower scores on measures of verbal abilities (Blake, 1989) have been associated with larger families. Luster and McAdoo (1994) found that families of more competent African-American children had relatively small numbers of children. In the current study, number of children living in the home was significantly correlated only with the Motor/Visuomotor domain score. Downey (2001) suggested that the resource dilution model seems to explain why children in families with fewer children perform better on tests of cognitive skills than those that come from families with more children. The resource dilution model holds that resources of parents are finite and, as the number of children within a home increase, resources available for any one child decrease. The effects of the relationship between family size and intellectual functioning have been found to be more pronounced in families of low and middle SES as compared to those of high SES

(Lancer & Rim, 1984). However, Rodgers et al. (2000) have argued that the dilution model, which posits that large families result in low IQ children, is not correct. Based on analysis of data from the National Longitudinal Survey of Youth, they concluded, instead, that low-IQ parents make large families. It is unclear why number of children in the home was significantly correlated with Motor/Visuomotor scores and not with other domains, particularly verbal domains. Although birth order was not assessed for the children in this study, it could be that older children "help" younger children in a way that limits opportunities for younger children to challenge their own motor systems (e.g. opening and closing boxes, drawing or writing for them). In addition, more children in the home may mean that each individual child has access to fewer toys, activities, and play time that may support the development of these skills.

The PIP difficulty score was correlated with a number of neuropsychological outcome measures. Since PIP frequency was not correlated with these outcome measures, it is concluded that the level of success in coping with difficult events associated with their child's chronic illness is more important than the frequency of these events for this sample of caregivers. It may be that the self-reported level of stress and distress associated with these events affects parenting style and parenting skills. For example, parents experiencing more stress or distress may be less available for interactions related to play or learning activities, leading to decreased performance in children. Thompson, Gustafson, and colleagues (1999) highlighted the importance of maternal stress as a marker of the caregiving environment that can alter the effects of biomedical risk factors associated with SCD. Examination of individual PIP scales suggested that children's intellectual functioning was negatively impacted by maternal distress associated with problems communicating with medical staff and family members. Although maternal intelligence was not measured, it can be hypothesized that mothers with higher intelligence may be more effective at communicating with medical staff and family members around issues related to their child's illness and that they would be more successful in interpreting information provided by medical

staff, thereby reducing stress related to communication difficulties. If this were true, then the relationship between the PIP Communication scale difficulty score and neuropsychological outcome may be mediated by maternal intelligence.

The relationship between hours per week in school or day care and the Language domain score is consistent with the literature. In an examination of 538 kindergartners, Christian, Morrison, and Bryant (1998), found that number of months in child-care predicted academic skills. These findings were most pronounced for children that came from families of less educated mothers and relatively poor literacy environments. Burchinal and colleagues (1997) also found that child-care experiences were associated with better cognitive performance. It is assumed that children that have access to peers and adults outside of the home are provided with additional opportunities for language development through formal education and/or through experience and practice. Children that come from families with more limited resources in terms of family size, maternal education and intelligence, and quality of the literacy environment may benefit the most from child-care experiences outside of the home.

Although the Home Environment Questionnaire was not significantly correlated with any of the neuropsychological outcome measures, it was correlated with family income, such that families with higher incomes had better home environments. Results of partial correlation analyses suggested that, when the Home Environment Questionnaire score was controlled for, maternal education/income remained significantly correlated with the neuropsychological outcome measures suggesting no mediational role of home environment as measured in this study. However, the role of the quality of home environment on cognitive development has been highlighted in the literature. Some studies found that home environment was as important or more important a factor than SES when examining cognitive functioning, particularly in young children (Bradley et al., 1989; Brooks-Gunn, Klebanov, & Duncan, 1996; Espy, Molfese, & DiLalla, 2001; Luster & Dubow, 1992; Molfese, DiLalla, & Bunce, 1997). Others, however,

suggest that home environment as measured by the HOME does not delineate families within the same income level (Lotas et al., 1992), and does not add to predictability beyond that accounted for by SES in black toddlers (Johnson et al., 1993). The Home Environment Questionnaire used in this study did not include an observation component and was completed by the parent. Limitations of this questionnaire and their impact on findings related to the home environment will be discussed in the next section.

Of all the severity and psychosocial variables examined, only maternal education/income was significantly correlated with the Memory/Attention domain score. The results of hierarchical regression analyses conducted with the remaining domains indicated that maternal education/ income accounted for much of the variance in Full Scale IQ, the Language domain score and the Visuospatial/Visuoconstructional domain score. Most of the variance in the Motor/Visuomotor domain score was accounted for by number of children living in the home. Across most regression analyses, only one variable in each regression significantly contributed to the model. In the Language domain regression, although it is unclear why all individual variables did not contribute significantly to the model when all variables were entered, even though the full model was significant, maternal education/income seemed to account for a significant amount of the variance in the Language domain score. Although the disease process may differentially affect certain parts of the brain and, in turn, certain areas of cognition, it is likely that the effects of environmental factors are universal and affect general cognitive functioning. In this way, the powerful effect of maternal education/income across areas tested is not surprising (Brown, Buchanan, et al., 1993; Lotas et al., 1992).

4.2 Limitations

4.2.1 Sample size

The study sample was small, such that there may not have been enough power to pick up differences across domains or differences between subgroups. There were a number of trends suggested by the data analyses; with a larger sample size, some of those findings may have been significant. Although expected differences between genotype groups were found in terms of disease severity measures, the lack of findings related to the relationship between disease severity and neuropsychological functioning may have been related to low power. Low power may have also affected findings related to the correlation and regression analyses, such that relationships between disease severity or some psychosocial factors and neuropsychological functioning were not detected. Larger sample size may have resulted in an increased number of variables significantly contributing to the regression models. Although the sample size was smaller than that achieved in most of the reviewed studies, the targeted age range of 3 to 5 years was much more limited than that of other study designs. In fact, other studies that included a sample of young children within a limited age range had comparably small sample sizes (Best et al., 2002; Chua-Lim et al., 1993; Steen, Hu, et al., 2002).

Almost all of the children recruited for this study were deemed eligible and completed participation. The high participation rate was likely due to the number of home visits that were completed (n = 18). When visits in the clinic were scheduled, they often resulted in no-shows. It is assumed that protocol completion would have been difficult and less successful without the option for home visits. This highlights the challenges of performing research with the SCD population. Care for SCD is chronic and infections and pain episodes occur unexpectedly, heavily taxing the resources of these families, many of which fall within a low to middle SES group. For example, employed parents must miss work frequently and are often in jobs threatened by such absence. In addition, for families without a car, regular and emergent medical

visits require costly trips on public transportation. Also, securing childcare for other children can be time-consuming and costly. Therefore, traveling to clinic on a day when their child does not already have an appointment, or remaining in clinic for an additional 2 hours to participate in a research study is not an easy endeavor for many of these families.

In addition to the option for home visits, successful recruitment was thought to be associated with other factors. The children in this study were recruited from a larger group of children already participating in a longitudinal grant-funded study examining aspects of pain in infants and toddlers. Therefore, the sample came from a self-selected group of people who had found the time and interest to participate in another study for an average of 27 months at the time they consented to the current study. In addition, these children with SCD were seen regularly in the hematology clinic since infancy. Over time, these families may have become highly connected to the clinic and the clinic staff. It is possible that this positive connection made it more likely that they would want to participate in research studies offered through the clinic. Finally, parents may have perceived reasonable benefits from their participation in this study. Parents were provided verbal and written feedback regarding the results of their child's evaluation, and were given recommendations. Many parents expressed an interest in knowing how their child was functioning and being able to seek intervention, if indicated.

4.2.2 Representativeness of sample

The representativeness of the sample may have also impacted the results of this study. The study sample had a relatively higher male:female ratio and a lower HbSS:HbSC ratio when compared to the general preschool-aged population treated at the clinic from which these children were identified. Many of the reviewed studies did not report the gender of their samples, so it was difficult to compare the gender ratio of this study sample with that typically described in the literature. Several studies examining functioning in preschool-aged children had a more even

distribution of males and females as compared to the current study (Chua-Lim et al., 1993; Steen, Hu, et al., 2002). There is some evidence that males with SCD are more likely to express behavioral problems, have more complications, and report poorer family functioning than females (Barakat et al., in press). However, these findings have been with older children and adolescents. The reviewed studies did not investigate whether there were gender differences in terms of the effects of SCD on neuropsychological functioning. There was no reason to believe that males and females would be differentially affected at this young age, so the high male to female ratio is not thought to affect study results in a meaningful way.

As mentioned earlier, the samples described in many other published studies, including those from the multi-site Cooperative Study of SCD, had significantly more subjects with SS than SC disease (Brown et al., 1993; Brown et al., 2002; Steen et al., 2001; Thompson et al., 2002). Only Noll and colleagues (2001) described a similar genotypic ratio to that of the current study. Those assessing preschoolers only included participants with SS (Chua-Lim, et al., 1993; Steen, Hu, et al., 2002). SS disease was more represented in the longitudinal study from which this sample was recruited; however, only children ages 3 to 5 years were eligible for this study. Since almost all eligible children participated, it is assumed that the children in this limited age group had a more even distribution of SS and SC disease than the general SCD population. As expected, those with SS in this study sample had a higher disease severity score based on the variables that were considered. However, the fact that the current study had a lower percentage of children with SS than many other published studies and underestimated population rates for SCD (Bonner et al., 1999) may have affected the results related to scores on neuropsychological measures, the profile of neuropsychological functioning, and the role of disease severity on neuropsychological outcome. For example, the study sample may not have included an appropriate range of disease severity and may not have included enough children with relatively severe disease, therefore limiting the ability to detect differences based on disease severity or

identify the contribution of disease severity to neuropsychological outcome. Significant group differences and significant contributions of disease severity may have been found with a more genotypically representative sample.

Environmental factors, specifically maternal education and family income, were highly correlated with neuropsychological outcome measures and accounted for much of the variance in neuropsychological functioning. The current study sample had higher levels of maternal education and more married/partnered mothers than several other published studies, including those describing the large sample participating in the Cooperative Study of SCD (Brown et al., 2000; Thompson et al., 2002; Thompson et al., 2003). Although no family that was recruited declined participation, recruited families were already a self-selected sample. That is, the sample consisted of families with resources allowing them to feasibly participate in a longitudinal study requiring routine visits and involvement with pain diaries, monthly phone calls, and/or a pager system. Those families with lower income/education or with single parents may have opted out of or dropped participation in the larger study because of limited resources making participation difficult. In fact, Steen and colleagues (2001) found that the estimated mean family income of the families that consented for their study was significantly higher than that of families that did not consent, highlighting the role of family income and resources on likelihood to participate in research studies. A tendency towards higher SES than expected may have limited the variability in other factors that were not found to be related to neuropsychological outcome, for example family functioning and the home environment. However, lack of findings related to family functioning may also have been related to problems with the FES summary score that was used to represent family functioning. Due to the small sample size, it was not possible to appropriately assess reliability of this summary score in this sample. A more socioeconomically representative sample may have also resulted in expected lower mean scores on tests of neuropsychological functioning.

4.2.3 Lack of control group

Many studies examining the impact of SCD on neuropsychological functioning compare children with SCD across different stroke status or against comparison groups (siblings or matched peers). This study did not employ a control group. The lack of a control group limited the conclusions that could be drawn when examining overall functioning of this group. A control group would have allowed conclusions to be made regarding whether or not resulting performance or the pattern across domains is unique to preschool-aged children with SCD. Although results were available from a meta-analysis, the analysis was primarily based on results with school-aged children and do not necessarily generalize to a preschool-aged population.

4.2.4 Disease severity measures

Because this sample consisted of proportionately less SS children than the general SCD population, disease severity, as a group, was likely less than that found in other samples. The lack of findings related to disease severity in this study may be due to the limitations in how disease severity was measured, particularly in a very young population with minimal variability in regards to pain episodes and hospitalizations. However, there is no consistently used way to measure disease severity in SCD.

Although SS genotype has been associated with more severe medical and cognitive problems, including higher risk for stroke, there is a lot of variability in outcome of children with SCD, leading to examination of other measures of disease severity (Barakat et al., in press). Hemoglobin (or hematocrit) is often used as a measure of disease severity and indicates level of anemia, which could represent hypoxic effects. The benefit of using hemoglobin is that it can be directly measured and is not affected by subjective factors. Steen et al. (1999) found that hematocrit levels alone were associated with changes on quantitative MRI as young as 4 years of age, even with normal conventional MRI findings. Although hemoglobin levels seem to be

strongly related to genotype and do not account for variability in disease severity within genotype groups, there are a number of inherent difficulties in relying on more subjective measures of disease severity. That is, visits to the ER and number and length of hospitalizations could be affected by factors other than severity of symptoms. For example, different hospitals may have different criteria for admitting and discharging patients. Also, families may have different criteria for bringing their child to the ER, such that some families bring less severely ill children for hospital care than others. Variables related to hospitalizations are not consistently associated with cognitive outcome measures (Brown, Buchanan, et al., 1993; Wang et al., 2001). Number and length of pain episodes have also been used to represent disease severity. In fact, one unique aspect of the current study is the prospective nature of data collection related to pain episodes. As part of their participation in the longitudinal study, data regarding pain episodes were collected using various methods. The measure of pain episodes used for this study was valid and reliable; however, very young children tend not to suffer from pain episodes to the same extent that older children with SCD do, limiting the variability of this measure.

Given expected group differences in terms of hospitalizations and pain episodes based on genotype, objective disease measures may be sufficiently useful in predicting severity of medical complications. However, there are limitations in using either genotype/hemoglobin levels or documented hospitalizations and pain episodes to represent disease severity, and neither type of measure has been consistently related to cognitive outcome. It may be that TCD and MRI results would have been a more appropriate way of determining disease severity, especially in terms of its effect on integrity of the CNS. However, conducting such tests with very young children carries a number of risks and is not routinely done. There is some suggestion that the family's subjective perceptions of disease severity may have a greater impact on aspects of adaptation and psychological outcome in children with SCD (Barakat et al., in press). Because the outcome measures in this study were relatively objective in nature and have been linked to specific

neurological integrity, this suggestion may not apply. However, further investigation of the association between perceived disease severity and cognitive functioning, perhaps through its effect on maternal stress, is warranted.

Despite limitations of the measures of disease severity used for this study, the methodology was consistent with that employed by other researchers. Also, the severity summary score calculated for this study resulted in an expected significant difference in severity between children with SS and those with SC disease, suggesting that the variables used to measure disease severity were valid.

4.2.5 Test battery

The length of the test battery used in this study seemed to be appropriate for most of the children that participated. Some of the younger children in the sample (age 3) became tired towards the end of the assessment and required additional short breaks; however, child age was not significantly correlated with any of the domain standard scores. Proposed neuropsychological domains were altered as a result of reliability analyses. The measures included in the various domains for subsequent data analyses seemed appropriate.

One limitation was the lack of inclusion of measures of visuospatial/visuoconstructional functions outside of subtests comprising the Performance Scale WPPSI-III. As explained, the Design Copying test seemed to fit more appropriately with the Motor/Visuomotor domain and was dropped from the Visuospatial/Visuoconstructional domain. The Performance IQ represented an individual domain and the Verbal IQ was included as part of the Language domain because it held together strongly with other language tasks in the battery. This allowed for interpretation of the domain scores apart from the Full Scale IQ, but limited the ability of Full Scale IQ (general intellectual functioning) to represent a separate construct. In a sample that does not include children as young as 3-years-old, where Object Assembly is an optional subtest on the

WPPSI-III, it could be considered as a measure of visuoconstructional abilities. Other appropriate subtests may include the Picture Similarities on the DAS, which may tap into similar abilities as that assessed by the WPPSI-III Picture Concepts subtest.

It was expected that children with SCD would perform least well on tests of attention and executive functioning. However, this hypothesis was not supported. As mentioned previously, the tests included in this battery may not have been appropriate or sensitive enough to identify deficits in areas associated with frontal lobe functioning. It is not clear how to specifically define or measure frontal lobe functioning in preschool-aged children. The children over the age of 3 seemed to be able to appropriately perform the Visual Attention subtest, and this test may continue to be appropriate for a 4-5-year-old sample. In addition, a hand movement task, that assesses sequencing abilities and may detect perseverative responses, may be appropriate for this group. The NEPSY Tower subtest may be appropriate in assessing problem-solving abilities. However, it is expected that the youngest children in this sample would have had difficulty on such tasks also, and that poor performance would not necessarily have represented executive deficits.

4.2.6 Measure of home environment

The Home Environment Questionnaire did not perform as expected. That is, unlike results of other studies (Bradley et al., 1989; Brooks-Gunn, Klebanov, & Duncan, 1996; Espy, Molfese, & DiLalla, 2001; Luster & Dubow, 1992; Molfese, DiLalla, & Bunce, 1997), the quality of the home environment was not found to be a significant factor in neuropsychological outcome. It is possible that these results reflect the finding of Johnson et al. (1993), that quality of home environment does not add to the predictability of intelligence over and above that provided by SES for a sample of black toddlers. Although small sample size and bias in sample

representativeness may have affected these results, they were also likely impacted by limitations in the way the quality of the home environment was assessed.

The Home Environment Questionnaire was adapted, in part, from interview questions included in the HOME scale and was completed by parents. Parents may have provided responses that were socially acceptable in order to paint themselves in a more positive light. As no formal observation was included in the assessment of the home environment, there was no way to check the accuracy of responses provided by parents. Although the Home Environment Questionnaire score was significantly correlated with family income, this may highlight the fact that few items were included that assessed aspects of the home environment that did not rely on financial resources. For example, there was no measure of the interaction between the parent and child, which is a primary component of formal measures of home environment, such as the HOME. Also, more educated parents may have wanted to and been able to respond in a socially appropriate manner. It is expected that a multi-method, multi-informant measurement of home environment that did not rely solely on parent report would have revealed an association between these factors and neuropsychological outcome.

4.3 Conclusions, Implications, and Future Directions

The literature and the results of this study suggest that there may be two processes interacting to impact neuropsychological development in children with SCD. That is, neurological integrity is affected by disease process at the same time that many of these children are dealing with the effects of less-than-ideal psychosocial status on their cognitive development (Brown, Armstrong, & Eckman, 1993; Brown, Buchanan, et al., 1993; Fowler et al., 1985; Schatz et al., 2002; Thompson et al., 2002).

Differences in functioning between school-aged children with SCD and comparison groups consisting of siblings or matched peers suggest the presence of age- and disease-related

effects on neuropsychological functioning (Schatz et al., 2002). In addition, there is evidence of MRI and MRA changes in very young children with SCD (Kwiatkowski, 2002). However, quality of social environment seems to moderate the effects of biomedical risks (Schatz et al. 2002) and can function to place children at increased risk or to serve a protective role. It seems that the interaction between the environmental context and the disease may be the important factor in developmental outcome (Schatz et al., 2002). In addition, despite many limitations, this study highlights the possibility that disease-related effects on neuropsychological functioning in the absence of stroke may be minimal early in development. It is suggested by these results that environmental factors, particularly maternal education and family income, are strong predictors of neuropsychological functioning in 3- to 5-year-olds with SCD without stroke.

There was no meaningful pattern of strengths and weaknesses across neuropsychological domains. Although researchers have found that tests of attention were the most useful in distinguishing children and adolescents with SCD with silent stroke from those without (DeBaun, 1998), relative difficulties with attention may not be relevant in earlier stages of development. Early on, disease-related neurological effects may be more widespread and related to diffuse effects of anemia, as opposed to specific stroke activity. Children in this study performed less well than normative samples across all areas. General intellectual functioning was similar to that of school-aged comparison groups used in other studies. These findings suggest that general measures of intellectual functioning may be sufficient in helping to identify children who are at-risk for problems in cognitive development due to environmental factors. This may be true particularly early on in development, when no clear pattern of functioning emerges to suggest specific neurological effects of SCD. In fact, when Verbal IQ, Performance IQ, and all other subtests comprising the neuropsychological test battery are considered together in a reliability analysis, the Cronbach's alpha was .75, which is higher than that of any individual domain. In an examination of performance across different domains, Noll and colleagues (2001) found that the

SCD sample had lower scores across the board as compared to a comparison group. At a young age, a global representation of functioning may be appropriate, such that an IQ screen may be sufficient in identifying children in need of further neurological evaluation or services.

Because very young children are at-risk for stroke, effective identification of young children who are at-risk for disease-related neurological effects is important. Neuropsychological screening may play a vital role in identifying these children. Although a SCD-specific pattern does not seem to be emerging, the presence of significant intra-individual variability may be able to identify children in need of broader assessment or neuroimaging. In a recent study, Grueneich and colleagues (2004) found a significant relationship between positive findings on structural and/or perfusion neuroimaging and increased variability in neuropsychological performance in a sample of children and adolescents, although these abnormalities were not correlated with level of neuropsychological performance. It seems that the intra-individual variability was most accounted for by variability in memory functioning as compared to general cognitive abilities. It is not clear if a similar finding would be expected in sample of very young children. However, the sample in this current study appeared to have a large amount of intra-individual variability. The benefit of using an index of variability to identify at-risk children warrants further exploration.

Prevention and intervention efforts should aim to address biomedical and environmental risk factors in order to reduce neuropsychological morbidity. In children who are considered at-risk, it is first important to identify whether problems exist and then try to determine what interventions are most appropriate. It is clear that children with SCD perform less well than normative populations at an early age. Although the specific role of disease-related factors is not well-understood in the absence of overt stroke, the effect of socioeconomic status on intellectual functioning is well-established. If environmental effects are reduced early in development, it is possible that children could develop some level of resilience against negative outcomes following

silent infarcts and effects of chronic anemia. Prevention of disease-related effects has been improving over the last decade. However, there are few interventions used in general hematology clinics to address negative environmental factors. Such interventions could address parental distress, improve effective communication between parents and medical staff, and address children's developmental risk associated with limited access to appropriate learning environments.

Bonner (1999) recommended regular biannual neuropsychological evaluations for children with SCD and also recommended evaluation of preschoolers to assess functioning and school readiness. It seems that children with SCD should be screened earlier, starting in infancy, in order to identify appropriate areas for intervention in at-risk children and provide a baseline level of functioning in case of silent or overt stroke. Children with SCD are usually connected to a medical clinic and participate in routine medical follow-up from infancy. It may be possible to take advantage of this routine contact between families and medical clinics in order to promote cognitive development from a very early age, regardless of whether or not developmental problems are disease-related. Although MRI and TCD studies could be helpful in identifying young children with neurological morbidity, conducting these tests in young children carries a number of medically-related risks. In addition, many centers do not have the funding necessary to perform routine MRI or TCD studies on every child with SCD. Results of this study suggest that an IQ screen or brief neuropsychological test battery may be sufficient to identify young children in need of neuroimaging and/or intervention, and may reduce costs.

Children identified as having problems with cognitive development may be eligible for early intervention services or other specialized educational programs through day cares and public preschools. In a review of early intervention programs aimed at economically disadvantaged children (e.g. Head Start), Warr-Leeper (2001) outlined benefits such as improvements in cognitive development, emotional functioning, and achievement. Intensity and

length of programs were associated with outcome. There has been consistent research showing that intensive early educational experiences can support cognitive development in at-risk children. The cognitive benefits of preschool prevention programs have been found to be most intense in the preschool period, but often last many years (Gorey, 2001; Nelson, Westhues, & MacLeod, 2003). Long-term, positive effects of a full-time, high quality, educational child-care experience through the preschool years were found among a poor, minority sample (Campbell, Pungello, Miller-Johnson, Burchinal, & Ramey, 2001). Because attendance in early intervention programs has been found to be associated with the level of financial and social support (Kuchler-O'Shea, Kritikos, & Kahn, 1999), families may require social work services in order to make early educational opportunities a realistic possibility.

One possible avenue for promotion of cognitive development in children with SCD is through education of medical staff, families, and teachers/schools. If neuropsychological screening cannot become part of routine follow-up, medical staff can be trained to look for signs of developmental delays. In addition, staff often plays the role of liaison between families and social workers or other services. Educating staff on how to help families gain access to appropriate child-care, early intervention evaluations, and formal learning opportunities would be important. Parents could be provided education in the clinic through seminars and/or handouts that outline normal developmental expectations, in order to help them identify delays in their children. In addition, Burchinal and colleagues (1997) suggested that in young African-American children determined at-risk based on low SES, higher scores on cognitive tests and less decline over time was partly associated with intensive early educational child care, which occurred in a child care setting from infancy until entry to kindergarten. Outcome was mediated by child's responsiveness to the environment. Weekly home visit interventions did not seem to have a positive impact on cognitive outcome. This study highlights the importance of intensive, quality child-care experiences for at-risk children. Families should be encouraged to provide their

children such experiences, when possible. However, since access to quality child-care often requires significant financial resources, such opportunities may not be available to many young children with SCD. Parents of children with SCD may also be cautious about placing their children in child-care or allowing their child to attend preschool at a young age because of concern about their child's health. Parents should be educated and encouraged to provide their children with as many positive learning experiences as possible. Teachers and schools could be provided in-service educational programs and formal information about the nature of SCD and risk for neurological problems affecting cognitive and academic functioning. Consistent communication with teachers could encourage teachers to provide information to medical staff about unexpected changes in school performance that may suggest changes in neurological functioning.

In healthy African-American children, mother's education, maternal age, supportive home environments, smaller number of children in the home, and maternal self-esteem have been associated with more positive outcomes (Luster & McAdoo, 1994). In addition, the results of this study suggest that higher levels of maternal distress, particularly that related to communication difficulties, were associated with poorer neuropsychological functioning. Although formal family-based interventions designed to address some of these factors may not be feasible, professionals that treat families of children with SCD should be aware of the effects of these factors on child outcomes. In this way, at-risk parents could be referred for psychological or social services early on. Helping families, particularly parents with lower education, comprehend the nature of the information provided about their child's disease and its effects is important. Families could be provided resources to help them communicate this information to other family members and school personnel. The PIP findings in this study may also be related to the use of effective coping strategies in these parents. It has been found that more active and engaged methods of coping have been related to better treatment adherence and more positive outcomes in

children with SCD as compared to the use of more passive or disengaged methods of coping (Barakat et al., in press). There is likely a relationship between other environmental factors and use of and access to coping strategies. Intervention can focus on providing families resources and education that allow them to employ effective methods of coping. This may have an indirect effect on disease severity by increasing parents' abilities to provide appropriate medical care, adhere to treatment recommendations, and promote cognitive development in their children.

In addition to implications for assessment and intervention, the results of this study suggest areas for future research. Investigation of neuropsychological development in children with SCD from infancy is a fairly new endeavor. Successful participation rate in the current study highlights the effective method of home visits in eliciting involvement from this population. Such a method allows families with more limited resources to engage in research studies. The role of number of siblings is not well understood and deserves further study. Better delineation of the aspects of the home environment that play a role in cognitive development would allow more appropriate recommendations for interventions. Further study of patterns of neuropsychological functioning with a larger and more representative sample is important in order to determine whether specific deficits are associated with the disease process in the absence of stroke in young children. Studies should include more formal and well-defined tests of executive functioning in order to determine the age at which effects on frontal lobe functioning start to appear. Longitudinal studies are necessary in order to more appropriately describe the developmental course of children with SCD. Although the difficulty of performing MRI and TCD with young children is admitted, studies correlating neuroimaging data with neuropsychological test scores over time could lead to identification of neuropsychological measures that are sensitive to stroke risk. Finally, the results of the Language domain regression analysis provides support for further examination of the interaction between various psychosocial factors and how these interactions in turn affect neuropsychological development.

In conclusion, this study highlights the importance of examining and identifying neuropsychological effects of SCD early in development. The results of this study suggest that preschool-aged children with SCD perform less well than normative samples across domains. No specific, meaningful pattern of functioning emerged. Disease severity measures were not related to any of the neuropsychological outcome measures and performance was not different between groups based on genotype. It is possible that the disease process may not have a significant effect on neurological integrity in very young children without overt stroke. However, since most children did not have MRI studies conducted, this could not be confirmed. A number of psychosocial factors, particularly SES represented by maternal education and household income, accounted for a significant amount of the variance in neuropsychological outcome measures. Maternal distress associated with disease-related communication difficulties was also an important factor. In addition, number of children living in the home appeared to have a significant impact on development of motor and visuomotor skills.

Overall, the results of this study highlight the importance of screening children with SCD very early in life for developmental problems. In addition to the vigilant management of illness-related factors, cognitive development can be supported and promoted through the ongoing connection between these families and medical clinics. Children with SCD would seemingly benefit from formal educational experiences to promote development. Because these children remain at-risk for silent and overt strokes and the effects of chronic anemia throughout their lives, it is important to ensure that they have access to intensive opportunities for intellectual development. Such access may increase resilience to the effects of neurological events and reduce neuropsychological morbidity. Further investigation of the early developmental effects of SCD, the interactions between disease-related and psychosocial factors, and outcome studies examining interventions addressing psychosocial factors is warranted. Such investigation should

attempt to address the study limitations discussed, including small sample size, sample representativeness, and possible problems related to the measures used.

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Table 1. *Proposed Summary of Study Measures*

Measure	Variables
Illness-related Risk Factors	SCD genotype avg. of last 3 Hgb levels # visits to hosp/ER in past 12 mos. # pain episodes in past 12 mos.
Illness severity summary score	(difference between 12.5 g/dL and average of last 3 Hgb levels) + (number of pain episodes in the last 12 months) + (numbers of visits to hospital/ER in last 12 months)
Psychosocial Risk Factors	Parental marital status Maternal education Family income # of children living in home Family Environment Scale (FES): Total Score Pediatric Inventory for Parents (PIP): Total frequency, Total difficulty scores Home Environment Questionnaire: Total score
General Intellectual Functioning	WPPSI-III: Full Scale IQ
Language	WPPSI-III Picture Naming NEPSY Phonological Processing DAS Verbal Comprehension
Memory/Attention	NEPSY Sentence Repetition NEPSY Narrative Memory NEPSY Visual Attention DAS Picture Recognition
Visuospatial/ Visuoconstructional	NEPSY Design Copying WPPSI-III Block Design
Motor/Visuomotor	NEPSY Visuomotor Precision Purdue Pegboard Test

Table 2. *Order of Test Measures*

A	B
NEPSY Design Copying	NEPSY Design Copying
WPPSI-III (+Picture Naming)	WPPSI-III (+Picture Naming)
NEPSY Narrative Memory	NEPSY Sentence Repetition
Purdue Pegboard Test	NEPSY Visuomotor Precision
NEPSY Phonological Processing	DAS Verbal Comprehension
NEPSY Visual Attention	DAS Picture Recognition
NEPSY Sentence Repetition	NEPSY Narrative Memory
NEPSY Visuomotor Precision	Purdue Pegboard Test
DAS Verbal Comprehension	NEPSY Phonological Processing
DAS Picture Recognition	NEPSY Visual Attention

Table 3. *Comparison of Alpha Values for Proposed and Reconfigured Neuropsychological Domains*

Domain	Proposed Variables	*Alpha*	New Variables	*Alpha*
Language	Picture Naming	-.22 (*n*=18)	Picture Naming	.65 (*n*=18)
	Phonological Processing		Verbal Comprehension	
	Verbal Comprehension		WPPSI-III VIQ	
Memory/Attention	Sentence Repetition	.51 (*n*=18)	Sentence Repetition	.66 (*n*=20)
	Narrative Memory		Narrative Memory	
	Visual Attention		Recognition of Pictures	
	Recognition of Pictures			
Visuospatial/ Visuoconstructional	Block Design	.47 (*n*=21)	WPPSI-III PIQ	N/A (*n*=21)
	Design Copying			
Motor/Visuomotor	Visuomotor Precision	.70 (*n*=20)	Visuomotor Precision	.72 (*n*=20)
	Purdue Pegboard Test (3 trials)		Purdue Pegboard Test (3 trials)	
			Design Copying	

Table 4. *Demographic Characteristics*

Variable	*M (SD)*	Number (Percentile[a])
Gender		
Male		16 (72.7)
Female		6 (27.3)
Age (in months)	51.3 (9.4)	
Ethnicity		
African American		20 (90.9)
Hispanic		2 (9.1)
Handedness		
Right		18 (81.8)
Left		2 (9.1)
Predominantly right		2 (9.1)
Attend school or day care		
Yes		17 (77.3)
No		5 (22.7)
Hours in school or day care (if applicable)	33.6 (11.1)	
Number of adults living in home	2.0 (.65)	
1		3 (13.6)
2		16 (72.8)
3 or more		3 (13.6)
Number of children living in home	2.6 (1.1)	
1		4 (18.2)
2		6 (27.3)
3		7 (31.8)
4 or more		5 (22.7)
Person completing forms		
Mother/ female guardian		20 (90.9)
Father		2 (9.1)
Mother's age	31.1 (7.7)	
Marital status		
Married/Partnered		12 (54.6)
Single		9 (40.9)
Divorced		1 (4.5)
Maternal education		
Less than high school		4 (18.2)
High school		9 (40.9)
Some college		4 (18.2)
College graduate		3 (13.6)
Post college		2 (9.1)

Table 4. *(continued)*

Variable	*M (SD)*	Number (Percentile[a])
Household income		
Less than $9,999		4 (18.2)
$10,000-19,999		3 (13.6)
$20,000-39,999		9 (40.9)
$40,000-59,999		3 (13.6)
$60,000-79,999		2 (9.1)
$80,000-99,999		1 (4.5)
History of learning/reading problems in family		
Yes		3 (14.3)
No		18 (85.7)

[a] Percentiles based on total number for which data are available for each variable

Table 5. *Illness-related Characteristics*

Variable	*M (SD)*	Number (Percentile[a])
Genotype		
HbSS		12 (54.5)
HbSC		9 (40.9)
HbßThal		1 (4.5)
Average of last 3 hemoglobin levels	9.56 (1.5)	
Number of hospitalizations in past year	1.50 (1.9)	
Number of (documented) pain episodes in past year	3.18 (4.6)	
Days of pain (documented) in past year	10.30 (15.3)	
Severity summary score	7.57 (5.5)	
TCD or MRI performed		
Yes		5 (22.7)
No		17 (77.3)

Table 6. *Comparison of Illness-related Characteristics by Genotype*

Variable	HbSS (*n*=12)	HbSC/ Hbß$^{+}$Thal (*n*=11)	*df*	*F*	*p*
Average of last 3 Hgb levels	8.45 (1.0)	10.90 (.5)	1,20	3.77	<.001
Number of hospitalizations in past year	2.33 (2.2)	.50 (.9)	1,20	4.29	.020
Number of documented pain episodes in past year	3.42 (4.5)	2.90 (4.9)	1,20	.118	.800
Days of pain (documented) in past year	11.50 (15.6)	8.85 (15.7)	1,20	.001	.696
Severity summary score	9.80 (5.2)	4.90 (4.7)	1,20	.172	.032

Note: Data are presented as means (standard deviations)

Table 7. *Summary Scores for Psychosocial Data*

Variable	*M*	*SD*	*Range*
PIP Total Frequency [a]	99.6	21.9	52 – 145
PIP Total Difficulty [a]	86.0	22.7	43 – 135
FES Supportive [b]	262.1	26.3	223 – 321
FES Conflicted [b]	-70.8	17.2	-101 – -36
FES Controlling [b]	125.8	19.3	86 – 157
FES Total Score [b]	119.4	24.9	74 – 164
Home Environment Questionnaire total score [a]	25.0	5.8	15-38

[a] data presented as raw scores; [b] data presented as summary of T-scores

Table 8. *Summary Scores for Neuropsychological Data*

Variable	*N*	*M*	*SD*	*Range*	Z-score equivalent
WPPSI-III Full Scale IQ	22	89.6	9.1	74-105	-.70
Language	18	88.1	9.3	70-105.7	-.73
Memory/Attention	20	94.9	10.3	85-108.7	-.33
Visuospatial/ Visuoconstructional	21	89.7	10.6	70-105	-.70
Motor/Visuomotor	20	87.7	8.9	72.2-105.6	-.73
WPPSI-III Verbal IQ	22	91.5	11.4	73-112	
WPPSI-III Performance IQ	21	89.7	10.6	70-105	
WPPSI-III Information	22	91.6	9.6	75-110	
WPPSI-III Vocabulary	12	92.1	15.6	60-115	
WPPSI-III Word Reasoning	12	96.3	13.5	75-115	
WPPSI-III Block Design	21	87.6	10.6	65-110	
WPPSI-III Matrix Reasoning	12	94.2	10.2	80-110	
WPPSI-III Picture Concepts	12	96.7	14.2	65-115	
WPPSI-III Coding	11	99.5	13.3	85-120	
WPPSI-III Receptive Vocab.	11	95.9	11.6	85-120	
WPPSI-III Object Assembly	10	90.5	12.3	75-110	
WPPSI-III Picture Naming	19	89.2	13.5	70-120	
NEPSY Design Copying	22	91.4	11.7	70-120	
NEPSY Visuomotor Precision	20	84.8	12.6	65-105	
NEPSY Visual Attention	19	104.2	11.0	75-115	
NEPSY Phonological Process.	22	93.6	12.6	60-115	
NEPSY Sentence Repetition	22	93.2	9.2	75-110	
NEPSY Narrative Memory	21	96.2	14.3	70-120	
DAS Verbal Comprehension	21	78.9	11.8	60-106	

Table 8. *(continued)*

Variable	*N*	*M*	*SD*	*Range*	Z-score equivalent
DAS Recognition of Pictures	21	94.7	15.8	69-126	
Purdue Pegboard (dominant)	22	89.6	13.9	60-114	
Purdue Pegboard (nondominant)	22	81.5	13.0	60-100	
Purdue Pegboard (both hands)	22	89.5	13.1	60-111	

Note: Data presented as standard scores

Table 9. *Intercorrelations Between Neuropsychological Measures and Severity Summary Score*

Variable	Full Scale IQ	Language	Memory/ Attention	Visuospatial/ Visuoconstruc	Motor/ Visuomotor
Severity Summary	.20 (.366)	.22 (.376)	.17 (.468)	-.02 (.937)	.25 (.283)

Note: p-values are presented in parentheses

Table 10. *Intercorrelations Between Neuropsychological Measures and Psychosocial Factors*

Variable	Full Scale IQ	Language	Memory/ Attention	Visuospatial/ Visuoconstruc	Motor/ Visuomotor
Income/ Education	.66 (.001)***	.66 (.003)***	.56 (.011)**	.58 (.005)***	.37 (.109)
Child age	.34 (.125)	.19 (.445)	.22 (.348)	.07 (.771)	.14 (.571)
Maternal age	.22 (.334)	.02 (.930)	.34 (.143)	.05 (.842)	-.03 (.887)
# Children in home	-.39 (.069)*	-.16 (.537)	-.12 (.628)	-.35 (.118)	-.77 (<.001)***
# Adults in home	-.10 (.655)	.05 (.839)	-.33 (.157)	-.17 (.470)	-.21 (.367)
Hours per week in school/care	.14 (.559)	.55 (.022)**	.03 (.901)	.06 (.798)	-.14 (.563)
Total FES score	-.01 (.980)	.17 (.489)	-.02 (.942)	.02 (.927)	.20 (.404)
PIP Frequency	-.22 (.320)	-.12 (.638)	-.10 (.663)	-.25 (.284)	-.33 (.159)
PIP Difficulty	-.41 (.057)*	-.44 (.065)*	-.19 (.423)	-.47 (.034)**	-.47 (.035)**
Home Environ Questionnaire total score	.25 (.267)	.06 (.817)	.15 (.519)	.15 (.530)	.10 (.677)

Note: p-values are presented in parentheses; *$p < .10$, **$p < .05$, ***$p < .01$

Table 11. *Intercorrelations Between Demographic and Family Structure Variables (Group A)*

Variable	Home Environ Questionnaire total score	Marital status	# Adults in home	# Children in home	# Hours per week in day care/school
Maternal education/ Income	.45 (.043)**	-.16 (.471)	.11 (.636)	-.23 (.308)	.12 (.683)
Home Environ Questionnaire total score		-.30 (.180)	-.03 (.914)	-.13 (.577)	.02 (.932)
Marital status			-.14 (.526)	.02 (.949)	.11 (.711)
# Adults in home				.02 (.918)	-.18 (.532)
# Children in home					-.21 (.448)

Note: p-values are presented in parentheses; **$p < .05$

Table 12. *Intercorrelations Between Parent/Family Functioning Variables (Group B)*

Variable	PIP Difficulty Total	FES Total Score
PIP Frequency Total	.77 (<.001)***	-.30 (.186)
PIP Difficulty Total		-.26 (.256)

Note: p-values are presented in parentheses; ***$p < .01$

Table 13. *Summary of Hierarchical Regression Analysis for Variables Predicting Full Scale IQ*

					Change Statistics		
Variable	B	SE B	Beta	p	Δ R^2	F	p
Step 1							
Maternal education/ income summary	2.11	.70	.55	.007	.43	15.09	.001
Step 2							
Number of children living in the home	-1.89	1.40	-.24	.193	.06	2.37	.140
Step 3							
PIP difficulty total	-5.09	.07	-.13	.503	.01	.47	.503

Note: $R^2 = .51$, $F(3,21) = 6.15$, $p = .005$

Table 14. *Summary of Hierarchical Regression Analysis for Variables Predicting Language Domain Score*

					Change Statistics		
Variable	B	SE B	Beta	p	Δ R^2	F	p
Step 1							
Maternal education/ income summary	1.09	1.41	.27	.451	.44	11.61	.004
Step 2							
Hours per week in day care/school	.16	.14	.30	.260	.04	.91	.355
Step 3							
PIP difficulty total	-.13	.13	.29	.343	.04	.97	.343

Note: $R^2 = .51$, $F(3,13) = 4.47$, $p = .023$

Table 15. *Summary of Hierarchical Regression Analysis for Variables Predicting Visuospatial/ Visuoconstructional Domain Score*

					Change Statistics		
Variable	B	SE B	Beta	p	Δ R^2	F	p
Step 1							
Maternal education/ income summary	2.16	.97	.47	.040	.34	9.84	.005
Step 2							
PIP difficulty total	-.11	.10	-.24	.280	.04	1.24	.280

Note: $R^2 = .38$, $F(2,20) = 5.60$, $p = .013$

Table 16. *Summary of Hierarchical Regression Analysis for Variables Predicting Motor/ Visuomotor Domain Score*

					Change Statistics		
Variable	B	SE B	Beta	p	Δ R^2	F	p
Step 1							
Number of children living in the home	-5.14	1.09	-.69	<.001	.59	25.36	<.001
Step 2							
PIP difficulty total	-.11	.06	-.29	.062	.08	3.99	.062

Note: $R^2 = .66$, $F(3,19) = 16.77$, $p = <.001$

APPENDIX A: HOME ENVIRONMENT QUESTIONNAIRE

A. Learning stimulation

1. About how often do you read books to your child?
    a) never – few/year *(0 points)*
    b) few/month – 1/week *(2 points)*
    c) 3/week – daily *(4 points)*

2. About how many children's books does your child have of his/her own?
    a) None *(0 points)*
    b) 1 or 2 *(1 point)*
    c) 3 – 9 *(2 points)*
    d) 10 or more *(3 points)*

3. Does your child have the use of a tape recorder at home and have at least 5 children's tapes?

    Yes *(3 points)* No *(0 points)*

4. How often does your child go on an outing (e.g. shopping, picnic, movie, etc.) with a family member?
    a) few times per year or less *(0 points)*
    b) once a month *(1 point)*
    c) 2 – 3 times per month *(2 points)*
    d) several times per week *(3 points)*
    e) once a day *(4 points)*

5. How often has your child gone to any type of museum with a family member in the past year?
    a) Never *(0 points)*
    b) 1 – several times *(2 points)*
    c) monthly or more *(4 points)*

B. Teaching

6. Indicate which of the following your or another adult are helping your child or have helped your child learn at home? *(score one point for each item circled)*

    Numbers The alphabet Colors Shapes/Sizes

C. Other

7. About how many magazines does your family get regularly?
    a) None *(0 points)*
    b) 1 *(1 point)*
    c) 2 or 3 *(2 points)*
    d) 4 or more *(3 points)*

8. How much choice does your child have in deciding what foods he/she eats at breakfast and lunch?
   a) a lot *(2 points)*
   b) some *(1 point)*
   c) little or no choice *(0 points)*

9. About how many hours each day is the TV on in your home?
   a) 1 or 2 hours *(3 points)*
   b) 3 – 5 hours *(2 points)*
   c) 6 – 8 hours *(1 point)*
   d) 9 – 14 hours *(0 points)*

10. Does your child see his/her father on a regular basis?

    Yes *(2 points)* No *(0 points)*

11. How often does your child eat a meal with both his/her mother and father/father figure?
   a) once per day or more *(3 points)*
   b) several times per week – once per week *(2 points)*
   c) once per month or less *(1 point)*
   d) never *(0 points)*

12. About how often do you read books yourself for pleasure?
   a) never – few/year *(0 points)*
   b) few/month – 1/week *(2 points)*
   c) 3/week – daily *(4 points)*

The following question is not included in the total score.

13. Does anyone in your family have a history of a learning/reading problem?

    No_____ Yes_____

    If yes, please explain: _____

VITA

Name: Reem Alexandra Tarazi

Education:

Drexel University, Philadelphia, PA
Ph.D., Clinical Psychology (June, 2004)
Dartmouth College, Hanover, NH
B.A., Psychology; Genetics, Cell, and Developmental Biology (June, 1997)

Publications, Paper Presentations, and Poster Presentations:

Tarazi, R., Cunningham, J., & Barakat, L. (2003, October). *The utility of the BehaviorAssessment System for Children (BASC) in identifying behavioral functioning following pediatric TBI.* Poster presented at the annual conference of the National Academy of Neuropsychology, Dallas, TX.

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