DOMAIN SPECIFIC COGNITIVE EFFECTS OF SICKLE CELL DISEASE IN CHILDREN

Bridgette Carroll, B.S.

Thesis Prepared for the Degree of

MASTER OF SCIENCE

UNIVERSITY OF NORTH TEXAS

December 2021

APPROVED:

Jennifer L. Callahan, Major Professor
Anthony Ryals, Committee Member
Randall Cox, Committee Member
Donald Dougherty, Chair of the Department of Psychology
Tamara L. Brown, Executive Dean of the College of Liberal Arts and Social Sciences
Victor Prybutok, Dean of the Toulouse Graduate School
Carroll, Bridgette. *Domain Specific Cognitive Effects of Sickle Cell Disease in Children.*

Master of Science (Psychology), December 2021, 36 pp., 4 tables, 2 figures, references, 35 titles.

Multiple contributors to neurocognitive impairment in individuals with sickle cell disease have been identified. Research indicates that a history of cerebrovascular accidents, such as silent infarcts and strokes are associated with greater cognitive decline among children with sickle cell disease. Additionally, disease effects such as hemoglobin and hematocrit levels significantly effect cognitive performance among this population and should be taken into consideration when examining neurocognitive impairment. Further, previous studies show a significant relationship between child behavior problems, family functioning, and cognitive performance in children with sickle cell, marking those as important targets for intervention among this population. While cognitive decline with increased age is not typically examined in healthy child populations, some research indicates the presence of age effects in those with SCD. A majority of the literature addresses cognitive impairment from a broad perspective, while a limited number of studies have begun to address effects among specific cognitive domains. Using archival data from the National Institutes of Health’s Cooperative Study of Sickle Cell Disease, results revealed that disease severity was negatively correlated with some aspects of cognitive functioning, including visual-spatial domains. Additionally, some measures of cognitive performance were inversely correlated with age. Consistent with hypothesized outcomes, family functioning was strongly associated with measures of cognitive functioning. Implications are discussed.
Copyright 2021

By

Bridgette Carroll
ACKNOWLEDGEMENTS

I would like to extend thanks to my supervisor, Dr. Jennifer Callahan, who helped make this work possible. Her guidance and advice was invaluable during every stage of this project. I would also like to thank my committee members Drs. Randall Cox and Anthony Ryals for their thoughtful comments and suggestions, and for facilitating a collegial environment that allowed my defense to be an enjoyable moment. I would like to extend my deepest gratitude to laboratory assistant Meredith Hall, whose vital assistance made a seemingly insurmountable task possible.

I would like to thank my family for their continuous support and encouragement during all of my educational endeavors. I would like to thank my daughter, Skylar, who motivates me every day in ways she doesn’t even realize. I would like to give a special thanks to my partner, Tiffany, for her unwavering support and understanding. Thank you for seeing me, believing in me, and not letting me give up.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>iii</td>
</tr>
<tr>
<td>LIST OF TABLES AND FIGURES</td>
<td>v</td>
</tr>
<tr>
<td><strong>CHAPTER 1. REVIEW OF THE LITERATURE</strong></td>
<td>1</td>
</tr>
<tr>
<td>Cognitive Effects and Brain Imaging Abnormalities</td>
<td>3</td>
</tr>
<tr>
<td>Cognitive Functioning, Hematocrit Levels, and Other Disease Effects</td>
<td>7</td>
</tr>
<tr>
<td>Cognitive Functioning, Child Behavior Problems, and Family Functioning</td>
<td>10</td>
</tr>
<tr>
<td>Cognitive Functioning and Age Effects</td>
<td>14</td>
</tr>
<tr>
<td>Cognitive Functioning and Other Physiological Effects</td>
<td>16</td>
</tr>
<tr>
<td>Current Study</td>
<td>18</td>
</tr>
<tr>
<td>Hypotheses</td>
<td>19</td>
</tr>
<tr>
<td><strong>CHAPTER 2. METHODS</strong></td>
<td>20</td>
</tr>
<tr>
<td>Participant Selection and Procedures</td>
<td>20</td>
</tr>
<tr>
<td>Measures</td>
<td>21</td>
</tr>
<tr>
<td><strong>CHAPTER 3. RESULTS</strong></td>
<td>23</td>
</tr>
<tr>
<td><strong>CHAPTER 4. DISCUSSION</strong></td>
<td>29</td>
</tr>
<tr>
<td>Diagnosis Subtype and Domain-Specific Deficits</td>
<td>29</td>
</tr>
<tr>
<td>Cognitive Function and Age Effects</td>
<td>30</td>
</tr>
<tr>
<td>Cognitive Performance and Family Functioning</td>
<td>30</td>
</tr>
<tr>
<td>Study Limitations and Future Directions</td>
<td>31</td>
</tr>
<tr>
<td>Summary</td>
<td>32</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>33</td>
</tr>
</tbody>
</table>
LIST OF TABLES AND FIGURES

Table 1. Mean Intelligence and Academic Scores of Children with HbSS ...................................... 4
Table 2. Mean Intelligence and Academic Scores of Children with HbSS ...................................... 5
Table 3. Mean Behavioral, Family, and Intellectual Functioning Scores of Children with HbSS .. 11
Table 4. Descriptive Statistics Associated with CDC Diagnosis..................................................... 23

Figure 1. Pearson Correlation for Family Environment Scale and Wechsler Intelligence Scale for Children-Revised/Third Edition..................................................................................................... 26

Figure 2. Pearson Correlation for Family Environment Scale and Woodcock-Johnson Tests of Achievement .............................................................................................................................................. 27
CHAPTER 1

REVIEW OF THE LITERATURE

The Cooperative Study of Sickle Cell Disease (CSSCD) was a 10-year prospective cohort study initiated by the National Heart, Lung, and Blood Institute of the National Institutes of Health (Gaston & Rosse, 1982). The CSSCD was aimed at defining the natural history of sickle cell disease and characterizing its socioeconomic impact. At the time of the study launch, in 1978, the clinical course of sickle cell disease from early childhood to death was poorly understood due to the variability of the manifestation, severity, and complexity of the disease. Because available information was anecdotal, retrospective, and deficient in analytical repute, the institute initiated a large multi-site prospective study to improve understanding of the disease and its interactions in the patient’s life (e.g., impact on the patient and their family in the areas of social, economic, educational, vocational, and psychological adjustment). The chief aim of the study was to furnish knowledge that would spawn the enhancement of the quality of life for patients with sickle cell disease and their families. Sickle Cell Disease impacts a significant number of black Americans living in the United States, and this study sought to compare demographic and socioeconomic variables within the CSSCD population to analogous variables within the United States Black Population (USBP). These variables included education, family structure, occupation, and income in addition to other demographics, medical history, and clinical as well as laboratory information.

As described by Gaston and colleagues (1987), a recruitment and retention committee, as well as a policy board of external advisors was formed to facilitate recruitment efforts across 15 participating clinical centers involving 23 geographically dispersed institutions. Recruitment
goals included the inclusion of mild patients, special interest patients (newborns and pregnant women), patients from rural areas, and entry of only those with major phenotypes of the disease. The sample target was 3200 patients over a period of 2 years, with 350 patients in each sex group. Age was also a consideration, with a recruitment goal of 350 patients each in the newborn, child, adolescent, and adult age groups. Participants were recruited using a roster of patients previously seen at university clinics, screening programs (for newborns only), and referrals from physicians and other health care providers. Overall, recruitment efforts of the CSSCD were successful in the areas of total patient population, major phenotype population, and age/sex categories. Such success is largely attributed to recruiting from the “in-place” system of the clinics, recruitment coordinators, and the previously established positive relationships between the patient population and health care providers. The target sample size was reached after a period of 27 months, though the goal for sex/age group numbers was not fully realized. Specifically, the target size was not reached for adolescent and adult males or female children. Additionally, efforts were not successful to recruit the proposed number of newborn or mild patients. Nevertheless, the final study sample consisted of 3,538 black patients across the lifespan. Thus, despite not reaching the desired enrollment targets, the authors anticipated sufficient power to make statistical inferences about newborn patients and different age/sex groups with respect to at least the major phenotypes.

Results from a study by Farber, Koshy, and Kinney (1985) indicated several characteristic differences between the CSSCD population and the USBP. The family structure of CSSCD patients was different than the USBP, containing fewer two-parent families and more single female heads-of-households. There were also differences regarding employment. Though
higher portion of CSSCD patients were unemployed and disabled, twice as many who were employed worked in white collar positions when compared to the USBP. Income was also affected, with male CSSCD patients having a lower median income than USBP males. Findings also displayed some similarities between populations, including education levels and female income.

Although causal relationships to explain these differences were not explored, the findings underscored individuals with SCD as capable of reaching the same educational levels as their USBP counterparts. In fact, the success of CSSCD patients in white collar positions was noted as potentially helpful to vocational counselors in guiding SCD patients to such occupations. More generally, findings highlight the importance of both family functioning and occupational success to improved quality of life among SCD patients.

Cognitive Effects and Brain Imaging Abnormalities

Armstrong et al. (1996) conducted a quantitative, correlational study using archival data from the CSSCD. Data included scores from the Weschler Intelligence Scale for Children-Revised (WISC-R), the Woodcock-Johnson Revised Tests of Achievement (WJ-R), the Purdue Pegboard test, and the Child Behavior Checklist (CBCL), in addition to brain imaging data capture via magnetic resonance imaging (MRI). Upon examination of data associated with 194 children enrolled in the CSSCD, Armstrong and colleagues found that children whose structural MRIs indicated silent infarcts evidenced poorer performance in the areas of arithmetic, vocabulary, and visual motor speed and coordination than those with normal structural MRI readings. Silent infarcts have a 21.8% prevalence rate in children with SCD (Kwiatkowski et al., 2009). Further, as summarized in Table 1 below, children with a history of cerebrovascular accident (CVA) had a
significantly poorer performance in most areas of neuropsychological performance than either those with silent infarcts or those with no structural MRI abnormalities. There was no significant difference in behavioral problems among the three groups. Based upon these findings, the authors suggested future studies evaluate whether neuropsychological decline progresses with age or is accompanied by other sensory / motor deficits.

Table 1

*Mean Intelligence and Academic Scores of Children with HbSS*

<table>
<thead>
<tr>
<th>Measure</th>
<th>MRI Status</th>
<th>Stroke</th>
<th>Silent Infarct</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>WISC-R</td>
<td>FSIQ</td>
<td>70.8</td>
<td>82.8</td>
<td>90.0</td>
</tr>
<tr>
<td></td>
<td>VIQ</td>
<td>72.1</td>
<td>79.9</td>
<td>88.8</td>
</tr>
<tr>
<td></td>
<td>PIQ</td>
<td>74.1</td>
<td>88.1</td>
<td>92.9</td>
</tr>
<tr>
<td>WJ-R</td>
<td>Reading</td>
<td>75.3</td>
<td>81.8</td>
<td>91.2</td>
</tr>
<tr>
<td></td>
<td>Math</td>
<td>65.7</td>
<td>83.6</td>
<td>93.1</td>
</tr>
<tr>
<td>CBCL</td>
<td>Total</td>
<td>57.1</td>
<td>55.6</td>
<td>55.9</td>
</tr>
<tr>
<td></td>
<td>Internalizing</td>
<td>53.9</td>
<td>55.6</td>
<td>56.9</td>
</tr>
<tr>
<td></td>
<td>Externalizing</td>
<td>56.9</td>
<td>54.6</td>
<td>54.0</td>
</tr>
<tr>
<td>Purdue Pegboard</td>
<td>Dominant</td>
<td>11.0</td>
<td>11.1</td>
<td>11.8</td>
</tr>
<tr>
<td></td>
<td>Nondominant</td>
<td>4.6</td>
<td>10.0</td>
<td>10.6</td>
</tr>
</tbody>
</table>

*Note:* HbSS = Hemoglobin SS (sickle cell anemia); MRI = Magnetic Resonance Imaging; WISC-R = Wechsler Intelligence Scale for Children-Revised; FSIQ = Full Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; WJ-R = Woodcock-Johnson Psycho-Educational Battery – Revised; CBCL = Child Behavior Checklist.

Neuropsychological testing and structural MRI scans in the CSSCD were repeated every two to three years during the course of the 10-year study and subsequent 10-year follow-up. In exploring whether neurocognitive scores changed over time, Wang and colleagues (2001) again found that children who had silent infarcts had significantly lower intelligence quotient (IQ) and achievement scores when compared to those with normal structural MRI findings (shown in
Table 2). By examining repeat data though, Wang and colleagues further concluded that school-aged children with sickle cell disease who also suffered from silent infarcts had significant deficits in neuropsychological functions and declines in performance in certain areas of function over time. Although the study lacked a control group matched for age, race, sex, or SES, the effects were sufficiently large to provide support for early childhood therapeutic intervention (i.e., before school age) to address cognitive deficits associated with silent infarcts.

Table 2

Mean Intelligence and Academic Scores of Children with HbSS

<table>
<thead>
<tr>
<th></th>
<th>Stroke</th>
<th>Silent Infarct</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>WISC-III: FSIQ</td>
<td>76.9</td>
<td>77.2</td>
<td>84.8</td>
</tr>
<tr>
<td>WISC-III: VIQ</td>
<td>79.9</td>
<td>77.1</td>
<td>85.3</td>
</tr>
<tr>
<td>WISC-III: PIQ</td>
<td>77.3</td>
<td>81.1</td>
<td>86.7</td>
</tr>
<tr>
<td>WJ-R Math</td>
<td>77.3</td>
<td>82.0</td>
<td>90.7</td>
</tr>
<tr>
<td>WJC-R Reading</td>
<td>84.6</td>
<td>81.8</td>
<td>93.9</td>
</tr>
<tr>
<td>WISC-R/III: Digit Span</td>
<td>6.5</td>
<td>6.8</td>
<td>7.5</td>
</tr>
</tbody>
</table>

Note: HbSS = Hemoglobin SS (sickle cell anemia); WISC-III = Wechsler Intelligence Scale for Children-3rd Edition; FSIQ = Full Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient; WJ-R = Woodcock Johnson Psycho-Educational Battery – Revised; WISC-R = Wechsler Intelligence Scale for Children - Revised.

Beyond the CSSCD study, a literature review by Berkelhammer and colleagues (2007) regarding neuropsychological functioning and the associated neuroimaging findings in children with sickle cell disease identified 28 published articles between 1991 and 2005 and concluded that there was evidence of neurocognitive deficits in each of the following domains: intelligence, attention, executive functioning, memory, language, visuomotor abilities, and academic achievement. The global level of cognitive functioning was hypothesized to be related
to the degree and location of neurological injury. Deficits in attention and executive functions were especially prevalent and were associated with abnormalities in the frontal lobe. Findings again suggested early identification and intervention for children with SCD who are at-risk for academic problems might help promote scholastic and occupational success. Although a fairly systematic review, the included studies frequently evidenced limitations associated with small sample sizes, lack of control groups, and inconsistent measurement approaches.

Most recently, a narrowly focused meta-analysis examined the relationship between intelligence quotient (IQ) and pediatric sickle cell disease (SCD) via inclusion of data from 19 studies that included a pediatric SCD population, MRI data, and a Weschler Intelligence Scale (Kawadler, Clayden, Clark, & Kirkham, 2016). The results of the meta-analysis indicated decreased IQ in children with SCD. Those with a history of stroke performed worse than those with silent cerebral infarcts (SCI) and those with SCI performed worse than with a normal MRI. Additionally, children with SCD and normal MRI performed worse than healthy controls. As deficits in IQ were observed even in the absence of cerebral lesions, other biopsychosocial factors were thought to be likely influence cognitive functioning as well. However, there were several limitations to this study. There was some variability in the versions of Wechsler scales, which may account for some differences in full-scale intelligence quotient (FSIQ). Additionally, the meta-analysis only consisted of cross-sectional studies and was unable to account for age-related effects. There was no specific accounting of how many children, aggregated across the included studies, were in each group. It is also possible that some of the included studies used overlapping participants which could skew the data. Overall, the current status of the field suggests a need for further research that may elucidate the variables responsible for the
differences in IQ among children with SCD. Once identified, interventions may be created to help improve these differences. Beyond infarct and cerebral accidents, other disease effects of SCD also influence cognitive functioning in children.

Cognitive Functioning, Hematocrit Levels, and Other Disease Effects

There are many physiological effects that can accompany SCD, and these factors also influence cognitive functioning. Connolly, Bills, and Hardy (2019) conducted a quantitative, correlational study to assess the cognitive effects of persistent pain in children with sickle cell disease (SCD). The sample size was 89 children between the ages of seven and sixteen. The study protocol included the WISC, WJ, Wechsler Individual Achievement Test (WIAT), Behavior Rating Inventory of Executive Function (BRIEF), Conners-3, and Pediatric Quality of Life Inventory (PedsQL)-SCD Module.

The results demonstrated that children with persistent pain had poorer performances in working memory, processing speed, and reading fluency. They also reported a lower quality of life as it relates to health. Additionally, caretakers of those with SCD and persistent pain were more likely to rate them as having significant levels of defiance and aggression and lower organizational abilities. Findings indicate that children with SCD and persistent pain are likely to have even greater cognitive and achievement difficulties as well as socio-emotional challenges than those with only SCD, making persistent pain a helpful marker in assessing disease burden.

Steen and colleagues (2003) conducted a quantitative, correlational study to evaluate the relationship between cognitive impairment, hematocrit levels and neuroimaging abnormalities in children with hemoglobin SS sickle cell disease (HbSS). The sample size was 49 patients between ages 4 and 19 with HbSS genotype and no history of clinical stroke. The study
protocol included hematocrit data, MR imaging data to examine brain lesions, and the WISC-R and WISC-III to assess cognitive function.

The results revealed greater levels of verbal impairment among children with imaging abnormalities, in comparison to those with normal imaging findings. Additionally, hematocrit levels were found to have a significant correlation to FSIQ, verbal comprehension, and freedom from distractibility. Both factors were independent predictors of FSIQ. The data suggests both diffuse and focal brain injury contributions to cognitive impairment among children with SCD. The authors acknowledge that cognitive impairment could be due to a number of factors not evaluated in this study and encouraged future research to account for these confounds.

Lance, Comi, Johnston, Casella, and Shapiro (2015) conducted a retrospective chart review examining associations among sickle cell disease-related characteristics and neurodevelopmental disorders. The sample consisted of 59 children with SCD and a recorded neurodevelopmental diagnosis. The study found that children with the genotype HbS-β thalassemia plus were more likely to have attention issues than children with HbSS or HbSC genotypes. The authors indicate this could be due to the less common genotype having fewer complications and not meeting full criteria for ADHD but having apparent issues with attention. The study also found that children with SCD and a history of asthma were at higher risk for behavioral issues than those without asthma. No additional relationships between SCD complications and neurodevelopmental disorders were identified. Particularly of note, this study did not find a history of stroke to be associated with neurodevelopmental disorders.

In a cross-sectional study conducted across 19 sites of the Silent Infarct Transfusion Trial, King and colleagues (2014) examined 150 children with sickle cell anemia (SCA) between
ages 5 and 15. In addition to hemoglobin oxygen saturation levels, the study accessed structural MRI data and cognitive functioning scores (as measured by either the Weschler Preschool and Primary Scale of Intelligence, Third Edition, WPPSI-III, or Wechsler Abbreviated Scale Intelligence, WASI). The results showed that parental socioeconomic status (as measured by parental education and income) was positively correlated with FSIQ estimates among SCA patients. In contrast, infarcts were negatively associated with estimated FSIQ. Similar correlations were seen between hemoglobin oxygen saturation levels and age though there was no statistically significant interaction between age and infarct status. Taken together, the findings seem to suggest that the home environment and disease effects may separately impact impaired neurocognitive performance in children with SCA. The primary limitation of this study was the exclusion of those with stroke history, hydroxyurea therapy, or blood transfusion therapy, all of which are common within this population and are known to impact cognitive functioning.

A very recent, large meta-analysis of 47 published studies examining the biological, environmental, and behavioral correlates of cognitive function in sickle cell disease (SCD) (Prussien et al. 2020). The sample size across studies consisted of 2573 individuals with SCD. The results displayed a positive relationship between hemoglobin and hematocrit with measures of broad intelligence (FSIQ), executive function, and language and verbal reasoning. A negative correlation was observed between Transcranial Doppler (TCD) velocity and executive functioning, visual-spatial, and perceptual reasoning. SES was also positively associated with FSIQ, executive function, language, verbal reasoning, visual-spatial, and perceptual reasoning. However, a negative correlation was noted between behavioral problems and FSIQ. Although a
Cognitive Functioning, Child Behavior Problems, and Family Functioning

In a quantitative, correlational study using cross-sectional data collected from the CSSCD, Thompson and colleagues (1999) include a sample size of 289 children who ranged in age from 5 to 15 years old. The study protocol included the WISC-R and the WJ-R to assess neurocognitive functioning, as well as the CBCL and Family Environment Scale (FES) to assess child behavior problems and family functioning, respectively. Brain imaging from a structural MRI was also included. Findings revealed conflicted family functioning, rather than neurocognitive functioning, to be significantly associated with behavioral problems in children with SCD. While important, a notable caution to the data was that maternal report was the sole evidence of child behavioral problems.

Thompson and colleagues (2003) conducted a longitudinal follow-up to their earlier study drawing data from 222 children (ages 5 to 17) enrolled in the CSSCD to reconsider associations among family functioning, behavioral problems, and intellectual functioning among children with sickle cell disease. The study protocol included the WISC-R and WISC-III, CBCL, FES, and MRI data, with repeat testing every 2 years. As is evident from Table 3 below, results indicated a decline in intellectual functioning over time, but not significant changes in family functioning or behavioral problems. Behavioral problems were not associated with MRI classification but were positively correlated with family conflict and negatively correlated with
full-scale IQ scores. Findings reiterate the results of the previous study, again indicating that maternal assessment of poor family functioning is associated with behavioral problems, making family functioning a salient target for intervention to promote adaptation to chronic childhood illness.

Table 3

Mean Behavioral, Family, and Intellectual Functioning Scores of Children with HbSS

<table>
<thead>
<tr>
<th>MRI Status</th>
<th>Visit</th>
<th>CBCL</th>
<th>Family Environment</th>
<th>Intellectual Functioning</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Supp</td>
<td>Conflict</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td>55.1</td>
<td>255.5</td>
<td>-65.2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>55.9</td>
<td>255.1</td>
<td>-67.7</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>56.0</td>
<td>260.3</td>
<td>-66.1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>56.4</td>
<td>259.8</td>
<td>-67.6</td>
</tr>
<tr>
<td>Silent Infarct</td>
<td>1</td>
<td>57.2</td>
<td>247.5</td>
<td>-60.0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>58.0</td>
<td>242.6</td>
<td>-61.9</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>57.5</td>
<td>255.1</td>
<td>-68.6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>55.2</td>
<td>247.2</td>
<td>-74.8</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>57.2</td>
<td>278.8</td>
<td>-77.8</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>56.5</td>
<td>263.4</td>
<td>-72.5</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>59.4</td>
<td>259.4</td>
<td>-63.6</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>57.8</td>
<td>254.2</td>
<td>-70.3</td>
</tr>
</tbody>
</table>

Note: HbSS = Hemoglobin SS (sickle cell anemia); MRI = Magnetic Resonance Imaging; CBCL = Child Behavior Checklist; Supp = Supportiveness; Contr = Controlling; FSIQ = Full-Scale Intelligence Quotient; VIQ = Verbal Intelligence Quotient; PIQ = Performance Intelligence Quotient

Limitations of the study include the sole reliance on the maternal report as a measure of child behavioral problems, and the possibility of the logistic regression model overfitting the data given the sample size. Additionally, this study did not examine confounding variables related to behavior problems, including socioecological elements or other SCD symptoms not
pertaining to brain impairment. Inclusion of these confounds in further studies would aid in devising appropriate interventions for patients and families.

In a quantitative, correlational study to assess neuropsychological functioning in preschool-age children, Tarazi, Grant, Ely, and Barakat (2007) collected data from participants enrolled in other sickle-cell research studies at a children’s hospital in Philadelphia. The resultant sample size was 26 children between the ages of three and five. The study protocol included medical chart review, the FES, the Pediatric Inventory for Parents (PIP), and a short form of the Home Observation for Measurement of the Environment (HOME).

Neuropsychological functioning was assessed using subtests from the WPPSI-III, A Developmental neuropsychological Assessment (NEPSY), the Differential Abilities Scales (DAS), and the Purdue Pegboard test. The findings demonstrated that disease severity was not related to cognitive functioning among young, largely preschool, children with sickle cell. However, socioeconomic status was positively correlated with cognitive functioning with other psychosocial factors evidencing a negative correlation. Income levels were higher in this sample than similar studies and may influence levels of family functioning and home environment. Increased time in day/school care was positively associated with language skills. Taken together, the findings implicate psychosocial factors as salient targets for intervention to improve long-term cognitive functioning.

In a quantitative, correlational study conducted over 16 months, Downes, de Haan, Telfer, and Kirkham (2019) examined 22 children between 3 and 6 years of age with sickle cell anemia and HbSS genotype, but without history of stroke or developmental disorders. Their findings indicated that a positive family environment was the strongest predictor of better
executive functioning, except in the areas of information processing and goal setting.

Similar findings have been observed in other countries as well. In a cross-sectional study of 128 Brazilian children (7 – 13 years of age), 64 of whom had sickle cell anemia and 64 matched controls, cognitive functioning was assessed using the WISC-III (Castro & Viana, 2019). Results indicated that children with sickle cell anemia had lower IQs than healthy controls. Findings also revealed a positive correlation between socioeconomic status and cognitive functioning. The results suggest that sickle cell anemia is a strong predictor of overall IQ after adjusting for socioeconomic effect.

Overall, early cognitive assessment as a part of routine care for children with sickle cell appears to be critical to minimizing the risks of cognitive impairment. Targeted interventions may be academically focused as well as include strategies to address environmental and social conditions. Further studies are needed to address the pathophysiological aspects of cognitive impairment within children with sickle cell anemia.

Research on the impact of psychosocial factors is ongoing. In a quantitative, correlational study to evaluate the effect of social-environmental factors on cognition and behavioral functioning in children with sickle cell disease (SCD), Bills, Schatz, Hardy, and Reinman (2020), recruited 70 children between the ages of 4 and 8 from a developmental screening program at an outpatient clinic. Results indicated that parent and family functioning (PFF) was a factor distinctly separate from elements generally linked with socioeconomic status (SES) such as parent education and income. Given that many studies include SES as a measure of social-environmental risk but not PFF, they may underestimate the impact of PFF on child outcomes.
Results show that PFF was significantly correlated with ADHD symptoms and phonological processing, while SES was correlated with early reading skills and semantic and syntactic processing. This indicates that SES is a significant predictor of language-related effects while parenting factors predict externalized symptoms. Notably, the impact of both factors was subject to biological risk, with a smaller effect on children with higher-risk genotypes, suggesting a greater influence by disease factors. The implication of these results is that PFF is a modifiable social-environmental risk factor and is a vital target for intervention to improve psychological outcomes, especially for those with lower-risk genotypes.

There were several limitations to the study, including the broad nature of the PFF factor, the impact of other social-environmental risks, reliance on proxy reports, and small sample size. Future studies should have a larger sample with greater age diversity to account for age effects, include other risk factors, and a narrower scope of the PFF factor. Additional research should also address the interaction between social-environmental and medical factors.

Cognitive Functioning and Age Effects

There is some evidence of age-related effects that influence cognitive functioning in this population. Although fairly dated at this time, a meta-analysis of published studies (including the CSSCD) evaluating the effects of Sickle Cell Disease on cognitive functioning, particularly on those without cerebral infarcts, captured a large sample size (Schatz, Finke, Kellet, & Kramer, 2002). The sample size across studies totaled 631 children with SCD and 446 comparison children. The results revealed a small reduction in cognitive functioning of children with SCD who do not have cerebral infarcts, particularly in the areas of attention and executive function. The findings were suggestive of a decline in cognitive functioning with increased age and
underscored the need for a prospective study to clearly establish the age effects on specific
cognitive domains in children with SCD. Though cognitive effects in SCD are well documented,
the cause of such effects remained unclear following the Schatz and colleagues’ meta-analysis
because their findings pointed to possible indirect effects such as social or environmental
disadvantages in addition to the direct effects of SCD. In a subsequent literature review of
published works examining psychological complications in sickle cell disease, with a particular
focus on coping, quality of life, and neuropsychological problems, Anie (2005) again concluded
that neuropsychological impairments increase with age and have significant educational
implications.

Steen and colleagues (2005) completed a quantitative, correlational study to examine
the cognitive deficits among 98 children with sickle cell disease who were matched to a control
group of children randomly selected from the standardization sample of the WISC-III. Cognitive
functioning was examined using the WISC-R and WISC-III. Within this sample, SCD patients were
more cognitively impaired than the control group in every comparison, with the largest
difference being in verbal comprehension. Results also indicated that cognitive impairment in
SCD patients was positively correlated with age, which was thought to represent the aggregate
effect of disease burden on the brain. Of note, there was no significant difference between
patients with a normal MRI and patients with an abnormal MRI, which contradicts some
findings while confirming others. The authors addressed this apparent conflict within the
finding by stating that structural MRI is not sensitive to brain injury types and cognitive
impairment could be related to diffuse or focal brain injury. Nevertheless, a limitation of the
study is the uncertainty surrounding the cause of cognitive impairment. Further, this study does
not account for possible confounds including missed days of school and parental education.

In a quantitative, cross-sectional study to examine neurodevelopmental function in very young toddlers with sickle cell anemia, Armstrong and colleagues (2013) drew a sample size of 193 infants between 7 and 18 months of age. Neurodevelopment was assessed using the Bayley Scales of Infant Development, second edition (BSID-II), the Vineland Adaptive Behavior Scales (VABS). Results demonstrated that despite overall functioning of the patients falling in the average range, some functions such as communication, socialization, and behavior were negatively associated with age. The findings implicate that cognitive and behavioral decline in children with sickle cell anemia begins earlier than previously expected. Given the number of factors that may contribute to poorer neurocognitive function, more research within this population was encouraged to determine independent significant predictors. This study also provides valuable data about infant and toddler neurodevelopmental function before treatment which may be used to help enhance risk assessment and develop targeted interventions for this understudied population.

Cognitive Functioning and Other Physiological Effects

Clinicians have also begun to examine the relationship between physical growth and cognitive functioning in those with SCD. A small sample of 46 children between the ages of 4 and 8 was recruited for a quantitative, cross-sectional study examining the relationship between cognitive functioning and somatic growth velocity in young children with sickle cell disease (Puffer, Schatz, & Roberts, 2016). The results indicated a positive correlation between BMI-for-age velocity and both global cognitive and visual-motor ability. The same effect was not present for academic achievement or processing resources, indicating that BMI-for-age velocity
can predict neurocognitive risk in some domains but not all. Additional measurements
displayed stable increases in BMI status for some, but further studies are needed to examine if
this is associated with increased cognitive scores. No significant relationship was found
between growth velocity and cognitive performance, which contrasts with previous studies but
may reflect inconsistent ages and growth measurement intervals.

More recently, Prussien, Jordan, DeBaun, and Compas (2019) published their meta-
analysis of 110 published studies related to cognitive function in sickle cell disease across
domains, lifespan, and cerebral infarct status. The sample size across studies totaled 3,600
individuals with SCD and 1,127 healthy controls. Results of analyses indicate substantial
impairment across all domains, age groups, and infarct status. Deficits were more profound in
school-aged children than preschool children, but less profound in adults compared to school-
aged children. Deficits across all domains increased with the severity of infarct status. The
findings offer compelling evidence that individuals across the lifespan with SCD are at risk for
cognitive impairment. However, this meta-analysis failed to control for confounds such as
environmental and biological factors that influence cognition.

The issue of variable diffuse and focal effects as well as the role of non-cognitive
variables has shaped discussion about the way that SCD is conceptualized. Based on a
systematic review of extant literature, Schatz and McClellan (2006), framed sickle cell disease as
a neurodevelopmental disorder and noted that many effects of SCD that resemble those of
other neurodevelopmental disorders. However, other factors such as socioeconomic status,
social stigma, and medical complications were characterized by Schatz and McClellan as causing
even greater stress in those with SCD. It was the authors’ contention that a
neurodevelopmental approach is needed to address SCD due to the onset of the various cognitive effects at a time when genetic differences, nutrition, and parenting practices are likely to play a major role in patients. Family functioning, and more specifically parenting behaviors, are a significant influence on social adjustment and, with a more holistic appreciation of how SCD is conceptualized, thought to present a salient target for interventions that promote better development and quality of life. Greater public awareness was also characterized as a vital step for improved treatment adaptations. Additional longitudinal studies were again encouraged to better understand developmental aspects as well as interactions between disease effects and social-environmental risk factors.

Current Study

The current study sought to examine the cognitive effects of sickle cell disease (SCD) in children using longitudinal data from a sample of children enrolled in the Cooperative Study of Sickle Cell Disease (CSSCD). Data associated with quantitative neuropsychological assessment (e.g., WISC-R, WISC-III, & WJ-R) were used to explore domain specific cognitive deficits in children with sickle cell disease. Additional data pertaining to family environment were accessed for secondary analyses.

Prior studies examined the relationship between SCD and broad cognitive impairment without accounting for age-related decline, whereas the current study assessed cognitive function via narrower domains while considering age effects. Previous research examining the relationship between family functioning and domain specific cognitive function (Downes et al., 2019) was limited by a small sample size. As proposed, the expectation of this study was that the significantly larger size of this study’s sample could provide an opportunity to replicate
findings generalizable to the larger population. Further, research by Steen et al. (2003) indicated a significant relationship between hematocrit levels and FSIQ in children with no clinical history of stroke. The current study therefore hoped to examine the relationship between hematocrit levels and FSIQ in children with a history of stroke.

**Hypotheses**

1. Cognitive deficits in children with SCD were hypothesized to vary by diagnosis subtype, with greater impairment expected in visual-spatial abilities (consistent with findings by Prussien et al., 2020).

2. The study was expected to replicate findings from Schatz et al. (2002) and show that decline in cognitive functioning increases with age in young children with sickle cell disease.

3. The current study was hypothesized to be consistent with results from Downes et al. (2019) and show that positive family functioning is strongly associated with better neurocognitive functioning among children with SCD.

4. Hematocrit levels were predicted to be positively correlated with cognitive functioning in those with a history of stroke. This hypothesis was based on research stating hematocrit levels have a significant correlation to FSIQ (Steen et al., 2003)

5. The study was expected to replicate findings from Armstrong et al. (2013) and show that decline in functioning begins during infancy, which is earlier than previously believed.
CHAPTER 2

METHODS

Participant Selection and Procedures

Data from the Cooperative Study of Sickle Cell Disease (CSSCD) was used for the current study. The CSSCD was a longitudinal, multicenter study launched in 1978 by the National Heart, Lung, and Blood Institute to document the clinical course of sickle cell disease from birth to adulthood. To maximize variability in disease manifestation and severity within the sample, individuals with SCD were only excluded from the original data collection efforts if they met any of the following conditions: they (or their parents) were unable or unwilling to give informed consent; they were involved in another research project requiring a large commitment; or there was an unreasonable distance to travel to clinical centers for regular follow-ups. Over 3,000 participants were involved, ranging in age from newborn to 70 years of age. Information collected includes medical, economic, and psychosocial data.

For the current study, the dataset was restricted to include only those aged 14 or younger ($N = 2,408$). Of those children, 47.8% ($n = 1,152$) identified as female and 52.2% ($n = 1,256$) were male. The sample nearly exclusively identified as Black or African American (96.9%, $n = 2,334$), with the remainder of the sample coded as “other” (2.8%, $n = 68$) and only one missing data point. Household demographic information revealed that 12.2% ($n = 293$) of children resided in an intact family unit, with 3.9% ($n = 95$) of children having divorced parents, 6.3% ($n = 151$) with parents who never married, 1.7% ($n = 42$) with one widowed parent, and 5.5% ($n = 132$) with parents who were currently separated. With respect to the highest educational level of achievement associated with the child’s household, the mode was high
school completion (10.8%, \( n = 260 \)), with 11.1% \( (n = 268) \) having less than a high school education and 7.6% \( (n = 184) \) having progressed into higher education or trade school beyond high school. However, a large amount of missing data \( (n = 1,696) \) was associated with this variable. Finally, household income data indicated most of the sample 93.6% \( (n = 1,495) \) reported 25K or less in annual income. Notably, this variable was also associated with large amounts of missing data \( (n = 811) \).

Measures

- **Demographics**: Questionnaires were used to collect baseline data regarding sex, age, race/ethnicity, and familial socioeconomic status (SES).

- **Medical and disease information**: CDC diagnosis, disease severity, medications, hematology, and neurologic event information were obtained from medical records. Of these, diagnosis, hematology and neurologic event information, specifically infarct/stroke status, were used in the current study.

- **Wechsler Intelligence Scale for Children-Revised Edition (WISC-R; Wechsler, 1974)**: The WISC-R was used in assessing participants prior to April of 1994 to evaluate cognitive functioning in children between the ages of 5 and 15. The following subtests were administered: Information, Picture Completion, Similarities, Picture Arrangement, Arithmetic, Block Design, Vocabulary, Object Assembly, Comprehension, Coding, and Digit Span.

- **Wechsler Intelligence Scale for Children- Third Edition (WISC-III)**: The WISC-III was used in assessing participants after March of 1994 to evaluate cognitive functioning in children between the ages of ages 6 and 16. The following subtests were administered: Information,
Picture Completion, Similarities, Picture Arrangement, Arithmetic, Block Design, Vocabulary, Object Assembly, Comprehension, Coding, Symbol Search, and Digit Span.

- *Woodcock-Johnson, Revised, Tests of Achievement (WJ-R)*: The WJ-R was used to measure academic abilities. Broad Reading (Letter-Word and Passage Comprehension) and Broad Math (Calculation and Applied Problems) subtests were administered.

- *Peabody Picture Vocabulary Test (PPVT)*: The PPVT was administered to children beginning at 2 years and 6 months of age. It produces a scaled score that is used to assess vocabulary and verbal ability.

- *Achenbach Child Behavior Checklist (CBCL)*: The CBCL was used to measure a broad range of behavioral and emotional problems including social problems, aggressive behavior, anxiety/depression, and delinquent rule-breaking behavior. Scores from the syndrome scales are combined to yield a score for internalizing problems and externalizing problems. The measure is considered to be psychometrically sound, with validity falling between .82 - .92 and reliability between .78 - .86.

- *Family Environment Scale (FES)*: The FES was used to assess the dimensions of relationship, personal growth, and system maintenance within the family environment.10 Scores are derived from subscales to create an overall profile of family environment. Reliability ranges from .61 to .78.
CHAPTER 3

RESULTS

Among the disease severity variables in the archival data, missing data was the modal occurrence for all but two of the variables: presence of seizures and hemoglobin diagnosis (by CDC standards). With respect to seizures, 94.9% of the sample \( (n = 2284) \) reported no history of seizures and no occurrence of seizure during the study. Table 1 provides frequency information for CDC hemoglobin diagnosis. Mean hematocrit in a subset of this sample \( (n = 694) \) was found to be 26.56 (SD = 5.43).

Table 4

*Descriptive Statistics Associated with CDC Diagnosis*

<table>
<thead>
<tr>
<th>Hemoglobin Diagnosis</th>
<th>Frequency ( (n = 2379) )</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>1216</td>
<td>50.5</td>
</tr>
<tr>
<td>SC</td>
<td>569</td>
<td>23.6</td>
</tr>
<tr>
<td>S B+ THAL</td>
<td>105</td>
<td>4.4</td>
</tr>
<tr>
<td>S B0 THAL</td>
<td>54</td>
<td>2.2</td>
</tr>
<tr>
<td>SS ALPHA</td>
<td>355</td>
<td>14.7</td>
</tr>
<tr>
<td>SB0 + ALPHA THAL</td>
<td>43</td>
<td>1.8</td>
</tr>
<tr>
<td>SB0 + DELTA THAL</td>
<td>7</td>
<td>0.3</td>
</tr>
<tr>
<td>Other Variant</td>
<td>2</td>
<td>0.1</td>
</tr>
<tr>
<td>Transfused</td>
<td>28</td>
<td>1.2</td>
</tr>
</tbody>
</table>

No significant demographically-based group differences associated with gender were evident with scores on the Family Environment Scale, the Peabody Picture Vocabulary Test, or the Achenbach Child Behavior Checklist. A revised version of the WISC was published during the course of the study, resulting in some participants being administered the WISC-R and others
the WISC-III. Reported data is labeled WISC-R/III and does not differentiate between which version was used. With respect to WISC-R/III scores, a few subtests evidenced significant group differences: Coding ($t(413) = 3.12, p = .002, d = .31$), Arithmetic ($t(417) = 3.3, p = .001, d = .33$), and Digit Span ($t(399) = 2.9, p = .004, d = .29$). However, no statistically significant group differences were evident on any summary indices or full-scale score for the WISC-R/III. Scores on Woodcock Johnson subtests evidenced more gender-based group differences. Statistically significant gender-based differences were evident on the following subtests and scales: Broad Reading $t(407), p = .003, d = .30$, Letter Word $t(406), p = .018, d = .24$, Passage Comprehension $t(406), p = .002, d = .31$, Broad Math $t(403), p = .002, d = .31$, Calculation $t(404), p = .014, d = .25$, Applied Problems $t(404), p = .013, d = .25$, Processing Speed $t(44), p = .02$. d = .73, Visual Matching $t(49), p = .026, d = .66$, and Cross Out $t(44), p = .039, d = .86$. Research shows evidence of gender-based differences in cognitive abilities within healthy child populations as well (Keith et al., 2008; Roivainen, 2011), so these group differences are not assumed to be disease-related.

To test the hypothesis that cognitive deficits in children with SCD vary by diagnostic subtype, with greater impairment in visual-spatial domains, an ANOVA was performed on the three largest diagnosis subtype groups: SS, SC, and SS Alpha. There was a significant effect of subtype diagnosis on one subtest and two indices of the WISC-R/III: Block Design [$F(2, 1) = 4.42, p = .013, \eta^2 = .02$], Freedom from Distractibility [$F(2, 1) = 3.32, p = .048, \eta^2 = .16$] and Processing Speed [$F(2, 1) = 3.55, p = .040, \eta^2 = .17$]. No other statistically significant differences on WISC-R/III subtests or index scores were found based on diagnosis subtype. Post-hoc testing revealed the only statistically significant difference between two specific groups was on Block Design,
which distinguished subtype diagnosis SS (\(m = 7.5, \ SD = 2.80\)) from SS Alpha (\(m = 8.54, \ SD = 2.74\)). On the WJ, the only statistically significant effect of disease subtype diagnosis was for the Calculation subtest, [\(F(2, 1) = 4.83 \ p = .008, \eta^2 = .03\)]. Post-hoc testing revealed the specific statistically significant difference between groups was for subtype diagnosis SS (\(m = 92.66, \ SD = 18.59\)) from SC (\(m = 99.30, \ SD = 16.16\)). No statistically significant differences associated with disease subtype were found on the PPVT.

To test the hypothesis that decline in cognitive functioning increases with age in young children with sickle cell disease, bivariate correlations between age and cognitive variables were calculated. Consistent with the hypothesis, bivariate correlations revealed age to be inversely significantly correlated with two subtests (Coding \(r = -.12, \ p = 0.19\); Information \(r = -.11, \ p = .02\)) and one index (Perceptual Organization \(r = -.36, \ p = .02\)). In conflict with the hypothesis, scores on the Similarities subtest were significantly positively correlated with age (\(r = .16, \ p = .001\)). No other significant correlations were observed between age and WISC-R/III variables. On the WJ ACH, only the summary score assessing Visual Motor Integration was inversely significantly correlated with age (\(r = -.49, \ p = .001\)). No statistically significant differences associated with age were found on the PPVT.

To test the hypothesis that positive family functioning is significantly associated with neurocognitive functioning among children with SCD, bivariate correlations between the family relationship index score and the three subscales of the FES (Supportiveness, Disorganized Conflict, and Controlling) with cognitive scores were calculated. Figure 1 summarizes those correlations for the WISC-R/III measures and Figure 2 summarizes those correlations for the WJ ACH.
### Pearson Correlation for Family Environment Scale and Wechsler Intelligence Scale for Children-Revised/Third Edition

<table>
<thead>
<tr>
<th>FESSFS</th>
<th>FEDCF</th>
<th>FESSFS</th>
<th>NPCIFS</th>
<th>NPCIQ</th>
<th>NPCIFIQ</th>
<th>NPCICIQ</th>
<th>NPCIFD</th>
<th>NPCIPS</th>
<th>NPCIPID</th>
<th>NPCISP</th>
<th>NPCSSIM</th>
<th>NPCSPARR</th>
<th>NPCSDS</th>
<th>NPCCOMP</th>
<th>NPCCSS</th>
<th>NPCSSS</th>
<th>NPCIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.16</td>
<td>0.26</td>
<td>0.74</td>
<td>0.26</td>
<td>0.76</td>
<td>0.13</td>
<td>0.15</td>
<td>0.04</td>
<td>0.01</td>
<td>0.16</td>
<td>0.06</td>
<td>0.13</td>
<td>0.05</td>
<td>0.03</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>1</td>
<td>0.13</td>
<td>0.13</td>
<td>0.16</td>
<td>0.14</td>
<td>0.17</td>
<td>0.12</td>
<td>0.13</td>
<td>0.04</td>
<td>0.01</td>
<td>0.10</td>
<td>0.02</td>
<td>0.10</td>
<td>0.05</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>0.38</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
<td>0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>0.02</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>0.19</td>
<td>0.17</td>
<td>0.16</td>
<td>0.17</td>
<td>0.17</td>
<td>0.16</td>
<td>0.17</td>
<td>0.04</td>
<td>0.01</td>
<td>0.05</td>
<td>0.02</td>
<td>0.05</td>
<td>0.05</td>
<td>0.03</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>0.01</td>
<td>0.00</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
<td>0.01</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Note: Bold font indicates significance at .05 or less. Abbreviations key: FESSFS = Supportiveness; FEDCF = Disorganized Conflict; FESSFS = Controlling; FESFRIS = Family Relationships Index; NPCIFS = Full Scale IQ; NPCIQ = Full Scale IQ; NPCIFIQ = Verbal IQ; NPCICIQ = Performance IQ; NPCIFD = Freedom from Distraction; NPCIPID = Perceptual Organization; NPCISP = Processing Speed; NPCIPIC = Picture Completion; NPCIPID = Information; NPCIPID = Symbol Search; NPCIPID = Digit Span.
### Figure 2

**Pearson Correlation for Family Environment Scale and Woodcock-Johnson Tests of Achievement**

<table>
<thead>
<tr>
<th>FESSFS</th>
<th>FESDCFS</th>
<th>FESCFS</th>
<th>FESSFRIS</th>
<th>NPCWJARC</th>
<th>NPCWJALW</th>
<th>NPCWJAWA</th>
<th>NPCWJAWA</th>
<th>NPCWJAPC</th>
<th>NPCWJAMC</th>
<th>NPCSPEED</th>
<th>NPCSTMEM</th>
<th>NPCSSENT</th>
<th>NPCSWORD</th>
<th>NPCSAS</th>
<th>NPCSSR</th>
<th>NPCSVMISS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-0.18</td>
<td>-0.35</td>
<td>-0.24</td>
<td>0.63</td>
<td>0.20</td>
<td>0.26</td>
<td>0.34</td>
<td>0.41</td>
<td>0.41</td>
<td>0.30</td>
<td>0.16</td>
<td>0.13</td>
<td>0.09</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>0.38</td>
<td>1</td>
<td>0.70</td>
<td>0.80</td>
<td>0.74</td>
<td>0.74</td>
<td>-0.12</td>
<td>0.41</td>
<td>0.23</td>
<td>0.19</td>
<td>0.16</td>
<td>0.13</td>
<td>0.09</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-0.12</td>
<td>-0.17</td>
<td>-0.17</td>
<td>-0.17</td>
<td>0.18</td>
<td>0.18</td>
<td>0.17</td>
<td>0.17</td>
<td>0.16</td>
<td>0.13</td>
<td>0.09</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.27</td>
<td>-0.27</td>
<td>-0.27</td>
<td>0.74</td>
<td>0.74</td>
<td>0.73</td>
<td>0.73</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.04</td>
<td>-0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.04</td>
<td>-0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Note: Bold font indicates significance at .05 or less. Abbreviations key: FESSFS = Supportiveness; FESDCFS = Disorganized Conflict; FESCFS = Controlling; FESSFRIS = Family Relationships Index; NPCWJARC = Broad Reading; NPCWJALW = Letter Word; NPCWJAWA = Word Attack; NPCWJAPC = Passage Comprehension; NPCWJAMC = Broad Math; NPCWJACA = Calculation; NPCWJAAP = Applied Problems; NPCSPEED = Processing Speed; NCCSVM = Visual Matching; NPCSCO = Cross Out; NPCSTMEM = Short Term Memory; NPCSSENT = Memory for Sentences; NPCSWORD = Memory for Words; NPCSAS = Analysis/ Synthesis; NPCSSR = Spatial Relations; NPCSVMISS = Visual Motor Integration
A statistically significant correlation was observed between the PPVT and the Supportiveness subscale \( (r = .34, p = .000) \). No other significant correlations were observed between family functioning factors and the PPVT.

Hypothesis 4 regarding the correlation between hematocrit levels and cognitive functioning in those with a history of stroke could not be assessed due to insufficient power. Within our sample, there were only 10 children with a reported history of one stroke and 3 children who had a reported history of two or more strokes; an amount too small to make any meaningful inferences. Hypothesis 5, which posits that a decline in functioning begins in the infant stage could not be assessed due to a lack of available cognitive variables. The earliest stage at which cognition was measured in this sample was at 2 years and 6 months (via PPVT).
CHAPTER 4

DISCUSSION

The current study examined the impact of disease severity, age effects, and family functioning on cognitive functioning in children with sickle cell. Analyses revealed that disease severity was negatively correlated with some aspects of cognitive functioning, including visual-spatial domains. Additionally, some measures of cognitive performance were inversely correlated with age. Consistent with hypothesized outcomes, family functioning was strongly associated with measures of cognitive functioning.

Diagnosis Subtype and Domain-Specific Deficits

The current study’s results are in line with research by Prussein et al. (2020) who identified a correlation between disease severity (as measured by hematocrit and hemoglobin levels) and cognitive functioning, especially in the areas of executive functioning and visual-spatial ability. Results from the current sample indicated cognitive performance, specifically visual-spatial abilities, significantly correlated with disease severity (as measured by diagnosis subtype). Given that HbSS is generally known as the most severe form of the disease due to earlier onset and more frequent symptoms, it is not surprising to see the strongest correlation within this group. Individuals with more significant symptoms could be missing more days of school or dealing with more medical complications such as chronic pain that are also associated with deficits in cognitive performance. Future research investigating that possibility is encouraged. No significant correlation was observed between diagnosis subtype and abilities typically associated with executive functioning. It is important to note that previous research indicates that traditional intelligence tests such as the WISC-R/III may not be making accurate
assessments of executive functions (Ardila et al., 2000).

Cognitive Function and Age Effects

Similar to research by Schatz et al. (2002), Anie (2005), and Steen et al. (2005), the findings from the current sample revealed a significant association between age and several measures of cognitive functioning. Specifically, performance was impacted by age on tasks of perceptual reasoning and visual motor integration skills. It is important to note that the measures used in these analyses were normed according to age, thereby presumably already controlling for age effects in calculation of standardized scores. The significant correlations between age and cognitive performance observed within this sample, suggests that the effects of sickle cell disease interacts may interact with age on cognitive variables.

Cognitive Performance and Family Functioning

As noted in the introduction, previous research has found a relationship between cognitive performance and family functioning in children with sickle cell disease (Bills et al., 2020; Downes et al., 2019). A common limitation of earlier studies was not controlling for socioeconomic status in analyses. The current study’s findings are consistent in observing the presence of associations between family functioning and cognition. Furthermore, no significant differences in household income or education were present in the sample, signifying the observed results were not significantly influenced by SES. Analysis revealed a significant correlation between the familial relationship and cognitive performance on the WISC-R/III and the WJ ACH. Family Supportiveness, Disorganized Conflict, and Controlling Factor all exhibited a significant correlation to cognitive functioning, with Supportiveness impacting a greater
number of areas than other factors.

The clinical implications of these findings are that increasing levels of family functioning would be beneficial to children with sickle cell disease. Practical measures include the early identification of children with SCD and targeted intervention such as family therapy and/or individual therapy for caregivers to provide skills necessary to help increase aspects of family functioning including supportiveness.

Study Limitations and Future Directions

There were several limitations to the current study that are important to note. First, there were many analyses conducted during the course of this study, but no Bonferroni corrections were used across analyses. It is possible that this may have resulted in some spurious correlations between variables and this study may overestimate the impact of SCD on cognitive variables. Given the rarity of this sample, we chose to limit the risk of not identifying true effects by not applying potentially too conservative Bonferroni corrections (Bender & Lange, 1999).

Additionally, some of the hypotheses this study set out to address could not be assessed due to a lack of information. Specifically, there were no cognitive measures for infants available in the data. Further research would benefit from including measures (e.g., Bayley Scales of Infant Development) in order to accurately analyze cognitive functioning in this subpopulation. Similarly, this study was not able to assess the relationship between hematocrit levels, cognitive functioning, and stroke status due to an insufficient number of participants with stroke history. Future research with targeted recruitment of participants with a history of stroke may be very helpful.
Despite its limitations, the current study offers important information. This robust sample of children with sickle cell disease, who are an understudied group at high risk of cognitive impairment, was extensively evaluated with neurocognitive measures. In addition, nearly all of the participants in this sample identified as Black or African American, a group that is historically underserved with regard to medical and mental healthcare, which contributes to ongoing clinical and research disparities. For this reason alone, this study as well as continued future efforts are necessary to fill gaps in the literature that hinder the discovery and establishment of targeted support that could help this marginalized population.

Summary

Research has identified a multitude of factors that contribute to deficits in cognitive functioning in individuals with sickle cell disease. These include a history of cerebrovascular accidents, disease effects, age effects, and family functioning. The results of the current study are consistent with findings in previous research and provide evidence of the relationship between these factors and cognitive functioning in children with SCD. Despite several limitations this study identifies several salient intervention targets to aid in adaptation and contributes to a body of research aimed at improving the quality of life for children with sickle cell disease.
REFERENCES


Bender, R., & Lange, S. (1999). Multiple test procedures other than Bonferroni’s desire wider use. BMJ (Clinical research ed.), 318(7183), 600-601. https://doi.org/10.1136/bmj.318.7183.600a


