Neuropsychological Assessment of Working Memory, Processing Speed, and Cognitive Fatigue Among Individuals with Sickle Cell Disease: A Biopsychosocial Developmental Perspective

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NEUROPSYCHOLOGICAL ASSESSMENT OF WORKING MEMORY, PROCESSING SPEED, AND COGNITIVE FATIGUE AMONG INDIVIDUALS WITH SICKLE CELL DISEASE: A BIOPSYPHOSOCIAL DEVELOPMENTAL PERSPECTIVE

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Sickle Cell Disease (SCD) is a chronic disease that continues to impact individuals of African American, Caribbean, Hispanic, Indian, Mediterranean, and Middle Eastern descent (Swain, Mitchell, & Powers, 2006). Children and adolescents with SCD are faced with numerous medical problems, which can arise unexpectedly throughout their lives, including an increased risk for cerebrovascular accidents (CVAs). Recent literature suggests that children with SCD and no detectable neurological insults may be at risk for neuropsychological difficulties. Further, there is evidence of possible cumulative effects of the disease on cognitive functioning with age. Despite evidence that specific measures of cognitive functioning are more sensitive in detecting cognitive deficits, there remains a dearth of literature on specific neuropsychological domains among children and adolescents with SCD and no evidence of CVA as well as literature examining the theory of an age-related decrement.

Participants were 14 children and adolescents with SCD and no documented history of stroke and 19 unmatched healthy controls ages 9 through 22 years old. The results of the current study reveal mixed findings. Children with SCD demonstrated significantly lower scores on the WRAML-2 Working Memory Index and the WISC-IV/WAIS-III Processing Speed Index compared to control group. An age-related decrement was not found with regard to working memory and processing speed. Moreover, working memory was positively related to age, indicating that working memory scores potentially improve with age. Finally, on an objective
method for measuring cognitive fatigue on the CPT-II, differences between groups did not reach statistical significance; however, there was an indication that the SCD group slowed in the second half, as expected. The findings of the SCD group provide important implications for future research and practice.
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CHAPTER 1

Introduction

Sickle cell disease (SCD) is currently the most common group of inherited diseases among African American children, with approximately 1 in every 500 African Americans being born with SCD (Armstrong, 2006). Further, about 1 in 12 African Americans and about 1 in 100 Hispanic Americans are carriers of the sickle cell trait (Gustafson, Bonner, Hardy, & Thompson, 2006; Ris & Grueneich, 2000). While individuals of African and Caribbean descent comprise the greatest percentage of SCD cases, individuals of Indian, Mediterranean, and Middle Eastern descent are also affected (Swain, Mitchell, & Powers, 2006). It is estimated that SCD affects over 2 million people worldwide, with approximately 72,000 of these being Americans (U.S. Department of Health and Human Services, 2002). Hence, SCD is a public health concern, particularly with young American ethnic minority groups.

Medical Problems during Childhood and Adolescence

Children and adolescents with SCD are faced with numerous medical problems which can arise unexpectedly throughout their lives. Throughout infancy, babies with SCD are at risk for acute illnesses and pain crises during the infant stage of development, colic-like symptoms, and feeding problems (Ris & Grueneich, 2000). These infants are also at risk for streptococcus pneumonia, although treatments with penicillin are now able
to prevent many of these infections from occurring. Other risks for infants with SCD include low birth weight, mild fetal hypoxia, and brain injury (Schatz & Puffer, 2006).

There is significant concern for children with SCD as they remain at risk for cerebral vascular accidents, commonly known as strokes and infarctions, or even cell death (Ris & Grueneich, 2000). Approximately 5-10% of children with SCD experience cerebrovascular accidents, and 11-20% of children with SCD experience silent strokes, strokes that are not detectable by radiographic techniques (Gustafson et al., 2006). Individuals who are homozygous for hemoglobin S (HbSS) are primarily affected by these cerebrovascular accidents (Armstrong, Thompson, Wang, Zimmerman, Pegelow, Miller, 1996). Recent literature suggests that children and adolescents with SCD and no detectable neurological problems may also be at risk for neuropsychological problems, which may impact their performance at school (Gold, Johnson, Treadwell, Hans, Vichinsky, 2008; Noll, Stith, Gartstein, Ris, Grueneich, & Vannatta, 2001).

Although mortality rates have decreased in recent years due to newborn screenings, prevention of infections, and improvements in medication and education, statistics clearly demonstrate a decreased life expectancy among individuals with SCD (Ashley-Koch, Yang, & Olney, 2000). Adolescents continue to remain at risk for death, permanent disabilities, or infections (Armstrong, 2006).

Neuropsychological Sequelae

Neuropsychologists have recently begun to understand how SCD and the associated medical problems can negatively impact neurocognitive functioning. There is limited research exploring the neuropsychological effects of SCD among children and
adolescents. Advancing neuropsychological studies among individuals with SCD will help provide a better understanding of the brain functions affected by the disease itself as well as allow professionals to better accommodate the educational and psychological needs of these individuals.

Neuropsychological Deficits

The biology of SCD may contribute to neurocognitive declines in intellectual functioning (Steen, Fineberg-Buchner, Hankins, Weiss, Prifitera, Mulhern, 2005; Swift, Cohen, Hynd, Wisenbaker, McKie, & Makari, 1989). Additionally, the gamut of medical problems described above, such as cerebral infarctions, resulting from SCD has been associated with cognitive deficits. These medical problems and associated neuropsychological deficits will be explored more thoroughly in Chapter II.

Neuropsychologists have played a significant role in addressing the neurocognitive and emotional sequelae of SCD that arise from the vast amount of medical problems associated with the disease. Specifically, neuropsychologists have demonstrated that there are significant psychological and neuropsychological effects of SCD in children and adolescents (Noll et al., 2001; Ris & Grueneich, 2000; Steen et al., 2005). Hence, SCD poses a serious risk for academic and intellectual problems for this developing population. Many of the findings address global effects of SCD on neurocognitive functioning. There has not been sufficient explanation of specific neurocognitive functions such as working memory.

In general, the research to date on chronically ill children has consistently documented risks for psychoeducational and learning disorders (Lubker, Bernier, &
Vizoso, 1999). Indeed, several studies indicate that individuals with SCD perform lower than their same-age peers without SCD on verbal and performance measures (Hogan, Kirkham, Isaacs, Wade, & Vargha-Khadem, 2005; Noll et al., 2001). Additionally, neuropsychological assessments and research have begun to increase knowledge of specific neurocognitive domains derived from theories of brain organization, such as language, visual-spatial, and executive functions (Schatz & Puffer, 2006). Based on these findings, it is crucial to understand the underlying neurocognitive functions and processes which may contribute to learning disorders and other cognitive deficits in children and adolescents with SCD.

The dearth of literature with regard to academic difficulties among children and adolescents with SCD indicates a strong need to expand upon neuropsychological testing in order to address the prevalence of learning deficits and provide appropriate interventions (Peterson, Palermo, Swift, Beebe, & Drotar, 2005). In fact, Peterson and colleagues contend that more information is needed with regard to daily school functioning of children and adolescents with SCD, such as changes in attention and memory. They also maintain that academic problems in the classroom are often unnoticed by faculty and administrators or attributed to school absences. Understanding these changes or deficits in daily functioning is crucial in order to provide appropriate accommodations such as Individuated Educational Plans and Section 504 plans as well as psychoeducation to the professionals involved in their everyday lives.

Processing speed and working memory have been considered significant executive functions underlying many of these neurocognitive processes which are essential to learning. A better understanding of the relationship among these factors in
children and adolescents with SCD will help to delineate the neuropsychological deficits in individuals with and without Sickle Cell Disease. Of note, Schatz, Finke, Kellett, and Kramer (2002) conducted a meta-analysis on cognitive functioning in children with SCD. Their findings suggest that specific abilities are more sensitive than IQ scores to cognitive impairments in children and adolescents with SCD. Thus, examining the effects of SCD relating to cognitive fatigue, processing speed, and working memory among children and adolescents will help to identify needs, appropriate recommendations and accommodations, and interventions which will ideally foster learning.

Background

Sickle Cell Disease is a genetic disorder caused by a mutation of hemoglobin, which has been traced to chromosome 11 (Ashley-Koch et al., 2000). The most common types of sickle cell disorders are Sickle Cell Anemia (Hb SS), Sickle-Hemoglobin C Disease (Hb SC), and Sickle Beta-Plus Thalassemia (Hb S β-thalassemia) (Gustafson et al., 2006). Hemoglobin, which is found in red blood cells, is responsible for helping transport oxygen from the lungs to other parts of the body. Individuals with SCD are born with cells that are affected by abnormal hemoglobin (Hb); mostly hemoglobin S, and in other cases, hemoglobin C. This abnormality causes red blood cells to become distorted in shape; these sickle shaped cells have difficulty passing through blood vessels, causing less blood to reach various parts of the body. Vaso-occlusions, which result from sickle cells obstructing blood flow, pose serious risks for children and adolescents including, but not limited to, organ damage, neurological diseases, hypoxia, and severe pain (Gustafson et al., 2006; Swain, Mitchell, & Powers, 2006). Anemia, tissue damage of the
lung, and stroke are also possible outcomes (Ashley-Koch et al., 2000). Further, a significant proportion of strokes and infarcts occur during early developmental years or before 14 years of age (White, Salorio, Schatz, & DeBaun, 2000).

Despite its historical prevalence with clinical findings dating from 1910, advances in SCD research are quite recent. According to Armstrong (2006), knowledge about the etiology, severity of symptoms, treatment, and management of SCD did not emerge until the 1980s. Since that time, significant improvements have emerged, yet, to date, there is no consistent cure for SCD.

**Treatment Protocols**

The treatment for SCD varies according to the needs of the patient. Once diagnosed, children with SCD are recommended to schedule healthy routine doctor visits. Routine immunizations and prophylactic medications are administered to children based on their age (Lane, Buchanan, Hutter, Austin, Britton, & Rogers, 2001). Typical therapies include medication, such as hydroxyurea, and in more severe cases, the use of bone marrow transplants. Medications have been implemented in most treatment protocols to help reduce pain symptoms (Ballas, Barton, Waclawiw, Swerdlow, Eckman, & Pegelow, 2006).

Immediate medical care is required under certain circumstances. Lane and colleagues (2001) provide a comprehensive list of medical problems including pain, respiration problems, abdominal pain, neurological signs or symptoms, fatigue, vomiting or diarrhea, and/or priapism episode (i.e., a painful condition in which an erect penis does not return to its flaccid state). Transfusion therapy is also utilized during some acute
illnesses in patients with SCD. For example, acute vaso-occlusive episodes, exacerbated anemia, and preparation for some medical procedures involving anesthesia, may warrant red blood cell transfusions (Lane et al., 2001). In cases when severe anemia that lasts over several days, termed aplastic crisis, individuals may be at risk for heart failure; thus, a slower type of transfusion is needed.

The Biopsychosocial Developmental Perspective

As noted above, many of the neurological consequences of SCD and problems associated with the disease place individuals at a greater risk for neurocognitive deficits and developmental effects (Ris & Grueneich, 2000). Schatz and Puffer (2006) purport that failure to include early developmental factors (e.g., birth risks, postpartum infection, hypoxia), may overestimate the impact of the disease on cognitive functioning. The biopsychosocial developmental perspective has facilitated a better understanding of SCD and the interaction between the disease and associated problems throughout the development of children and adolescents. This model has been considered the forefront of both medical and psychological research as it allows for a comprehensive view of the various factors affecting individuals with SCD: biological, cultural, social, emotional, developmental, and contextual (Armstrong, 2006; Gustafson et al., 2006). When performing neuropsychological assessments on children and adolescents with SCD, a developmental perspective should be incorporated into the model. As Bernstein (2000) notes, incorporating biology and development into models of assessment will provide a better understanding of neurological disorders and will benefit patients. Therefore,
several of these components, including age, birth, and neurological history were included in the current study.

Specific Executive Functions

Executive functions of the brain include a broad range of domains, including, but not limited to planning, organization, shifting, self-monitoring, information processing speed, working memory, and attention. These functions have been linked to the frontal lobe of the brain and are essential to efficient learning. Specific executive functioning domains have been examined considerably with the sickle cell population, with marked differences noted in specific areas of dysfunction. For example, many researchers have reported lower performance on memory and attention tasks (Fowler, Whitt, Lallinger, Nash, Atkinson, & Wells, 1988; Ris & Grueneich, 2000) when compared to healthy children. Notably, older children with SCD have been found to have lower scores than younger children (Steen et al., 2005). Thus, decrease in performance with age has been suggestive of cumulative effects of disease on the brain.

Brown, Buchanan, Doepke, Eckman, Baldwin, and Goonan (1993) reported that individuals with SCD demonstrate lower scores on tasks associated with executive functioning, such as attention and impulsivity, when compared to healthy individuals. The authors were unable to find support for an age-related decrement or sickle cell type among the individuals or variability between the types of sickle cell conditions, homozygous compared to heterozygous. Individuals who have inherited two copies of the sickle cell gene are considered homozygous for the disease and have Sickle Cell Anemia, while individuals who have inherited one copy of the gene (from one parent) are
considered heterozygous for the disease and have sickle cell trait (Ashley-Koch et al., 2000). The inconsistent findings with regard to specific executive functions of individuals with SCD and a possible age-related decrement need to be addressed with additional research. In addition, the authors did not include working memory, which is a significant component of neuropsychological assessment.

Vaso-occlusions (decreased oxygen and blood flow due to sickled cells) have contributed to stroke in some individuals with SCD. Researchers have examined the effects of stroke among sickle cell patients, often demonstrating a significant difference in many cognitive domains between individuals with SCD who have experienced stroke, compared to individuals who have no evidence of stroke and healthy controls. Possible neuropsychological effects from medical events, such as a stroke, should be considered in light of the patient’s current age. The highest incident of the first stroke in a child with SCD usually occurs between the ages of 2 and 5 years (Schatz & Puffer, 2006). Studies have demonstrated that children who experience strokes tend to score significantly lower on measures of intellectual functioning, when compared to individuals with SCD who have no evidence of stroke.

In order to address the possible age-related decrement in specific neurocognitive functions over time in children and adolescents with SCD, the present study on SCD included neuropsychological assessment from a biopsychosocial-developmental approach. The model focused on current age as a variable, and neurological history was requested to assure that the healthy controls did not have any form of chronic illness or any known history of disability. Individuals with SCD and a history of stroke were excluded from the study. Only children and adolescents with either Sickle Cell type SS
and type SC were included in the Sickle Cell group. Individuals with Sickle Cell trait and any other type of Sickle Cell, such as Sickle Beta-Plus Thalassemia, were excluded from both groups due to the variations in their disease, which would likely have impacted the presentation of cognitive symptoms.

Schatz and colleagues (2002) conducted a meta-analysis on cognitive functioning in children with SCD. Their findings indicate that individuals with SCD and no cerebral infarction demonstrate small, but reliable deficits on measures of IQ. In addition, the authors contend that specific cognitive and executive domains may show a greater effect than broad cognitive or intellectual domains alone. Therefore, examining specific executive functions, such as working memory and processing speed are more informative than solely relying on overall domains, which are not sufficient in researching individuals with SCD and no cerebral infarcts.

Working Memory

Working memory is a central component of complex cognition (Shah & Miyake, 1999). Working memory has been described by Baddeley and Hitch (1974) as a system or mechanism underlying the maintenance of task-relevant information during the performance of a cognitive task. Baddeley and Logie (1999) assert that working memory is involved in central executive functioning. Working memory is involved in numerous complex activities, including but not limited to, mental arithmetic, reasoning and language comprehensive. Thus, problems with working memory in individuals with SCD may impede other cognitive processes.
Several researchers have studied working memory in individuals with SCD. For example, Brandling-Bennett, White, Armstrong, Christ, and DeBaun (2003) examined individuals with SCD who have experienced stroke and compared them to individuals with SCD who have not had frontal cerebral infarcts, which are infarcts located in the frontal lobe of the brain. Their findings indicated that those with frontal infarcts have greater impairment with regard to manipulation of information in working memory (Brandling-Bennett et al., 2003). Another study by Brown, Davis, Lambert, Hsu, Hopkins, and Eckman (2000) examined the neurocognitive functioning of children with SCD who had either cerebrovascular accidents or silent strokes and were compared to children with no evidence of CNS pathology, which is a leukemic infiltration of the central nervous system. The data indicated that those with clinical strokes or silent strokes performed more poorly than their peers without any stroke (Brown et al., 2000). Children with SCD and no overt signs of CNS damage had lower scores on every measure of cognitive functioning, including attention, memory, and achievement, when compared to healthy control (Noll et al., 2001). However, findings were not significant for working memory domains on the Wide Range Assessment of Memory and Learning (WRAML). Based on these inconsistent findings, examining working memory in a population with SCD and no known history of stroke is essential in the current study. Understanding specific components, such as verbal working memory, may help illuminate reported deficits in many areas, such as intellectual functioning, in children and adolescents with SCD.

Processing Speed

Processing speed describes the rate at which basic cognitive operations can be
completed (Schatz, Kramer, Ablin, & Matthay, 2000). Processing speed has been considered a sensitive measure of sensory and motor changes that affect cognition (Salthouse, 1996). Because of the changes in cerebral blood flow among patients with SCD, processing speed may be an important construct to examine as it has been recently suggested that processing speed is correlated with cerebral blood flow. Processing speed underlies cognitive functioning and learning and has been considered a necessary component of working memory processes (Schatz et al., 2000). Some have considered processing speed a sensitive measure of cognitive functioning because the proportion of variance found to have been associated with differences in aging individuals has been almost fully accounted for by scores on simple tasks of processing speed (Salthouse, 1996). Despite its significant role in cognitive functioning, minimal studies have examined processing speed with SCD patients.

Several clinical populations other than SCD have been researched with regard to processing speed and working memory. Research indicates that individuals with a history of cerebrovascular accidents demonstrate impaired processing speed, while those patients with SCD who do not show evidence of any cerebrovascular accidents may be at risk to develop cognitive deficits, including slowed processing of information (Steen et al., 2005). Moreover, of the 55 children studied by Moser, Miller, Bello, Pegelow, Zimmerman, and Wang (1996) who experienced multiple lesions, the majority (78%) were found to have frontal lobe lesions, an area associated with executive functioning. Understanding the impact of SCD on these two variables, processing speed and working memory, may lead to improvements in learning for children and adolescents diagnosed with SCD.
A relationship between pain and processing speed has been documented, indicating that individuals with chronic pain performed poorly on tasks of delayed memory and information processing speed (Hart, Martelli, & Zasler, 2000). Similarly, Lezak and colleagues (2004) reported that individuals who experience pain are likely to demonstrate weaknesses in processing speed. Thus, in order to account for any impact of pain on any of the processing tasks, pain was assessed by self-report prior to the assessment. In addition, patients were monitored throughout the test for any complaints of pain.

**Cognitive Fatigue**

Fatigue is a chief complaint among individuals with SCD. Mental or cognitive fatigue has been conceptualized as difficulty performing certain mental tasks (Deluca, 2005). Deluca describes four possible approaches that exist when studying cognitive fatigue in a clinical population: (a) cognitive fatigue over an extended time (prolonged effect), (b) cognitive fatigue during sustained mental effort, (c) cognitive fatigue after challenging mental exertion, and (d) cognitive fatigue after challenging physical exertion. This definition of fatigue measures mental performance as a behavior, not as a subjective feeling. Toward this end, fatigue reported by an individual’s self-report of on a subjective scale generally has little to no correlation with objective measurements, or behavior.

Cognitive fatigue has been defined as the inability to sustain performance throughout the duration of a continuous, complex information-processing task (Bryant, Chiaravalloti, & DeLuca, 2004). Several studies demonstrate that over time, cognitive performance declines during mentally challenging tasks (DeLuca, 2005). The majority of
the clinical populations that have been studied with regard to cognitive fatigue includes, but is not limited to those people diagnosed with multiple sclerosis, chronic fatigue syndrome, depression, and traumatic brain injury (TBI). Most studies have examined adult populations and, to date, no studies have examined cognitive fatigue among sickle cell patients. In addition, due to the lack of consensus regarding definitions of cognitive fatigue, the present study examined cognitive fatigue during sustained mental effort among sickle cell patients.

Significance of the Study

SCD is a significant concern, particularly among African Americans in the United States. The extensive medical problems and challenges faced by children and adolescents with SCD have been associated with numerous problems, including academic difficulties and neurological problems that may affect processes involved with learning. Neuropsychological research on SCD remains limited. Researchers have demonstrated significant findings with regard to global deficits among individuals with SCD, particularly with regard to those who have experienced cerebrovascular accidents or infarcts.

Even more limited is research regarding specific neurocognitive functions such as processing speed and working memory among children and adolescents with and without a history of stroke. Because these processes are associated with specific aspects of learning, focusing on these processes may be advantageous when attempting to understand cognitive dysfunction in the SCD population and provide appropriate educational and academic accommodations and interventions. Therefore, the following
study examined two specific executive functioning components, processing speed and working memory among individuals with SCD and no known history of stroke compared to a sample of healthy controls.

Lastly, the goal of the current study was to be the first to examine cognitive fatigue through an objective, rather than subjective method, among a sample of children and adolescents with SCD.

Research Questions

1. How do children and adolescents with SCD and no known history of stroke differ in terms of processing speed and working memory, when compared to healthy children and adolescents?

2. How does SCD affect processing speed and working memory during development? Specifically, is age related to the performance of children and adolescents with SCD and no history of stroke on working memory and processing speed tasks?

3. Are symptoms of cognitive fatigue more pronounced in children and adolescents with SCD when compared to healthy children and adolescents?

Hypotheses

$H_1$ Children and adolescents with SCD and no history of stroke will have significantly greater deficits in processing speed and working memory than healthy individuals.

$H_2$ There will be significant differences between the SCD group and healthy group on scores of processing speed tasks and working memory tasks when controlling
for age. In addition, there will be a specific impact of age on performance according to these measures.

\( H_3 \) Individuals with SCD and no known history of stroke will demonstrate greater cognitive fatigue when compared to healthy participants.

Definition of Terms

*Sickle cell disease:* Includes individuals with either SCD Hb SS or Hb SC.

*Sickle cell disease (Hb SS):* Individuals who have inherited two copies of the sickle cell gene, Hb S, a variant of the \( \beta \)-globin gene called sickle hemoglobin (Hb S); individuals with this type are considered homozygous for the disease; also referred to as *sickle cell anemia (SCA).*

*Sickle-hemoglobin C disease (Hb SC):* Sickle cell disease caused by one copy of Hb S plus another \( \beta \)-globin variant, Hb C. Individuals with this type of the disease also meet criteria for sickle cell disease (Ashley-Koch, et al., 2000).

*Sickle beta-plus thalassemia (Hb S \( \beta \)-thalassemia):* Individuals who inherit one copy of Hb S plus another \( \beta \)-globin variant, Hb \( \beta \)-thalassemia. Patients with this type of sickle cell disease will be excluded from the study.

*Processing speed:* Processing speed describes the rate at which basic cognitive operations can be completed (Schatz, Kramer, Ablin, & Mattay, 2000).

*Working memory:* Working memory has been described as a system or mechanism underlying the maintenance of task-relevant information during the performance of a cognitive task (Baddeley & Hitch, 1974).

*Cognitive fatigue:* Consistent with DeLuca’s (2005) definition of cognitive fatigue
during sustained mental effort, cognitive fatigue will be measured by decreased performance on second half vs. first half of a sustained cognitive task.

**Delimitations**

The main limitation in quasi-experimental designs in research is with regard to the sample. Because participants were predetermined based on their health status (i.e., SCD without a history of strokes or healthy individuals), participants lack random sampling. In an attempt to control for some threats to validity, the healthy group was included in the present study. In addition, Pedhazur and Schmelkin (1991) note that subject selection and statistical adjustments can help control threats to validity, such as confounding variables. Toward this end, selection of participants was attempted to be selected based on similar demographic information. Although the patient sample was representative of children with SCD, the majority of these participants were from a low economic background. Therefore, the sample may have impacted its external validity, as larger populations of SCD may not necessarily have low annual income. With regard to generalizability, the current study was limited to children and adolescents with sickle cell disease, particularly types Hb SC and Hb SS. The results cannot be assumed to relate to literature on adults with SCD, as development is a significant factor for the current population or other types of sickle cell disease that were not included in the study.
CHAPTER II

Review of Related Literature

The purpose of this chapter is to provide a critical review and discussion of the literature relevant to the proposed study. Researchers have only recently begun to examine the psychological and neuropsychological impact of SCD on intellectual and cognitive functioning. Ample studies have provided evidence that SCD can cause significant impairments in psychological, neuropsychological, and educational domains (Lubker et al., 1999; Noll et al., 2001; Ris & Grueneich, 2000; Steen, Hu, Elliot, Miles, Jones, Wang, 2002). First, this review will discuss those findings. Next, the neuropsychological sequelae of SCD will briefly be discussed to provide a background for specific executive dysfunction. The susceptibility of two specific functions, processing speed and working memory, to neurocognitive deficits will be examined from a biopsychosocial developmental perspective. Further, individuals without cerebral vascular complications will be considered with regard to their neurocognitive functioning due to the substantial findings regarding those with stroke. Lastly, cognitive fatigue, a relatively novel construct in neuropsychological research, will be examined in light of SCD.

Academic and Cognitive Functioning

Individuals with SCD have been found to perform lower on certain academic and cognitive measures. While the disease itself may impact performance in school, other
factors such as fatigue, pain, and absences from school may contribute to educational performance that is below children and adolescents' true abilities (Peterson et al., 2005). Demographic factors, such as socio-economic status (SES) and age, have also been considered risk factors for children and adolescent's academic and intellectual functioning (Barakat, Lash, Lutz, & Nicolaou, 2006). For example, some researchers contend that financial difficulties among African American families may influence a child's adjustment (Gustafson et al., 2006). Toward this end, research has indicated that individuals from lower economic families tend to perform lower on cognitive and standardized tests during preschool and school age years. Stage of development is also believed to have implications for their academic performance. Thus, in order to account for factors such as absences and demographic information, all efforts were made in the current study to include comparisons of individuals with SCD to healthy individuals of similar economic and ethnic backgrounds, and controlled for age due to the possibility of cumulative effects on the brain over the course of development.

Brown and colleagues (1993) examined possible confounding variables and their effect on cognitive performance. Specifically, the researchers measured social class, age, sex, and disease severity on cognitive functioning. Seventy patients ages 2 to 17 with SCD were examined and matched with 18 healthy siblings as controls. Any child with neurological difficulties was eliminated from the study. Findings indicated that children with SCD performed significantly lower than their siblings on specific areas of functioning, particularly on measures of academic achievement and sustained attention. Intellectually, however, the children with SCD performed adequately. These findings indicate some evidence of frontal lobe involvement, which is particularly relevant to the
current study due to the role of the frontal lobe in specific executive functions. With regard to demographic variables, minimal evidence supported the notion that performance decreases with age; however, visual-motor functioning and sustained attention were found to decrease as children developed. Socio-economic status (SES) was found to be moderately related to the measures given, which demonstrates that SES may contribute to some of the variability in cognitive functioning. More importantly, however, when SES was controlled, hemoglobin was found to be predictive of intellectual functioning, fine motor skills, whereas academic achievement and school absenteeism was not related to academic or intellectual functioning. Overall, the article provides important evidence of the role of the frontal lobe in functioning of children and adolescents with SCD. Yet, a small number of controls was utilized in the sample, which should be expanded and examined further. Further, the age range included in the study may not have been extensive enough to examine the developmental effects of SCD.

The Hematology/Oncology Psycho-Educational (HOPE) Needs Assessment has facilitated in the understanding of those patients who are in need of educational interventions, neuropsychological evaluation, and academic planning. Peterson and colleagues (2005) utilized the HOPE assessment with 72 children and adolescents, ages five to thirteen. Overall findings indicated that regardless of sickle cell type and history of stroke, one-third to one-half of the individuals assessed were found to have significant academic needs and limitations, behavioral problems, and changes in attention or memory. This study is particularly relevant to the current study, because it provides evidence that more developmental screenings are needed. The authors purport that discrepancies between educational needs and school interventions remain, which alludes
to the importance of not only providing recommendations, but also pragmatically following through with the recommendations through an educational liaison. The importance of neuropsychological assessment with a school-age SCD population is also stressed, and the authors provide suggestions for securing appointments with a minority population who often experience difficulty with transportation as well as the understanding of the need for a neuropsychological evaluation.

Cognitive and neuropsychological research is relatively new among the sickle cell population. Several researchers have compared children and adolescents with SCD and cerebral vascular accidents (CVA) to those with SCD and no evidence of CVA to better demarcate the effects of SCD on the brain, without interference from CVA.

Armstrong and colleagues (1996) were some of the original researchers of cognitive functioning in SCD patients for the Cooperative Study of Sickle Cell Disease, a multicenter study. The authors' final sample included 194 patients, ages 6 through 16, with mostly HbSS represented in the sample. The study included a neuropsychological evaluation and MRI of the brain for each subject, and individuals were categorized based on cerebral infarction, atrophy, or healthy condition. In addition to neuropsychological domains, the researchers examined eight factors, four of which were significantly related to neuropsychological functioning: language spoken at home, parent education, age, and hematocrit levels (which measures the proportion of blood volume that is occupied by red blood cells) were used as covariates in the analyses. Overall findings of the neuropsychological assessment indicated that children with cerebral infarcts performed significantly lower than children with silent infarcts and children with no MRI abnormalities on global cognitive functioning, specific areas of language and verbal
abilities, visual-motor and visual-spatial processing and performance, and academic achievement. They also scored lower than children with no MRI abnormalities on visual motor speed of processing and sequential memory.

A significant finding in this study was that the majority of individuals with cerebral infarcts had Hb SS type of SCD. In addition to their pervasive impairment, individuals with silent infarcts performed poorer than healthy children on arithmetic, vocabulary, visual motor speed, and coordination. Thus, the authors provide sound evidence for inclusion of the genotype of SCD. The authors also helped to identify the locations of cerebral or silent infarcts by utilizing MRIs and neuropsychological research, which was determined mostly across the frontal cortex and basal ganglia; however, instruments utilized in the study, including the WISC-R, are now outdated. Thus, current assessments are needed. Additionally, the authors failed to examine developmental trends in performance, despite their acknowledgement that several studies provide evidence of impairment due to cumulative effects of infarcts over time. While individuals with infarcts demonstrated sequential memory problems, more extensive assessments of children and adolescents with SCD with and without infarcts should be studied.

Brown and his colleagues (2000) extended the study by Armstrong and his colleagues (1996) including SCD patients without any evidence of CNS damage. Children and adolescents were administered neuropsychological assessments along with magnetic resonance imaging (MRIs). MRI readings were classified as normal (without any CNS damage), cerebral infarction, atrophy, cerebral infarction and atrophy, or silent stroke. Six domains were assessed in the neurocognitive battery: intellectual functioning, academic functioning, attention and executive functioning, language, visual-spatial and
motor processing, and behavior (Brown et al., 2000). Six MANOVAs on each neurocognitive domain and post hoc analyses yielded several statistically significant results. Children with overt strokes performed lower on attention tasks than those without any CVA. Those with silent strokes performed similarly to those with overt strokes. The unique finding of this study is that both groups with CNS involvement demonstrated a high frequency of frontal lobe impairments revealed on the MRI. Thus, executive functioning and attention measures may be useful tools when working with children and adolescents with SCD, in order to screen for possible infarcts. Moreover, given the cost of magnetic imaging tools, the current study provided support for cases in which MRIs are not cost-effective. The authors were unable to demonstrate significant findings on global measures of cognitive functioning, academic functioning, or visual-motor functioning, which suggests that specific measures of cognitive functioning may be a more viable option. This study by Brown and his colleagues (2000) further supports the need for assessing specific executive functioning, which is being addressed in the current research study.

Cognitive dysfunction has also been found among children with SCD and no evidence of cerebral infarcts as evidenced by standard imaging when compared to healthy, unrelated individuals of the same age, race, and gender. Steen and colleagues (2005) examined 98 children, with an average age of 10.9 through administration of the WISC-III. Children with SCD performed lower on measures assessing the Full Scare IQ as well as the Performance IQ. An important component included in this study was parental level of education. When compared to healthy patients, children with SCD still performed lower than their healthy peers who had parents with minimal education.
Moreover, no significant findings were evident between children with or without stroke, which contradicts much of the literature. While this study provides strong evidence for global deficits in children with SCD without stroke, the majority of the sample consisted of SCD type HbSS, indicating that individuals who have two inherited genes of sickle cell and have sickle cell anemia, may be at greater risk for impairment. The results, however, cannot be generalized to other types of SCD. Further, the findings were unable to demonstrate evidence of any of the underlying mechanisms which contribute to these global measures; therefore, the research does not address any specific areas of weakness. Thus, a more comprehensive battery would have been informative.

Specific Neuropsychological Functions

In the following section, the neuropsychological sequelae of SCD will briefly be reviewed and discussed in order to provide a background for specific executive dysfunction.

A comprehensive neuropsychological battery was utilized in a study by Swift and colleagues (1989). Participants in the study consisted of 33 children between the ages of 7 and 16 years with homozygous sickle cell anemia and no history of any neurological complications. The battery included the WISC-R, the Beery Developmental Test of Visual Motor Skills, the Social Competence Scale, the Achenbach Child Behavioral Checklist, subtests from the Detroit Test of Learning Aptitude-2, and the Woodcock-Johnson Psychoeducational Battery. Overall, children with SCD scored one standard deviation below their siblings on measures of IQ, although only a very small number performed in the Borderline range. Children with SCD demonstrated deficits in attention,
memory, verbal function, perceptual organization, and academic functioning. The SCD group did, however, perform adequately with regard to visual-motor skills. These findings are significant because the authors demonstrate that children with SCD and no identified CNS damage may have difficulties in several neuropsychological domains, which could impact their performance in school. Of particular relevance is performance on memory tasks. Working memory, as evidenced by poor scores on digit span task on the WISC-R, was one of the significant findings, and this will be examined further in the current study. The susceptibility of two specific functions, processing speed and working memory, to neurocognitive deficits will be examined from a biopsychosocial developmental perspective, including their functioning with regard to development. Further, individuals without cerebral vascular complications will be examined in light of their cognitive and neurocognitive functioning.

Working Memory

Few researchers have begun to examine the underlying specific functions that contribute to impaired performance on academic and cognitive measures. Brandling-Bennett and colleagues (2003) studied verbal long-term and working memory in children with SCD and frontal infarcts. Episodic memory has been defined as momentary experience locked in one place and one time (Shimamura, 2002). They examined 10 children with SCD and cerebral infarcts and 21 children with SCD without infarcts, the control group. The California Verbal Learning Test- Children’s Version (CVLT-C) was used to assess long term episodic and learning memory. Of the 5 trials, children with infarcts recalled fewer words than the control group. No differences were found with
regard to recognition on any of the tasks. Thus, the authors concluded that memory retrieval was impaired for the group with infarcts, but that encoding and storage were adequate in both groups.

Working memory was assessed with the Digit Span of the Children’s Memory Scale (Brandling-Bennett et al., 2003). No significant differences were found on the digits forward task; however, the group with infarcts performed significantly lower on the backward digits span. The authors reported that children with SCD demonstrate an impaired ability to manipulate information in working memory. Overall, these findings are significant in that they suggest that children with SCD and frontal cerebral infarcts evidence some executive dysfunction, which is reported to have resulted from the infarcts which impacted the frontal brain region. The authors did not include any nonverbal memory tasks nor did they include developmental factors, such as possible age-related decrements in working memory and verbal learning.

Verbal working memory in children with SCD was also studied by White and colleagues (2000). Similar to the study by Brandling-Bennett and colleagues (2003) children with SCD and stroke were compared to children with SCD and no stroke. Prior to this study, minimal investigations examined the location of lesions through MRIs and their subsequent effects on specific cognitive performance. These authors included children with anterior and posterior infarcts, which revealed significant findings regarding patterns of working memory based on the location of infarctions. Specifically, individuals with anterior infarcts demonstrated a tendency to recall reduced word lengths, while the control group and the group with posterior infarcts performed adequately. Those with anterior infarcts performed equally well on overall span. These findings
provide evidence of possible dysfunction of the phonological loop of the working memory system, but an intact central executive component of this system.

An important consideration is that age at which infarcts occurred was not available to the researchers; therefore, the authors were unable to determine if the infarcts were new or old. This creates difficulty when trying to understand the impact of the lesions on neurocognitive performance. For example, if some of the children had experienced multiple infarcts, then their performance may have been more impaired than a child with one infarct. Lastly, the authors used a small sample size, which will be addressed in the current study.

Schatz and Roberts (2005) studied working memory and short-term memory span in children with SCD, and included both auditory and visual processing. Twenty five children with SCD and twenty five healthy controls were assessed and matched for age, household income, and levels of parental education. The battery of tests included the Wechsler Intelligence Scale for Children-Processing Instrument (WISC-PI), the Self Ordering Pointing Test, the Category Fluency test from the Delis-Kaplan Executive Functions Scale (D-KEFS), and a number of subtests from the Woodcock Johnson Psychoeducational Battery-Revised (WJ-R). Of particular relevance to the proposed study was the inclusion of a measure of processing speed as measured by Visual Matching on the WJ-R, which is often lacking in the literature.

The group with SCD demonstrated lower scores on several measures: Oral Vocabulary, Incomplete Words, and Visual Matching tests. They also scored lower on Digit Span (backward), but performed adequately on all of the other span tests. Thus, individuals with SCD demonstrated working memory deficits, particularly with
manipulating verbal information in memory as well as difficulties with processing speed of information. The majority of individuals with SCD demonstrating these impairments had a history of transient ischemic attacks or severe headaches. Thus, the authors concluded that neurological symptoms may have contributed to the lower scores for this subgroup of the sample. The sample of this study was limited, however, to individuals with SCD, the majority of which had a history cerebrovascular impairment. The current study will expand to this body of literature by examining individuals with SCD without any known history of stroke, on the premise that the disease itself, regardless of stroke, may also cause cognitive impairments.

The authors provide sound evidence for examining digits span forward and digits span backward separately, indicating that the processing memory component involved are separate and distinct modalities within central executive functioning processing. The authors were not, however, able to provide any further evidence regarding the extent to which these modalities are involved. The findings were reported to be consistent with previous literature maintaining that the modality specific rehearsal systems are involved in with digits forward and digits backward tasks.

Although significant, the majority of the findings with regard to impaired working memory consisted of individuals with SCD and transient ischemic attacks. In terms of children and adolescents with SCD and no cerebral infarcts, several authors have reported mixed outcomes with regard to working memory functions in children with SCD and no cerebral infarcts. For example, Noll and colleagues (2001) studied children with SCD with no evidence of cerebral infarcts and compared them to healthy individuals with similar race, gender, and age. Overall, children with SCD scored significantly lower than
healthy children on several neuropsychological measures of performance on verbal, spatial, achievement, attention/memory, and fine motor skills. Unique to this study, the authors conducted a factor analysis across the five domains mentioned above, in order to discern the discrepancies between the domains. The authors demonstrated mixed findings with regard to working memory. Children with SCD performed lower than their healthy peers on overall measures of attention and memory; however, children with SCD only performed significantly lower on some working memory tasks as measured by the WRAML. While the SCD group performed significantly lower on the Verbal IQ scale on the WISC-R, authors failed to report the specific scores on subtests, such as Digit Span. Therefore, inferences about the performance on this working memory task which contributes to the overall verbal IQ score cannot be made. Although the authors provide evidence of deficits among children with SCD and no cerebral infarcts, they purport that several possible medical conditions may have contributed to the general findings. Hypoxia, chronic anemia, and silent strokes were all considered possible factors for the deficits, yet these remain conjectures as the authors had not accounted for silent strokes in their methodology. Further, since demographic variables were not factored into the analysis, the individuals who came from primarily disadvantaged environments may have demonstrated scores which were overstated due to economic and educational differences, rather than solely performance differences on tasks.

Significant impairments in cognitive functioning were demonstrated with individuals with overt and silent stroke. In addition, low hematocrit levels were associated with cognitive deficits. Overall findings suggested that Full Scale IQ and Verbal and Performance IQs were lower in the SCD group when compared to their healthy siblings. Specifically, the digit span task from the Verbal Scale and processing speed score on Performance scale were significantly different. After exclusion of the group with overt strokes, however, no significant differences were found with regard to cognitive functioning. Thus, the majority of patients with deficits tended to have cerebral impairments.

Processing Speed

As noted earlier, processing speed is considered a sensitive measure of neuorocognitive functioning and it may be impacted by changes in cerebral blood flow among the SCD population.

Steen, Xiong, Mulhern, Langston, and Wang (1999) purported that individuals with SCD and no evidence of infarction or injury remain at risk for cognitive impairments. They compared individuals with SCD to healthy individuals. MR imaging and hematocrit levels were included in their analysis. Overall, individuals with HbSS demonstrated the lowest levels of cognitive performance. In addition, those with lowest levels of hematocrit demonstrated greater cognitive impairments in all cognitive domains, except for processing speed.

Bernaudin and colleagues (1999) utilized similar techniques including blood screening, transcranial Doppler ultrasonography, cerebral magnetic resonance imaging,
and neuropsychological evaluation by the WISC-III and WPPSI-R with children with
SCD siblings on several measures, including Full Scale IQ and Performance IQ. Specific
subtests such as Digit Span, Coding, and Symbols were also significantly lower in the
SCD group when compared to healthy siblings. The findings demonstrated clear
disturbances on processing speed and working memory among the SCD group when
compared to healthy individuals.

In addition to the differences between SCD and siblings on several measures,
individuals with overt strokes performed significantly lower on the Full Scale IQ and
Performance IQ and patients with silent strokes performed lower than SCD patients
without strokes on verbal measures. However, there were no significant differences
between processing speed and working memory in groups with overt or silent strokes.

Processing speed and working memory was found to be significantly lower in
severely anemic patients, indicating that hematocrit contributes to processing speed and
working memory. Platelet count was correlated with cognitive performance, including
working memory, but not processing speed. Based on these findings, it appears that
processing speed and working may be a sensitive measure of cognitive functioning in
individuals with SCD, particularly those with low levels of hematocrit.

Steen and colleagues (2005) later examined the cognitive functioning of
hemoglobin SS patients without any known history of clinical stroke. The examiners used
MRI findings and hematocrit levels in their analysis. Individuals with lower levels of
hematocrit and cognitive impairments as measured by MRIs demonstrated greater
impairments on several subtests on the WISC-III, including several verbal and
performance tasks. There were no impairments on measures of processing speed.
Although processing speed was not impaired for individuals with or without silent strokes, the findings are pertinent to the current study. The authors demonstrated that individuals with SCD and silent strokes as well as individuals with SCD and no evidence of cerebral vascular injuries experience cognitive impairments across various domains, when compared to normative data. These findings contribute to the body of literature with conflicting findings across neurocognitive domains. It is important to note that the older instruments, the WISC-III and WISC-R, were used in the study. Of further relevance are the findings that MR imaging and hematocrit were both independent predictors of Full Scale IQ. Thus, it is possible that hematocrit levels and MR imaging may influence specific cognitive functions that comprise the Full Scale IQ.

Age-Related Decrement

As noted in Chapter I, research has documented that older children with SCD have lower scores than younger children across various cognitive measures. The decrement has been postulated as a possible result of cumulative effects of the disease on the brain. Brown and colleagues (1993) assert that cognitive impairments in older children could provide evidence of cumulative damage to developing CNS. However, to date, findings remain unclear as to whether insults during CNS development in children with SCD become more pronounced in adolescence and early adulthood.

Brown and colleagues (1993) compared children with SCD to healthy children. The authors postulated that an age decrement would be found in children with SCD. Academic achievement and sustained attention were impaired in the SCD group. The only cognitive domain found to have decreased with age was visual-motor functioning.
The authors were unable to find support for an age-related decrement or sickle cell type among the individuals or variability between the types of sickle cell conditions (homozygous compared to heterozygous). As in many previous studies mentioned, hemoglobin was found to be a predictor of academic and cognitive functioning. The authors also found that children with SCD performed similarly, in the Low Average range, on tasks measuring expressive and receptive languages and visual-motor functioning, which made comparison difficult for these domains. Therefore, controlling for the effects of SCD as well as other chronic illnesses with the family or utilizing a control group outside the family, which was conducted in the present study, is necessary.

Fowler and colleagues (1988) found that children with SCD (Hb SS) performed lower on tests of reading, visual-motor skills, and attention compared to healthy peers who were matched according to age, sex, race, and socioeconomic status. In addition to the work by Brown and colleagues (1993), older children with SCA demonstrated lower scores than younger children with SCA on visual-motor and attention tasks, suggesting a cumulative disease effect. Notably, performance scores were not significantly related to disease severity. Each child was scored on disease severity based on a neuro-developmental examination across 10 items, including muscle tone, overall neurological status, and cerebellar function. The authors assert that this insignificant finding suggests that more subtle factors, such as silent infarcts, may have impacted the decrease in performance over time. Also, SES was correlated with academic performance. Although academic performance is not included in the current study, SES will be taken into account.
In a study conducted by Wang, Enos, Gallager, Thompson, Guarini, and Vichinsky (2001), children with SCD and silent infarcts performed significantly lower than children with SCD without any type of infarct. Their study concluded that there was a significant decline on the VIQ of the WISC-R/WISC-III as well as the mathematics subtest of the Woodcock Johnson, with increasing age, among individuals with SCD without MRI abnormalities.

Kral, Brown, Nietert, Abboud, Jackson, and Hynd (2003) examined the relationship between blood flow velocity as measured by Transcranial Doppler and neuropsychological functioning. A regression analysis indicated that age was a significant predictor of Full Scale IQ, VIQ, sustained attention, visual working memory, and executive functioning. With respect to an age-related decrement, performance on measures of intellectual functioning, sustained attention, and executive functions decreased with increasing age among the sickle cell group.

Steen and colleagues (2005) found that cognitive ability as measured by the Full Scale IQ of the WISC-III tends to decrease as patients age; these results were not found with the healthy controls in the study. All patients in the study had Hb SS and no MRI findings. Thus, there is some indication that the decrease with age suggests cumulative effects of disease on the brain.

A meta-analysis was conducted to examine cognitive functioning in children with SCD and no evidence of cerebral infarction (Schatz et al., 2002). The analysis included an evaluation of a possible decline in cognitive functioning with increasing age. The authors report that decline in cognitive functioning with increasing age exists. However, they caution that these studies may have been affected by possible confounding factors.
Therefore, the findings regarding age decrements should be considered as suggestive of cumulative effects, not accepted as definite result. In addition, the authors suggest that the age range in many of the studies reviewed was too limited, such as ages 7 to 12, and should be expanded from to a wider range to include younger children up to older adults. The current study will include children and adolescents aged 9 to 22 in order to address this concern.

One study compared performance on intellectual, academic, and neuropsychological functioning among children with SCD and no overt stroke to their siblings (Wasserman et al., 1991). In contrast to findings of an age-related decrement, children younger than 13 with SCD actually performed significantly lower than older children on measures of visual skills, expressive speech, writing, reading, and memory.

Swift and colleagues (1989) examined children ages 7 through 16 with HbSS and no neurological disturbances and compared them to healthy siblings. Overall, individuals with SCD scored approximately 1 standard deviation below their siblings on cognitive measures. The authors did not find a relationship between levels of hemoglobin and cognitive performance, nor were they able to find a decline in performance over time. In fact, they assert that the results indicate impairments before the age of seven and purport that additional variables influenced the cognitive impairment in those with SCD.

In sum, the inconsistent findings with regard to working memory, processing speed, and a possible age-related decrement among individuals with SCD, clearly warrant the need for additional research.
Cognitive Fatigue

Fatigue is truly a complex symptom because it can involve physical components medical conditions, and psychiatric states (DeLuca, 2005). Although fatigue has been studied for centuries, there is a lack of uniformity with regard to the definition. Specifically, some definitions allude to a more subjective measure of cognitive fatigue, while others are more objective.

Cognitive fatigue is a relatively novel construct in neuropsychological research. DeLuca (2005) indicates that measures of mental or cognitive fatigue can be discerned from physical or muscular fatigue, in that the former assesses concentration, while the latter assesses feelings associated with weakness or a weakened physical state. As discussed in Chapter I, cognitive fatigue has been classified into four major types. The current study will examine cognitive fatigue during sustained mental effort. An example of this definition in a clinical setting would include reduced cognitive performance during a sustained mental task, such as a working memory task.

Research on cognitive fatigue during sustained mental effort has mainly been conducted with specific medical conditions, mainly those patients diagnosed with multiple sclerosis (MS), traumatic brain injuries (TBIs) and chronic fatigue syndrome (DeLuca, 2005).

Schwid, Tyler, Scheid, Weinstein, Goodman, and McDermott (2003) conducted a pilot study to examine cognitive impairment in individuals with MS using the Paced Auditory Serial Addition Test (PASAT) and the Digit Ordering Test (DOT), each a measure of continuous working memory sustained attention. Results were found to be unreliable on the DOT. Patients with multiple sclerosis demonstrated a 5.2% decline in
performance on the PASAT, while healthy participants did not demonstrate any significant declines.

Similar methodology was used by Bryant, Chiaravalloti, and DeLuca (2004). The researchers examined cognitive fatigue during the Paced Auditory Serial Addition Test (PASAT), a continuous working memory task among individuals with multiple sclerosis (MS) and matched healthy participants. Cognitive fatigue was measured comparing performance over the second half of the trials on the PASAT to performance during the first half of the trials. Individuals with MS were grouped as cognitively impaired or cognitively in-tact according to performance following administration of neuropsychological measures. Both cognitively impaired and non-impaired individuals with MS performed similar to healthy participants with regard to correct responses on the PASAT. Notably, as working memory demands increased, both MS groups demonstrated cognitive fatigue earlier than healthy individuals.

Consistent with the above noted definition of cognitive fatigue during a sustained mental effort, Krupp and Elkins (2000) studied cognitive fatigue in patients with MS. The researchers administered two brief repeatable neuropsychological batteries which were separated by a continuous cognitive task, the A-A tasks. Comparisons of the two batteries indicated that during the first administration, no significant differences were found between the patients with MS and the healthy participants. However, following the A-A test, patients with MS demonstrated significantly lower scores on three measures. In addition, patients with MS demonstrated slowed reaction time in the second half of the A-A test, when compared to the group of healthy individuals. The authors failed to
include the number correct for the A-A test, which would have been more indicative of actual decrease in performance. Instead, they only included speed on the tasks.

Several of the studies that have examined cognitive fatigue have utilized self-report measures; therefore, many of the results can be considered subjective and not quantifiable. This newer definition of cognitive fatigue during sustained attention tasks demonstrates many significant results in certain clinical populations. However, to date, no studies have examined cognitive fatigue among individuals with sickle cell disease. Specifically, the current study will investigate the impact of cognitive fatigue on a sustained attention task.

Summary

The purpose of this chapter has been to provide a critical review and discussion of the literature relevant to the current study. This chapter included a section pertaining to overall academic and cognitive functioning among the SCD population. An overview of specific neuropsychological sequelae from a biopsychosocial developmental perspective, which underlies the theory for the current proposed study, was provided. Two specific neurocognitive functions, which will be analyzed in the current study, were reviewed in light of the dearth of literature among the SCD population. Although findings appear consistent with regard to strokes and their impact on specific neurocognitive functioning, it remains unclear how the disease itself without the impact of strokes, may affect specific functions, such as processing speed and working memory. These findings are conflicting.
The theory that SCD may cause cumulative effects on the brain, resulting in cognitive impairment over time, was also reviewed. While evidence has been provided that older children and adolescents may demonstrate greater cognitive impairment than younger children, other researchers (Brown et al., 1993) were unable to find evidence for an age-related decrement. Overall, the literature remains unclear as to whether insults during CNS development in children are more pronounced during adolescence and early adulthood. Thus, the present study will include an analysis focusing on age differences for specific functions, processing speed and working memory.

Lastly, cognitive fatigue, a novel construct in neuropsychological research was discussed. Substantial evidence was provided with regard to the need for more objective measures of cognitive fatigue. The current study will employ an objective measure conceptualized and assessed by DeLuca (2005). In addition, the current study is the first to examine cognitive fatigue among individuals with SCD.
CHAPTER III

Methodology

The purpose of this chapter is to explain the methodology that was implemented in the current study. Specifically, this chapter provides a detailed description of the population of interest, the method of sampling, data collections methods, the assessment instruments utilized, and a discussion of the reliability and validity for each of the measures. Lastly, the study design, hypothesis testing, and statistical analyses for all hypotheses are reviewed.

Participants

The current study focused on minority children and adolescents with sickle cell disease (SCD) without any known history of stroke compared to healthy children and adolescents. Due to the relevance of the biopsychosocial model when conducting research among a developing population, participants with and without SCD were assessed based on similar demographic variables, such as SES and/or race, and ethnicity. Specifically, 53 children and adolescents aged 9 to 22 were contacted if their diagnosis consisted of either SCD Hb SS or SCD Hb SC. Of the 20 recruited and confirmed to participate, 14 kept their appointments and completed the study. Individuals with sickle beta-plus thalassemia (Hb S β-thalassemia) and sickle cell trait were excluded from the study primarily because their medical complications tend to differ from the other two
groups included. Thus, their presentation of symptoms may vary and subsequently manifest differences in cognitive functioning. In addition, upon review of the medical record, a number of participants who had a documented IQs equal to or below 70 were excluded from the study.

The control group consisted of 19 healthy individuals without any chronic illness or documented disability. There were no controls that demonstrated IQ scores less than 70; therefore, all individuals tested were included.

Participants in the sickle cell group were recruited from a medical center in the Northeast. Healthy participants were recruited through friends and family members of the experimental group and through solicitation letters (see Appendix A).

Tables 1 presents demographic values aggregated by study group, respectively. There were 33 participants (19 healthy controls; 14 SCD) recruited for this study. As can be seen in Table 1, overall groups were generally well matched with regard to age, gender, and parent education. Parents of patients had completed a mean of 13.1 years of education ($SD = 2.3$), while parents of controls completed a mean of 14.7 years ($SD = 2.0$). The healthy control group (Mdn = $75k$) reported a greater parental income than the SCD group (Mdn = $30k$).

Despite attempts to match the control group through the recruitment process, the groups recruited were not well matched for race or SES. A chi-square analysis was run to compare the number of African American participants in the SCD group compared to the control group, which was predominately Caucasian. Table 2 demonstrates the relationship which indicates significant group differences according to race/ethnicity. As expected, the SCD group was represented by a significantly greater number of African
American participants ($n = 9$), $\chi^2(3) = 10.0, p = 0.02$, while healthy controls were predominately Caucasian ($n = 13$) and Hispanics were equally represented within the two study groups ($n = 4$, per group).

Of the 14 participants with sickle cell disease, 12 (85.71%) had SCD type HbSS, while 2 (14.29%) had SCD type HbSC. At the time of testing, patients ranged in age from 10 to 22 ($M = 15.4, SD = 3.7$). Figure 1 lists the age distribution of the groups. Both groups displayed variability with regard to age. The age distribution of the healthy group was bimodal with 7 participants falling between 10 and 12 years, 4 falling between 13 and 17 years, and 8 participants between 18 and 22 years. The sickle cell group had 3 participants between 10 and 11 years, 8 between 13 and 17, and 3 between 18 and 22 years old.
Table 1

*Demographic Characteristics of the Sample Aggregated by Group (n = 33)*

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Table 2

*Ethnicity by Study Group*

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<th>Healthy</th>
<th>SCD</th>
<th>Total</th>
<th>$X^2$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
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<td>9</td>
<td>11</td>
<td>4.5</td>
<td>0.04</td>
</tr>
<tr>
<td>Caucasian</td>
<td>13</td>
<td>0</td>
<td>13</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Hispanic</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>0.00</td>
<td>1.00</td>
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<tr>
<td>Caribbean</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Note.* Chi-square not computed for Caucasian (all Caucasian participants were in Healthy group). Chi-square not computed for Caribbean (not enough valid cases, $n = 1$)
Figure 1. Age Distributions According to Group
Procedure

Procedures for data collection were consistent with each participant. Approval was initially granted through the medical center’s Institutional Review Board and then through Seton Hall University’s Institutional Review Board to conduct research. Annual renewal was granted through each of these institutional review boards to continue the study until its completion.

Eligibility for the sickle cell group was based on patient demographic information (i.e., age and diagnosis) that was found in an accessible database permitted for use by the researcher. Individuals with SCD who met criteria for either type Hb SS or Hb SC were considered for the study. I reviewed each chart for neurological history. Recruitment letters were mailed to patients over 18 who met the criteria for inclusion in the proposed study as well as to parents/guardians of those patients under 18 years of age. The letter outlined the rationale for participation in the study, namely to gain better understanding of the impact of SCD on learning and cognition. The letter informed participants that, in exchange for allowing the researcher to work with the patient, the participant would be offered a monetary gift card of $25 at the completion of the testing session (see Appendix A).

Several steps were taken with each patient to maximize the possibility for successful recruitment. After I sent initial solicitation letters, follow up calls were made. During several instances, phone numbers were non-working numbers. In these cases, an administrative assistant of the hospital department helped to obtain current contact
information. After the first round of phone calls, psychosocial team members who worked with the recruitment population were assigned a set of patients and parents who were the clinicians that typically work with families during their clinic visits. I then made a follow up phone call once a family expressed interest to a staff member, to schedule an appointment. For those patients who were not contacted in person via a staff member, I made a final set of phone calls. No more than two messages were left per patient.

I called each patient the night before the scheduled appointment to confirm the appointment. As noted earlier, 20 patients were scheduled for appointments. Four of these patients did not show for their appointment and two individuals did not show on more than one occasion.

Healthy controls were identified by the patients and with solicitation letters (see Appendix A). Specifically, patients and their parents or guardians were asked to refer any friends or family members. If interested, they were provided with the solicitation letter describing the procedure and offering the researcher’s contact information.

Individuals who participated were scheduled by the researcher based on a time conducive to the research assistant’s schedule and patient’s schedule. A single blind study was conducted in that the researcher did not assess any of the participants. Two doctoral level research assistants were blindly assigned to the participants. However, given the difference in racial mix between the groups, some degree of being “blind” was likely lost with the control group as it is public knowledge that most people with these types of sickle cell are of minority status. The two researchers were trained in advance by the primary investigator and her supervisor to ensure mastery of the testing material.
The testing sessions were held on the hospital's premises. My supervisor or I administered the consent and assent forms and reminded participants of the voluntary nature of the study, which was also specified in the consent forms in the recruitment letter. Either my supervisor or I met with the participant and his or her parent/guardian if they were a minor, while the research assistant remained in a separate room. In addition to stroke history, exclusionary criteria for the SCD group included a current self-report index of pain greater than 5, which was assessed at the start of the testing session. Only one patient reported pain level greater than five; therefore, the consent process was terminated and he was deemed not eligible for the study.

Individuals aged 18 or older were not required to be accompanied by a parent or guardian. Participants under the age of 12 were read an oral assent form. Once the child gave his or her assent, the parent/guardian was required to co-sign the assent form and was provided a copy of the adult consent form to assure their understanding of the study to read and sign.

Individuals aged 12 through 17 were given an assent form to read and were required to sign the assent form in order to participate. The parent/guardian was required to countersign the document. My supervisor or I was responsible for giving patients demographic forms to complete. Those participants under 18 were required to have their parent/guardian complete the demographics form. Once assent and/or consent were granted, the participant then met with the research assistant. The research assistant administered the testing battery, which was completed with the research assistant without a parent/guardian present in the room. Total time for completion of the materials was approximately one hour.
Research Instruments

The research battery consisted of the following measures: (a) a demographic form, (b) the two subtests of the Processing Speed Index from either the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997) for participants older than the age of sixteen or the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler, 2003) for participants sixteen or younger, (c) the Working Memory subtests of the Wide Range Assessment of Memory and Learning-Second Edition (WRAML-2; Sheslow & Adams, 2003), and (d) the Connors’ Continuous Performance Test II (CPT II), Version 5 (Conners, 2000).

Psychological and Neuropsychological Instruments

Following are descriptions of each of the psychological assessments used in the current study, along with psychometric data for each scale. Further, studies in which the assessments have been validated will be reviewed.

Demographic Form

The demographic form was created for this study (see Appendix B). Participants in the study were asked to provide their birthdate, age, gender, race/ethnicity, current grade, number of years of parents’ education, approximate household income, age of diagnosis, prenatal problems, all medical conditions/diagnoses, type of sickle cell disease if applicable, documented disabilities, history of strokes, current medications, number of hospitalizations related to SCD in the past year and throughout one’s lifetime, history of
stroke, current report of pain, and bone marrow transplant history. In order to ensure that exclusionary criteria was met, questions related to this criteria (i.e. history of strokes, transplant history, pain) were starred and participants were told to inform the researcher immediately if they meet exclusionary criteria. None of the exclusionary criteria were met and therefore the testing process continued for all of the participants.

The following is a description of the neurocognitive measures used in the current study. The order of the measures below was counterbalanced to ensure that any order effects of the study were controlled and then participants were randomly assigned to design A-B-C, A-C-B, B-A-C, B-C-A, C-A-B, or C-B-A.

*Wechsler Intelligence Scale for Children-Fourth Edition and Wechsler Adult Intelligence Scale-Third Edition*

The Wechsler Intelligence Scales were originally developed in the 1930s to measure global intelligence and have since been revised to provide updated cultural norms and constructs of intelligence and to provide additional reliability and validity testing (Groth-Marnat, 2003). The WAIS-III includes six Verbal subtests and five Performance subtests and is normed for ages 16 to 89, while the WISC-IV which includes a total of 15 subtests, is normed for ages 6 to 16 years, 11 months. The reliabilities for the WAIS-III are generally high. With regard to the current study, only the core subtests of the Processing Speed Indices were utilized. The Processing Speed Index consists of two subtests, Digit Symbol-Coding and Symbol Search with subtests loading onto the Performance IQ.
Symbol Search is psychometrically a relatively good subtest for both the WAIS-III and the WISC-IV. Test-retest reliability was found to be high, .79 for the WAIS-III and .76 for the WISC-IV. The subtest also correlates highly with the Full Scale IQ and Performance IQs for the WAIS and the WISC-IV.

Coding is a fair measure of general ability (g) for the WAIS-III (.57) and WISC-IV (.48). Test-retest reliability for the Coding subtest of the WAIS-III is high (.86) and moderate for the WISC-IV (.85) (Flanagan & Kaufman, 2004; Kaufman & Lichtenberger, 1999).

The test-retest reliability coefficient for the Processing Speed Index is .87 (Groth-Marnat, 2003). Internal consistency reliability was also found to be high on the Full Scale (.96) and the Performance Scale (.91) but was more variable with regard to the specific subtests.

Research regarding the validity of the WAIS-III was primarily derived from research on the WAIS-R, such as correlations with ability and achievement tests (Groth-Marnat, 2003). In addition to strong reliability and validity coefficients, several strengths of the WAIS-III include normative cross-cultural data and an extended age range up to 89 years of age. Of particular relevance to the current study is strong clinical relevance and empirical support for interpretation of scores. For example, Groth-Marnat suggests that a low score on Processing Speed is clearly indicative of difficulty processing information rapidly.

Overall limitations of the Wechsler scales include data supporting ecological validity (Groth-Marnat, 2003). For example, minimal studies have examined subtests, such as Digit Span, with performance on everyday tasks. With regard to processing
speed, lower scores may be related to a child or adolescent’s level of motivation or poor motor control. Thus, observing an individual’s behavior across the testing will help monitor these possible confounding factors.

The degree of validity of research data when using cognitive measures with ethnic minorities has been considered culturally biased (Groth-Marnat, 2003; Ryan, Baird, Mindt, Byrd, Monzones, & Morgello, 2005). In older versions of Wechsler Scales, such as the WISC-R, when SES was controlled in statistical analyses, African Americans’ performance was generally reduced on IQ measures. Even with the development of updated cognitive measures, researchers have demonstrated that African Americans tend to perform lower than Caucasians on verbal and nonverbal assessments, when controlling for education and SES and have provided evidence that using norms that are not appropriate for minority populations may inflate levels of impairment on testing (Ryan et al., 2005).

Recent studies clearly indicate that updated versions of the Wechsler Scales remain biased against minority groups. For example, Sattler (2008) reported that Euro-American children obtained a mean Full Scale IQ that was approximately 11.5 points higher than African American children. Some researchers contend that the Processing Speed subtests (Coding, Symbol Search) of the WAIS-III and WISC-IV utilized in the current study are less likely to contain biases than other measures (Groth-Marnat, 2003). For example, Sattler found a much smaller discrepancy between Euro-American and African or Hispanic American children on measures of Processing Speed and Working Memory indices. In addition, African and Hispanic Americans performed about 3 to 6 points higher on the Working Memory and Processing Speed indices, compared to the
Verbal Comprehension and Perceptual Reasoning indices on the WISC-IV. Others maintain that discrepancies in reading level and education are significant factors for performance on several cognitive domains, including both processing speed and working memory (Ryan et al., 2005).

Given that a significant percentage of children with SCD live at or below the poverty level, SES has been found to be a significant predictor of cognitive problems for children with SCD (Schatz & Puffer, 2006). In addition, in a recent study by Ryan and colleagues (2005), social class and the educational quality were more indicative of cognitive performance than racial/ethnic minority status alone. As a result, normative standards for cognitive assessment have been questioned given the psychosocial advantages and privileges associated with the dominant group. These findings provide significant implications for the current study, which did not adequately compare specific racial/groups according to the specific cognitive measures assessed. Thus, there are clear inherent discrepancies between the SCD group and control group.

Wide Range Assessment of Memory and Learning-Second Edition

The WRAML-2 is an assessment battery applicable for with children and adults, ages 5 to 90, which measures various types of memory (Sheslow & Adams, 2003). For the current study, the tests which are designed to assess working memory were utilized. Specifically, the Working Memory Index, which consists of two subtests was used (Verbal Working Memory, Symbolic Working Memory). In terms of scoring, raw scores for both the Verbal Working Memory and the Symbolic Working Memory tests, were
converted into standard scores ($M = 10$ and $SD = 3$) and an overall Index score was calculated.

Norms for the WRAML-2 are based on the 2001 Census in terms of gender, race/ethnicity, education, and geographic region (Strauss, Spreen, & Sherman, 2006). Internal reliability scores were found to be high for the index scores (.86 to .92). Overall, test-retest reliability for the Working Memory Index is also high (.80 to .89), while test-retest reliability was found to be in the adequate range (.70 to .79) for the Verbal Working Memory subtest and in the marginal range (.60 to .69) for the Symbolic Working Memory subtest.

Data from the WRAML-2 was determined for several clinical groups compared to matched controls. Significant differences were found with regard to memory among many groups, including, but not limited to individuals with Alzheimer's disease, children with learning disabilities, and adults with traumatic brain injuries. Despite the studies conducted, researchers have recommended that more studies examining validity be conducted because the instrument was published recently (Strauss et al., 2006).

Strauss and colleagues (2006) acknowledge that these subtests may be advantageous over other working memory tasks. For example, the Verbal Working Memory task may be suitable for children because of the use of animals and real objects, as opposed to simply letters and numbers.

Despite the many strengths of the WRAML-2, some considerations are warranted. Specifically, the Working Memory Index was found to be highly correlated with the Attention/Concentration Index, indicating that these tasks may not be measuring unique constructs (Strauss et al., 2006).
Some researchers have noted that lowered scores on working memory tasks may be attributable to anxiety or poor executive functioning (Groth-Marnat, 2003). Thus, an individual’s performance must be evaluated carefully and should be compared with other measures which assess cognitive functions. Observing performance on other measures and comparing it to the individual’s behavior across vary tasks will help to discern if, perhaps, lower scores are indicative of an executive problem or the result of behavior.

Another significant limitation is that minimal studies on the validity of the WRAML-2 with minority populations have been published. However, it is important to note that the authors accounted for bias by including an item bias analysis of subtests. Moreover, factor analyses were conducted which revealed no effects of ethnicity on the structure of the WRAML-2 (Strauss et al., 2006).

Overall, the WRAML-2 is considered a substantial tool for examining memory impairment across a wide range of individuals, from early childhood through late adulthood. However, given that there is a dearth of research on minority populations when assessed with the WRAML-2, findings with regard to the Working Memory Index in the current study should be interpreted carefully.

**Conners Continuous Performance Test II**

The CPT II is a computerized measure of sustained attention for individuals aged 6 and older. The test consists of a short practice exercise prior to the main task to ensure that the individual understands the task. Respondents are instructed to hit the space bar (or click the mouse) whenever they see any letter on the screen, except for the letter ‘X.’ The CPT includes inter-stimulus intervals of 1, 2, and 4 seconds. The structure is
comprised of 6 blocks, with 3 sub-blocks each containing 20 trials. Stimuli are presented at varied intervals, and the order of these inter-stimulus intervals vary, which yields scores regarding performance on number of hits, omissions, and commissions, as well as reaction time by block, reaction time by inter-stimulus interval (Conners, 2000).

For the current study, number of hits and reaction time were the variables analyzed. Specifically, the number of hits and reaction time in the first half of the test, or the first three blocks, were compared to performance in the second half of the test, or the second set of three blocks.

Clinical norms are based on a sample of 2,686 individuals, ages 6 and older, of which 378 individuals were diagnosed as having Attention Deficit Hyperactivity Disorder (ADHD) and 223 individuals with varied neurological impairments. Strauss and colleagues (2006) report very high split-half reliabilities for hit reaction time ($r = .95$) and omissions ($r = .94$). Internal reliability was found to be marginal (Strauss et al., 2006). Test-retest reliability was tested with a small sample consisting of 13 clinical cases and 10 non-clinical cases. Confidence indices for the clinical cases, ADHD and neurological impairments, demonstrate good reliability. Coefficients were found to be in the low range for Test-Retest stability (<.59), marginal range (.60 to .69) for Commissions, and high range (.80 to .89) for Omission.

Strauss and colleagues (2006) acknowledge limitations regarding the clinical utility of the CPT II. Toward this end, the authors note that only a small number of studies have been conducted with clinical populations above and beyond the sample discussed above. Further, they caution against using the CPT II as a diagnostic tool. Lastly, the CPT II has been considered a better measure of executive functioning than
attention, due to the need for inhibitory responses when attending to stimuli (Strauss et al., 2006).

While these are important considerations for utilization of the CPT II, the current study is not using this instrument for the assessment of ADHD. Rather, cognitive fatigue is being assessed by comparing the number of hits and rates of responses across this sustained attention task. Therefore, the strong reliability and validity coefficients for variables included in the current study, number of hits and reaction time, indicate that the CPT II is an appropriate tool to measure cognitive fatigue.

Research Design

The overall purpose of the current study is to compare differences in neurocognitive functioning among children and adolescents with SCD and healthy children. The majority of the information was obtained through standardized assessment measures. According to Pedhazur and Schmelkin (1991), quasi-experimental designs are best suited for studies in which groups are formed based on the dependent variable, in this case, chronic illness. In order for assessments to control for any confounding variables, such as fatigue, the order of the instruments was counterbalanced, as described earlier.

The present study attempted to identify specific neurocognitive differences between individuals with SCD compared to healthy individuals. As previously noted, specific neurocognitive functions, such as processing speed, working memory, and cognitive fatigue, are domains in which minimal or no research has been conducted with this specific population. These domains can be examined and best understood using
quantitative methodology, through quasi-experimental design. This study examined the
differences between groups’ performance on specific tasks that measure the cognitive
domains discussed above. The study aimed to describe these differences in order to
provide more information about how children and adolescents with SCD may
demonstrate more struggles in learning when compared to individuals without a chronic
illness. Understanding these differences can provide invaluable information to
neuropsychologists, psychologists, and related disciplines about how to provide
appropriate interventions and accommodations for individuals whose cognitive
functioning has been impacted by SCD.

While the overall design for the current study could best be classified as quasi-
experimental, there are differences in the approaches by particular type of hypothesis.
Each of the hypotheses follow the causal comparative method known as ex post facto
research because the presumed causes are based on existing influences rather than causes
that true manipulations of variables that might otherwise have causes the differences
(LaFountain & Bartos, 2002). The type of statistical analysis used to test each hypothesis
varies, as will be discussed below.

Hypothesis Testing and Power Analyses

Each of the hypotheses included in the current study are listed below, followed by
a description of each of the hypotheses that were examined. The statistical analyses that
were utilized to test each hypothesis are discussed. Further, as noted above, the
discrepancy between the control group and the sickle cell group according to race and
SES poses a major threat to the validity of the study. Therefore, group differences must
be interpreted with caution, particularly with regard to differences in demographic variables between participants and controls and their potential impact on the outcome for each analysis.

Hypothesis 1

Children with SCD and no known history of strokes will have significantly greater deficits in processing speed, as measured by the Processing Speed Index, and working memory, as measured by the Working Memory Index from the WRAML-2, when compared to healthy individuals.

A one-way multivariate analysis of variance (MANOVA) was used to test $H_1$. A MANOVA is applicable when examining the statistical significance of the effect of one or more categorical independent variables on a set of two or more dependent variables (Weinfurt, 2001). In the current study, the independent variable was comprised of two groups, SCD without a history of stroke(s) and a healthy control group. The mean scores of the index measures for Processing Speed and Working Memory was compared using the MANOVA procedure. Specifically, the scores on the index scores for Working Memory and Processing Speed were the two dependent variables. The original power analysis yielded a minimum number of 42 subtests in order to conduct this statistical analysis with a power of .80 and medium effect size (.25). However, as previously noted, the present study recruited 28 participants. Inspection of post-hoc estimates of effect (please refer to Chapter IV, Hypotheses Tested section for detail) and power reveal that sufficient statistical power was present to appropriately test study hypotheses and there was accordingly minimal risk for Type II error. In brief, the study was adequately
powered to examine the primary hypotheses and insufficient sample size would not likely serve as a threat to internal validity of this study. Instead, the heterogeneity of groups posed a greater threat to validity.

A post-hoc power analysis (i.e., using G*Power) was conducted in order to understand actual observed power for the statistical analysis conducted in Hypothesis I. Using this methodology, actual observed effect size \( d = 1.1 \), alpha (0.05), sample size \( n = 33 \), number of groups (two), and number of dependent variables (two) were entered into the application which provided the actual power parameter of 0.99 (strong). Thus, this post-hoc power analysis revealed sufficient power to detect significance.

**Hypothesis 2**

After controlling for age, children with SCD will continue to have lower scores compared to healthy participants.

A one-way MANCOVA was utilized to estimate between-group differences on each of the 2 scores on the tasks of neurocognitive functioning according to age. Age, a continuous variable in this model, was the covariate in the analysis. Power analysis yielded 42 participants with a medium effect size of \( .50 \) and two independent variables and 1 covariate. Similar to Hypothesis I, post-hoc power analysis was conducted to understand actual observed power for the analyses conducted within this hypothesis. Again, actual observed effect size \( d = 1.01 \), alpha (0.05), sample size \( n = 33 \), number of groups (two), and number of dependent variables (two) were entered into the application which provided the actual power parameter of 0.98 (strong). Thus, power was not an issue related to appropriately testing this hypothesis.
Hypothesis 3

Individuals with SCD and no history of stroke will demonstrate greater cognitive fatigue when compared to healthy participants, as measured by the changes in hit rate and reaction time over the course of the CPT-II, a sustained attention continuous performance measure.

A power analysis was conducted for a medium effect size for a mixed between-within group ANOVAs (repeated measure: 1\textsuperscript{st} half of CPT vs. 2\textsuperscript{nd} half of CPT). Results indicated that 34 participants were needed for the current study.

Post-hoc power analysis was conducted to understand actual observed power, with observed effect size \((d = 0.10)\), alpha (0.05), sample size \((n = 33)\), number of groups (two), and number of repetitions (two) entered into the application which provided the actual power parameter of 0.06 (weak). As expected, given that multiple parameters were involved in this analysis (e.g., group and time), future studies might consider collecting a greater number of participants should inferences related to both groups and elements of the tests to be desired.

Power analyses were conducted in order to determine which of the following statistical analyses required the highest number of participants. Results of power analyses indicated that 42 participants were needed in order to conduct a MANOVA, MANCOVA, and matched pairs t-test consistent with hypotheses \(H_1, H_2,\) and \(H_3\) (Erdfelder, Faul & Buchner, 1996). However, there were recruitment challenges that allowed for the collection of 28 participants. Notably, post-hoc observed power analysis indicated that the two primary study hypotheses (I and II) were not impacted by the number of participants available for analysis. It may be postulated that Hypothesis III
would have benefited from additional participants, due to the actual power observed, which was weak. Despite minimal variability for CPT-II scores between groups, the pattern of scores suggests that a trend may have been observed with the addition of participants.

Summary

The purpose of this chapter has been to discuss the methodology which was used in the current study. The population of interest and method of sampling were reviewed. The methodology for determining the sample size needed for the current study was included. Data collections methods, the assessment battery, and the reliability and validity for each of the measures were discussed. Considerations and limitations were included for all of the instruments. Lastly, the study design, and each hypothesis test with the appropriate statistical analysis for each hypothesis was presented. Limitations of group differences given the lack of matched control group must be considered in interpreting the results.
CHAPTER IV

Results

Prior to conducting inferential analyses to test the study hypotheses, descriptive statistics were calculated. Table 3 presents intercorrelations for all of the primary study variables. As observed in the Table 3, a number of variables share variance, suggesting that the constructs assessed measure common factors. Notably, parent income, a proxy for socioeconomic status and factor often associated with performance on cognitive instruments, was related significantly with education (expected), working memory, processing speed, and CPT performance. The absolute correlations values indicated that income explained 34% of the variance in education, 15% of variance in processing speed, 26% of variance in working memory, and 23% variance in CPT hits. Intercorrelation results should be interpreted with caution given the possibility for Type I error occurring secondary to the multiple repeated correlation analyses (i.e., Family-wise error rate) conducted with this approach.
Table 3

*Table of Intercorrelations for Study Variables*

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
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</thead>
<tbody>
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<td>1. Age</td>
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<td>0.16</td>
<td>0.26</td>
<td>0.20</td>
<td>0.22</td>
<td>0.35*</td>
<td>0.54*</td>
<td>0.39*</td>
<td>0.22</td>
<td>0.00</td>
</tr>
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<td>2. Parent Income</td>
<td>1.00</td>
<td>0.58*</td>
<td>-0.23</td>
<td>0.39*</td>
<td>0.51*</td>
<td>0.48*</td>
<td>0.34</td>
<td>0.21</td>
<td>0.14</td>
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<tr>
<td>3. Parent Education</td>
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<td>-0.37</td>
<td>0.50*</td>
<td>0.44*</td>
<td>0.56*</td>
<td>0.35*</td>
<td>0.02</td>
<td>0.02</td>
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</tr>
<tr>
<td>4. Lifetime Hospitalizations</td>
<td>1.00</td>
<td>-0.68</td>
<td>-0.25</td>
<td>-0.11</td>
<td>-0.05</td>
<td>0.40*</td>
<td>0.35*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Processing Speed Index</td>
<td>1.00</td>
<td>0.46*</td>
<td>0.41*</td>
<td>0.23</td>
<td>-0.22</td>
<td>-0.37*</td>
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<td>6. Working Memory Index</td>
<td>1.00</td>
<td>0.49*</td>
<td>0.41*</td>
<td>0.02</td>
<td>-0.04</td>
<td></td>
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<tr>
<td>7. CPT # Hits 1st Half</td>
<td>1.00</td>
<td>0.89*</td>
<td>0.08</td>
<td>-0.12</td>
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<tr>
<td>8. CPT # Hits 2nd Half</td>
<td>1.00</td>
<td>0.12</td>
<td>-0.11</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>9. CPT Hit Rate (ms) 1st Half</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td>0.90*</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>10. CPT Hit Rate (ms) 2nd Half</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.00</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

*Note. *p < 0.05*
Table 4 presents descriptive values aggregated by study group, respectively. With regard to descriptive statistics related to the study measures, healthy controls performed better on all indices assessed and significantly better on the processing speed index (PSI; \( p < 0.001 \)) and working memory indices (WMI; \( p = 0.03 \)).

Table 4

*Descriptive Statistics for the Sample Aggregated by Group (n = 33)*

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 19)</th>
<th></th>
<th>SCD (n = 14)</th>
<th></th>
<th>Total (N = 33)</th>
<th></th>
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</thead>
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<tr>
<td></td>
<td>( M )</td>
<td>( SD )</td>
<td>( M )</td>
<td>( SD )</td>
<td>( M )</td>
<td>( SD )</td>
</tr>
<tr>
<td>PSI</td>
<td>109.63</td>
<td>11.68</td>
<td>88.57</td>
<td>14.26</td>
<td>100.70</td>
<td>16.46</td>
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<tr>
<td>WMI</td>
<td>100.95</td>
<td>13.19</td>
<td>90.43</td>
<td>12.81</td>
<td>96.48</td>
<td>13.87</td>
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<tr>
<td>CPT</td>
<td></td>
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</tr>
<tr>
<td>Hits Half 1</td>
<td>159.47</td>
<td>3.26</td>
<td>157.21</td>
<td>4.76</td>
<td>158.52</td>
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<td>Hits Half 2</td>
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<td>7.20</td>
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<td>6.25</td>
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<td>Hit Rate (ms) Half 1</td>
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<td>Hit Rate (ms) Half 2</td>
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<td>152.38</td>
<td>1165.79</td>
<td>195.21</td>
<td>1102.67</td>
<td>177.68</td>
</tr>
</tbody>
</table>

*Note.* PSI = Processing Speed Index; WMI = Working Memory Index; CPT = Continuous Performance Test. P-values based on one-way analysis of variance with SCD entered as independent variable to compare study group means.

Again, it must be emphasized that there was a lack of an appropriate matched control group in this study, and therefore group differences need to be interpreted with caution. While studies are limited with respect to specific cognitive functions among different racial/ethnic backgrounds, the findings that emerged in this literature and included variables such as those utilized in this study, namely working memory and
Hypotheses Tested

The following information shall summarize each of the study hypotheses, inferential analyses implemented to test the hypotheses, and the results obtained. Results must be considered within the context of the limitations of the control group discussed.

Hypothesis 1

In this initial hypothesis, it was expected that children with SCD and no known history of strokes would have significantly greater deficits in processing speed and working memory than the healthy controls. This hypothesis was tested using a one-way multivariate analysis of variance (MANOVA) with group (SCD/no stroke vs. healthy) entered as the independent variable and WRAML-2 Working Memory Index and WISC-IV/WAIS-III Processing Speed Index entered as the dependent variables.

The results provide support for this hypothesis. Specifically, the omnibus multivariate analysis, using the Wilks' Lambda procedure, indicated significant group differences for the combined PSI and WMI dependent variable, $F(2, 32) = 10.9, p < 0.001$, power = 0.98, partial $\eta^2 = 0.42$). Subsequent tests for group difference were conducted independently for each of the two dependent variables using the analysis of variance (ANOVA) procedure. The results indicate that for both the PSI, $F(1, 31) = 21.7, p < 0.001$, power = 0.99, partial $\eta^2 = 0.41$, and for the WMI, $F(1, 31) = 5.3, p = 0.03$, power = 0.60, partial $\eta^2 = 0.15$, the healthy group significantly outperformed the
SCD group. Specifically, on the PSI, the healthy group obtained a mean result of 109.6 ($SD = 11.7$) compared to the SCD mean of 88.6 ($SD = 14.3$) and on the WMI the healthy group produced a mean score of 100.9 ($SD = 13.2$) compared to a SCD mean score of 90.4 ($SD = 12.8$). Table 5 provides the ANOVA source table for these findings and Table 4 provides group means for comparison.

Table 5

ANOVA Source Values for Hypothesis 1 ($n = 33$)

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
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<th>MS</th>
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<td>891.9</td>
<td>5.2</td>
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</tr>
<tr>
<td>Error</td>
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<tr>
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<td>--</td>
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<tr>
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<td>31</td>
<td>169.9</td>
<td>--</td>
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<tr>
<td>Total</td>
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<tr>
<td>PSI</td>
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</tr>
<tr>
<td>WMI</td>
<td>313366.0</td>
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</tr>
</tbody>
</table>

*Note.* PSI = Processing Speed Index; WMI = Working Memory Index. Group provides for SCD vs. healthy.
Hypothesis 2

In the second hypothesis it was expected that, similar to hypothesis 1, children with SCD would produce lower scores on the Processing Speed index of the WISC-IV/WAIS-III and Working Memory indices of the WRAML-2 compared to healthy children; however, in this hypothesis the effect of age was controlled. Thus, the outcome postulated in Hypothesis I was again expected, however, in this hypothesis there was expected to be a significant effect of age within the overall multivariate model.

This hypothesis was tested using a one-way multivariate analysis of covariance (MANCOVA) with group (SCD/no stroke vs. healthy) entered as the independent variable, the Processing Speed and Working Memory indices entered as the dependent variables, and age entered as the dependent covariate.

The results provide mixed support for this hypothesis. Specifically, the omnibus MANCOVA analysis using the Wilks’ Lambda procedure was again statistically significant for group, $F(2, 29) = 11.3, p < 0.001$, power = 0.99, partial $\eta^2 = 0.44$, however, the multivariate analysis for the age covariate was not significant, $F(2, 29) = 2.6, p = 0.09$, power = 0.48, partial $\eta^2 = 0.15$. Thus, simultaneous consideration of all variables within the multivariate analysis indicated that there are differences between SCD and healthy participants, with limited impact of age on this relationship.

Inspection of the univariate analyses revealed, similar to hypothesis I, significant group differences between SCD and healthy participants for both the PSI, $F(1, 30) = 21.8, p < 0.001$, power = 0.99, partial $\eta^2 = 0.42$, and the WMI, $F(1, 30) = 5.5, p < 0.03$, power = 0.61, partial $\eta^2 = 0.15$ indices. Notably, however, in the univariate analyses the age covariate achieved statistical significance for the WMI, $F(1, 30) = 4.4, p = 0.04$, power =
0.53, partial $\eta^2 = 0.13$, but not for the PSI index, $F(1, 30) = 2.1$, $p = 0.16$, power = 0.29, partial $\eta^2 = 0.06$. Thus, these results indicate significant group differences on the PSI and WMI indices between SCD and healthy controls; however, age was a significant factor only for the WMI. These findings are summarized in Table 6.

As a further inspection of this hypothesis, a Pearson bivariate correlation was conducted to understand the simple linear relationship between WMI, PSI, and age. As expected, the relationship between age and PSI was not significant, $r = 0.23$, $p = 0.21$, however, there was a statistically significant, positive relationship between age and WMI, $r = 0.35$, $p = 0.047$, indicating that, across groups, WMI scores improved with age in this sample.
### ANOVA Source Values for Hypothesis II, Age as Covariate (n = 33)

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<tr>
<td>Error</td>
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<td>153.0085</td>
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<td>Total</td>
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</tr>
<tr>
<td>PSI</td>
<td>343289.00</td>
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<td>WMI</td>
<td>313366.00</td>
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</tr>
</tbody>
</table>

*Note. Age = covariate. PSI = Processing Speed Index; WMI = Working Memory Index.*

Group provides for SCD vs. healthy.
Hypothesis 3

In this third hypothesis, it was expected that individuals with SCD and no history of stroke would demonstrate greater cognitive fatigue when compared to healthy participants, as measured by the CPT-II. In order to test this hypothesis, performance from the first and second half of the CPT-II was subtracted to obtain a difference score for both the SCD and healthy control groups. An ANOVA was employed to examine mean differences between groups, with the expectation that differences would be greater in the SCD group (i.e., indicating a worsening of performance) than in the healthy control group.

The results indicated that difference scores did not vary for number of hits from the first half to the second half of the CPT between healthy control \( (M = 0.84, SD = 2.99) \) and SCD participants \( (M = 0.71, SD = 3.60) \), \( F(1, 31) = 0.01, p = 0.91 \). Similarly, the hit rate difference scores also did not vary between healthy control \( (M = 20.7, SD = 83.7) \) and SCD participants \( (M = -25.1, SD = 86.0) \), \( F(1, 31) = 2.40, p = 0.14 \). Thus, the degree of change between the first and second halves of the CPT did not vary as a function of study group.

In order to further explore this hypothesis, mixed between-within group ANOVAs were employed to simultaneously examine the impact of group (SCD vs. healthy) and time (repeated measure: 1<sup>st</sup> half of CPT vs. 2<sup>nd</sup> half of CPT) on both the hit and hit rate parameters of the CPT. Table 7 provides non-modeled means and standard deviations, aggregated by group and time, for these comparisons. With regard to number of hits, there was no main effect for time, \( F(1, 31) = 1.85, p = 0.18 \), power = 0.26, partial \( \eta^2 = 0.06 \), no main effect for group, \( F(1, 31) = 1.57, p = 0.22 \), power = 0.23, partial \( \eta^2 = \).
0.05, and the group x time interaction term was not found to be significant, $F(1, 31) = 0.12$, $p = 0.91$, power = 0.05, partial $\eta^2 = 0.00$. Similarly, with regard to the hit rate, there was no main effect for time, $F(1, 31) = 0.21$, $p = 0.89$, power = 0.52, partial $\eta^2 = 0.001$, no main effect for group, $F(1, 31) = 1.88$, $p = 0.18$, power = 0.26, partial $\eta^2 = 0.06$, and the group x time interaction term was not found to be significant, $F(1, 31) = 2.40$, $p = 0.14$, power = 0.32, partial $\eta^2 = 0.07$. Figure 2 depicts the pattern of these relationships. Given the outcomes of these analyses there has been no empirical support in this study for Hypothesis III, which would be expected given that visual inspection of the mean performance scores suggests minimal variability for CPT scores between groups.

Table 7

Descriptive Statistics for CPT Performance Aggregated by Group ($n = 33$)

<table>
<thead>
<tr>
<th></th>
<th>Control ($n = 19$)</th>
<th>SCD ($n = 14$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M$</td>
<td>$SD$</td>
</tr>
<tr>
<td>Hits Half 1</td>
<td>159.47</td>
<td>3.26</td>
</tr>
<tr>
<td>Hits Half 2</td>
<td>158.63</td>
<td>5.47</td>
</tr>
<tr>
<td>Hit Rate (ms) Half 1</td>
<td>1076.89</td>
<td>184.66</td>
</tr>
<tr>
<td>Hit Rate (ms) Half 2</td>
<td>1056.16</td>
<td>152.38</td>
</tr>
</tbody>
</table>

*Note.* CPT = Continuous Performance Test.
Figure 2. CPT Performance by Half
Clinical Group

Within the group of participants with sickle cell disease, significant and clinically relevant findings emerged. The sickle cell group consisted of 14 participants ranging in age from ten to twenty-two. As noted above, 3 patients were between ages 10 and 11 years, 8 patients were between 13 and 17 years, and 3 were between ages eighteen and twenty-two. Parents had a mean of 13.1 years of education, ranging from 10 years to 16 years of education. Median parental income was $30k, well below the median household income for the state of residency. One participant/parent did not report income.

With regard to race/ethnicity, 9 patients were African Americans, 4 were Hispanic, and 1 was Caribbean. Gender was well distributed, with 8 males and 6 females. Patients reported a mean of 35.1 hospitalizations, with numbers ranging as low as 5 up to as many as 100 in their lifetime.

On the WISC-IV and WAIS-III, mean performance for the Processing Speed Index was a Standard Score of 88.57, which is lower than average when compared to the normative population. Individuals with SCD yielded scores on the PSI ranging from 59 to 121 standard scores. Specifically, 1 participant’s score fell in the Extremely Low range, 2 in the Borderline range, 5 in the Low Average, 5 in the Average range, and 1 in the Superior range.

On the WRAML-2, participants from the SCD group yielded scores on the Working Memory Index ranging from standard scores of 68 to 108 with 90.43 representing the mean score. Specifically, 1 participant performed in the Extremely Low range, 2 in the Borderline range, 5 in the Low Average range, and 6 in the Average range.
On the CPT-II, participants with SCD performed similarly with regard to the number of hits they made in the first and second half. In terms of hit rate, how quickly each person responded, mean scores increased in the second half as expected, from a mean score of 1056 ms to 1165 ms, indicating that participants with SCD may have responded slightly slower in the second half; however, differences were not significant enough to reach statistical significance.

Overall, these findings reveal important findings for children and adolescents with no known history of stroke. The current study demonstrates that patients with sickle cell disease remain at risk for lower scores, particularly on measures of processing speed, when compared to the normative population.

Given that the majority of patients had the most severe type of sickle cell disease, it is possible that the level of anemia may have contributed to the findings within this group. Future studies should examine hematocrit and anemia levels within a sickle cell population who has not had any type of neurological insult.
CHAPTER V

Discussion

As previously discussed, SCD is a serious chronic health condition as it places individuals at risk for many problems including, but not limited to, pain and vas-occlusions such as overt or silent strokes or infarcts. The disease and its impact on cognitive and academic functioning can be best understood from a biopsychosocial developmental model because of the significant number of biological, cultural, social-emotional, developmental, and contextual factors that impact these children (Armstrong, 2006; Gustafson et al., 2006). Thus, the current study considered several of these components throughout the study, including age, type of SCD, stroke, SES, level of pain, and possible cumulative effects on the brain and in analysis of the data. Specifically, only individuals with SCD types SS and SC and no evidence of stroke were included in this study.

Summary and Conclusions of Research

Neuropsychological findings have frequently established that children with SCD who had CVAs are at risk for cognitive declines (Armstrong et al., 1996; Brown et al., 2000). To date, the majority of studies have focused on global impairments in children and adolescents with SCD (Steen et al., 2005; Swift et al., 1989; Wang et al., 2001). Yet, Schatz and colleagues (2002) contend that measures of specific cognitive abilities are more sensitive than IQ scores when determining functioning in children and adolescents.
with SCD. In addition, the studies that incorporated radiographic findings have often identified cognitive deficits associated with frontal lobe involvement in terms of attention and executive functioning (Armstrong et al., 1996; Berkelhammer, Williamson, Sanford, Dirksen, Sharp, & Margulies, 2007; Brown et al., 1993). Neuropsychological measures are also considered useful tools in helping predict localization of strokes (Debaun, Schatz, Siegel, Koby, Craft, & Resar, 1998). However, very few studies have examined specific executive functions among individuals with SCD and no evidence of CVAs (Gold et al., 2008).

The present study examined the relationship between children and adolescents with SCD compared to their healthy peers according to specific cognitive functions. SCD has been associated with global deficits, particularly among those with have experienced CVAs. Recently, it has been suggested that children with SCD and no detectable strokes may also experience cognitive difficulties; however, this finding remains irresolute (Brown et al., 2000; Gold et al., 2008; Noll et al., 2001). Researchers are beginning to examine a possible age-related decrement in children and adolescents, suggesting that perhaps as children develop and age, they have more difficulty due to the effects of SCD on their brain functioning (Brown et al., 1993; Fowler et al., 1988; Kral et al., 2003; Steen et al., 2005; Wang et al., 2001). The findings generally indicate a possible decline over time; however, there are many inconsistencies across the neurocognitive domains that have been assessed and the measures used to examine performance.

Cognitive fatigue is an important construct, yet most of the literature on cognitive fatigue has focused on subjective measures. Moreover, the researchers that have assessed objective measures of fatigue have been focused on conditions that tend to develop in
adult stages of development. The current study is the first to incorporate an objective measure of fatigue with a sample of children.

The current study was devised to provide a better understanding of specific cognitive functions among individuals with SCD and no evidence of any type of cerebrovascular event. As discussed in Chapter IV, findings with regard to cognitive deficits in children with SCD and no evidence of stroke are mixed. This Chapter will review the results of each hypothesis tested, which overall, revealed significant differences between groups for specific executive functions but not for cognitive fatigue. Lastly, implications for future research and suggestions for practice will be reviewed.

Despite attempts at matching controls, there were significant differences between the two groups according to race and SES which limits the interpretation of group differences. Due to the lack of a comparable control group, findings may be spurious and the statistical differences found may not accurately reflect what truly explains the differences revealed in the study. Moreover, intercorrelations found that parent income was associated with working memory and processing speed. Therefore, caution must be given when considering any between group differences, as parent income and race likely contributed to between group differences.

**Hypothesis 1**

The initial hypothesis sought to determine if there were differences in children and adolescents with SCD and no evidence of stroke compared to healthy controls with regard to their performances on the Processing Speed Index of the WISC-IV/WAIS III and the Working Memory Index of the WRAML-2. This question was prompted by the
extensive literature on global deficits (Steen et al., 2005; Swift et al., 1989; Wang et al., 2001). There remains a dearth of literature on specific executive functions despite a few studies that have reported lower performance on memory and attention tasks when compared to healthy children (Brown et al., 1993; Fowler et al., 1988; Ris & Grueneich, 2000). In addition, the majority of studies incorporated children with SCD and CNS abnormalities, and did not include individuals with SCD without cerebral events (Armstrong et al., 1996; Brandling-Bennett et al., 2003; Schatz & Roberts, 2005; White et al., 2000). Of those that examined SCD in the absence of stroke, outcomes are varied (Bernaudin et al., 2000; Brown et al., 2000; Brown et al., 1993; Fowler et al., 1988; Gold et al., 2008; Noll et al., 2001). Thus, the current study is quite unique in its evaluation of children and adolescents with SCD and no evidence of stroke.

As expected, the group of children and adolescents with SCD and no evidence of stroke performed significantly lower on working memory tasks and processing speed tasks than the control group. This finding is consistent with a more recent study that also found significant differences between children with SCD and no evidence of CVA in comparison to the normative population (Gold et al., 2008). However, since these groups were not matched for SES and race, it is quite possible that the differences in working memory and processing speed relate to the significant discrepancies between groups, such as race or SES.

Several possible explanations may have accounted for some of differences, aside from the limitations between the participant and control groups discussed. First, unlike many previous studies, the current study only included the most severe types of SCD: Hb SS and HbSC. In an analysis by Steen and colleagues (1999) individuals with HbSS,
those with lowest levels of hematocrit, demonstrated greater cognitive impairments in all
cognitive domains, except for processing speed. In a later study by Steen and colleagues
(2005) individuals with lower levels of hematocrit and cognitive impairments as
measured by MRIs demonstrated greater impairments on several subtests on the WISC-
III, including several verbal and performance tasks. However, there were no impairments
on measures of processing speed. On the contrary, Bernaudin and colleagues (1999)
found that processing speed and working memory were both significantly lower in
severely anemic patients, indicating that hematocrit contributes to both processing speed
and working memory deficits. Therefore, hematocrit levels may have been a factor in the
current finding; however, since hematocrit levels were not included, therefore, this is
merely speculation.

Second, although all charts were reviewed for history of CVAs, not every chart
included an updated MRI. Therefore, it is possible that a number of these children may
have experienced a silent stroke, in which a child could have been asymptomatic.
Moreover, previous findings suggest that the majority of silent strokes occur in the frontal
lobes, the location predominantly responsibility for processing speed and working
memory tasks (Debaun et al., 1998). Other researchers have theorized that physiological
changes, such as hypoxic events, that would not be depicted on standard imaging could
be responsible for cognitive effects in children with SCD without stroke (Schatz et
al., 2002). Finally, the etiology of cognitive deficits in children with SCD is not fully
understood and remains a relatively new focus in the field of neuropsychology (Steen et
al., 2005). Although researchers have generally agreed that the disease itself is likely to
have the greatest impact on cognitive functioning (Berkelhammer et al. 2007), others
have found evidence for greater risks depending on the severity of socioenvironmental risk factors coupled with anemia severity (Schatz, Finke, Roberts, & Roberts, 2004). Therefore, it is highly recommended that ongoing research be conducted with medical doctors in conjunction with neuropsychologists in order to better explain the relationship between anemia and cognitive functioning.

**Hypothesis 2**

The second hypothesis posited that, once again, children and adolescents with SCD would score lower on the Processing Speed and Working Memory indices when compared to healthy children and adolescents and that there would be a significant effect of age. This question was formulated, in part, based on previous research that found older children with SCD perform more poorly than younger children on some cognitive measures. However, most of the earlier studies focused on a limited age range. As suggested in previous research by Schatz and colleagues (2002), the age range of the current study included individuals ages 10 to 22, with a relatively fair distribution, in order to account for younger children, adolescents, and young adults.

The findings on an age-related decrement on specific cognitive measures have been variable. For example, as previously discussed, Steen and colleagues (2005) found that performance on the WISC-III Full Scale IQ decreased with age. Brown and colleagues (1993) only found that visual-motor scores decreased with age. Fowler and colleagues (1998) demonstrated that older children performed more poorly on reading, visual-motor, and attention tasks when compared to younger children. In the study conducted by Wang and colleagues (2000), children with SCD and no MRI abnormalities
performed worse over time on measures of verbal intellectual functioning and mathematics from the Woodcock Johnson Test of Academic Achievement. Kral and colleagues (2003) found significant results supporting an age-related decrement on measures of intellectual functioning, sustained attention, and executive functioning; however, their study failed to differentiate the SCD groups according to level of severity when examining the impact of age.

Still others (Swift et al., 1989) did not find any evidence for an age-related decrement (Wasserman et al., 1991). Furthermore, one study found that younger children performed lower than older children on visual, verbal, and memory tasks.

The results of hypothesis I revealed that, once again, there were significant differences between both groups; however, contrary to expectation, the covariate age was only a significant factor for working memory in the overall analysis.

Further inspection revealed an unexpected finding. The original hypothesis was developed under the assumption that age would be a significant factor and that there would be a negative relationship between age and index scores for both working memory and processing speed tasks. Age was not significantly related to processing speed. In fact, working memory was found to have a positive relationship with age, indicating that for both groups, working memory scores improve with age.

Although these findings are not consistent with the literature previously discussed that supports an age-related decrement, several factors should be considered. First, of the studies that have found an age-related decrement, the intellectual and cognitive domains utilized in the study were quite variable. These domains included intellectual components such as Full Scale IQ, Verbal IQ, cognitive domains such as visual-motor skills, visual
working memory, attention and executive functioning skills, as well as academic domains of reading. Given these inconsistencies across studies, it is not unexpected that the results were not readily generalizable to the current study. Toward this end, Schatz and colleagues (2002) contend that the measures most apt at assessing cognition in children with SCD without cerebral infarctions have not been established.

As previously discussed, the current study focused specifically on Processing Speed Index of the WISC-IV and WAIS-III, and the Working Memory Index of the WRAML-2. To date, no studies have found an age-related decrement with either of these indices. In fact, those studies that found significance for working memory utilized the Freedom from Distractibility Index from the Wechsler Scales of Intelligence, generally an outdated version, such as the WISC-R or WISC-III (Wang et al., 2001).

Another issue of generalizability relates to the sample. That is, only some of previous studies that established an age-related decrement examined children with SCD and no evidence of CVAs. Some researchers failed to delineate between children with SCD and no evidence of infarction and SCD with silent or overt stroke when examining the relationship between age and cognition (Kral et al., 2003).

As a final point, it is necessary to consider possible confounding variables that may have impacted the results. One such explanation that may have contributed to the improvement of working memory scores with age is related to psychosocial adjustment of the disease and possible maturation. Maturation can results from changes that occur within participants and often interfere with treatment (Pedhazur & Schmelkin, 1991). The possibility exists that younger children with SCD are not as adjusted or familiar to the effects of the disease itself, such as pain crises, while older children may be better
adjusted. Toward this end, older children with SCD may have learned to develop or compensate for cognitive weaknesses, such as working memory difficulties, which may have impacted their performance on the working memory tasks. Although this may have contributed to the positive relationship between age and performance on the Working Memory Index, a similar relationship would have been expected with the Processing Speed Index.

**Hypothesis 3**

The third hypothesis postulated in this study sought to explore whether individuals with SCD would perform more poorly than healthy controls on the CPT-II. As noted earlier, to date, no studies have examined cognitive fatigue as measured by performance during a sustained mental task with a Sickle Cell population, despite physiological factors that certain aspects of the disease, such as low hemoglobin, manifest itself by fatigue (U.S. Department of Health and Human Services, 2002).

In light of empirical research on cognitive fatigue and the evidence for fatigue among individuals with SCD, it was expected that performance for the SCD group would diminish in second half of the CPT-II due to cognitive fatigue. Contrary to this expectation, no difference was established for either measure employed, neither hit rate, nor reaction time.

A possible explanation for this finding may be related to the sample population differences, as the majority of studies that have examined objective forms of cognitive fatigue have been conducted with adults and medical conditions such as MS, TBIs, and chronic fatigue syndrome (DeLuca, 2005). In addition, the declines in performance found
across sustained attention measures were generally with adult populations, which would not directly generalize to a pediatric population.

With regard to instrumentation, the sustained attention task generally employed when measuring objective cognitive fatigue was the PASAT. The PASAT precluded utilization of this assessment tool in the current study with a pediatric sample, as its norms were developed on individuals ages 16 and up. Instead, a more suitable instrument which assesses a similar construct, sustained mental effort, and has similar variables, such as reaction time and hit rate, the CPT-II, was selected. Thus, instrumentation in the current study may have contributed to the lack of significance between the SCD group and the control group.

Given the threats of instrumentation, that this was the first study to examine an objective form of cognitive fatigue using the CPT-II and the first to implement a methodology based on Deluca’s (2005), coupled with the selection of the sample population, it is not unusual that the outcome was not significant. Of note, as evidenced in Figure 1, the trend of Hit Rate as measured by milliseconds in the SCD group was in the direction of slowed reaction time in the second half of the test as compared to the control group, as predicted. Although the difference between the variability between the two groups did not reach statistical significance, there was a suggestion of a relationship in the expected direction, which is similar to results found in children with other neurological diagnoses (Fleck, Shear, & Strakowski, 2002) who demonstrated processing speed and vigilance difficulties despite not reaching statistical significance. However, the effect size was too small to support the proposed hypothesis. Fleck and colleagues have noted that the variability measures of the CPT-II are at times insensitive to these
differences due to the ceiling level of hit rates and reaction time. In addition, the use of counterbalancing of measures for a study that lasted only about one hour, may have actually diminished the nuanced differences in fatigue. Given that one of the measures was assessing cognitive fatigue, the CPT-II probably should have been given consistently as the last measure in order to assess potential cumulative effects of the testing consistently across each session. Controlling for test administration sequence of the CPT-II may have better captured the level of fatigue across each participant.

Limitations

The outcomes of this study revealed several significant findings as well as implications for various children and adolescents with sickle cell disease. Despite these findings, the results must be interpreted within the limitations of the study design. The greatest limitation and an inherent threat to the validity of the study is the difference between the SCD group and the control group according to race and SES; therefore, any significant differences between groups may be spurious. Although several attempts were made to match patients with controls according to similar demographic information with success across age, gender, and parent education, there is a serious flaw in the disparity between the SCD group and the control group. For example, the control group reported a greater parental income compared to the SCD group. This finding is directly in line with the literature that reports that the majority of children with SCD belong to families with low incomes, often at or below the poverty line, which has been found to cause significant limitations in the quality of healthcare as well as challenges in a child’s social and academic success (Schatz & McClellan, 2006). As discussed and has been found in
numerous studies (Sattler, 2008), significant disparities remain between groups of different race/ethnicity, SES, and educational background. In addition, Ryan and colleagues (2005) found that the educational opportunities were more robust than racial/ethnic backgrounds alone in explaining neuropsychological performance differences between these groups. Due to the many influences of race/ethnicity, SES, and quality of education on cognitive measures, Manly (2005) suggests a number of possibilities to address these discrepancies in clinical work and research, such as developing alternative approaches to establishing normative data that adequately captures true cognitive abilities. In addition, the limited number of studies on large minority groups with measures such as with the WRAML-2, makes it difficult to extrapolate the meaning of the differences found in the current study. Therefore, neuropsychological differences between African Americans and unmatched groups should be merely speculative as failing to do so may result in erroneous interpretations of the differences found.

Schatz and McClellan (2006) suggested that the interaction between SES and disease severity as measured by type of anemia (HbSS or HbSC), could impact cognitive abilities. Thus, a limitation in the current study is that, despite significant efforts to control for biological and social factors that could potentially impact cognitive functioning, it did not evaluate potential interactions between disease effects and social-environmental risk factors beyond age. Since SES and anemia severity were not controlled for in the analysis, it is quite possible that these factors may have influenced the lower scores on the Working Memory and Processing Speed Indices.
Another significant limitation was the sample size. Several factors were responsible for the size of the sample. Only one treatment center was utilized in the current study, which reduced the opportunity to collaborate clinical samples across multiple clinical settings. Although the size of the sample was adequate in order to provide sufficient power and effect size, the possibility remains that the small sample size may have mitigated power and diminished effects for the covariate on processing speed in the second or third hypotheses, that otherwise would have been detected with a larger sample. The likelihood of detecting an effect for hypotheses 3 is not as great of an issue as the variance was so low in this particular analysis.

With regard to the sample, the heterogeneity of race is a considerable limitation and the result of the recruitment process. Controls were given solicitation letters through various methods of recruitment, such as family and friends of patients and undergraduates at an urban university. Since there was no screening process developed, when potential controls called to schedule an appointment with me, there was no way to ensure that the individual was matched for race/ethnicity with the patient sample. Therefore, many of the individuals that agreed to participate were of Caucasian background. Similarly, the control group was disproportionate with regard to gender. That is, a higher number of females was represented in this group.

In terms of selection of patients, charts were reviewed for documentation of any type of CVA which included neuroimaging studies, when identifying patients who met criteria for the study, SCD type Hb SS or Hb SC without any evidence of stroke. Although the participants were carefully selected and believed to have no vaso-occlusions, there was no way to control for the possibility of a cerebral vascular event,
namely a silent stroke, since the most recent imaging available at the time of the chart review.

As discussed in Chapter I, a significant limitation in quasi-experimental designs is that the design lacks random assignment, and therefore, true manipulation of treatment variables is not possible. In the absence of randomization, conclusions about casual relationships cannot fully be established. Instead, generalizations about the findings can be made.

Finally, the use of the CPT-II poses a limitation with regard to instrumentation. As previously discussed, no known studies have investigated an objective measures of cognitive fatigue with a sickle cell population. Although the CPT-II meets the criteria for examining performance on a sustained attention task, as measured by hit rate (number correct) and reaction time, there is no empirical evidence to support this is a reliable tool for assessing cognitive fatigue.

Notwithstanding these limitations, the data supports the body of literature of emerging evidence of specific neurocognitive deficits in children and adolescents with sickle cell disease and no evidence of stroke. Toward this end, the findings highlight the importance of using executive functioning measures, including working memory and processing speed, in order to gauge current functioning and educational or treatment needs.
Suggestions for Future Research and Practice

Future studies should continue to explore the differences in specific neurocognitive functions in children with SCD and no evidence of structural brain abnormalities, including silent infarcts. In addition, it is important to identify the measures that are sensitive to specific neurocognitive deficits and to replicate these findings using similar tools. As noted earlier, the variability across studies with regard to types of measures used when examining working memory, for example, is quite high. Finding a few measures that tap into cognitive deficits will help provide consistency not only in research but in practice. In addition, specific cognitive abilities have been empirically validated as having more sensitivity to cognitive effects than IQ measures.

When feasible, corroboration of neuroimaging studies and transcranial Doppler findings with data collection would help to control for the influence of silent strokes on cognitive functioning. Without certainty that individuals with silent strokes are excluded from a study places a significant limitation on the research, and may contribute to some of the cognitive decline. Toward this end, Moser and colleagues (1996) established that even in the absence of an overt stroke, MRI can detect infarction and ischemic disease. In addition, the impact of MRI versus neurological history, such as in the current study, has not been evaluated empirically (Schatz et al., 2002). Further exploration is needed to establish whether neurological history without MRIs is sufficient for controlling for silent strokes. Until then, this remains an unresolved issue.

Neuroimaging findings are not the only factors which can impact demonstrate and possibly identify cognitive deficits. Specifically, hematocrit has been considered a risk
factor (Bernaudin et al., 2000). Future studies should evaluate the factors related to declines.

In terms of the age-related decrement, prospective studies need to better examine the relationship between age and cognitive functioning by utilizing a control group and similar measures, since the exact relationship remains unknown. Ideally, the age range should include preschool children through school age and even young adults. Further, longitudinal studies would likely be the best methodological design in order to refine the understanding and impact of SCD as having cumulative effects on the brain, as many studies, including the current study, purported to measure.

With regard to cognitive fatigue, other studies are needed to establish validity on an objective measure of mental fatigue with pediatric populations. Given that cognitive fatigue has been well-established in adults with chronic illnesses, it is quite possible that a disease that manifests itself with similar symptomatology, chronic pain and fatigue, will also cause mental fatigue.

Although beyond the scope of the current study, very few studies have evaluated the contribution of direct and indirect causes of cognition in children with SCD. For example, studies have identified the significance of biological factors including hematocrit and silent infarcts, and psychosocial factors such as low SES; however, minimal studies have evaluated the relative contribution of all causes of cognitive outcomes. Larger scale studies across multiple sites and including multiple groups, including controls, silent strokes, and overt strokes as well as separating types of anemia (e.g., Hb SS, Hb SC) would afford researchers the opportunity to measure such outcomes.
These suggestions will help identify the cognitive functions that are most impacted by the disease itself as well as indirect factors, and have important implications for practice. Specifically, baseline assessments at an earlier age as well as routine screenings could help monitor the progress of children and adolescents with SCD and identify educational needs. Ultimately, the goal is have a sound methodology so that neuropsychologists can evaluate and identify neurocognitive weaknesses.

The current study yields important findings for psychologists. Specifically, it raises an important issue with regard to the many struggles that minority groups with chronic illness experience, including economic disadvantages. Psychologists need to be sensitive to the many issues that this group is susceptible to, particularly when working with children and adolescents in a therapeutic manner. Moreover, there is a social justice issue that calls for the attention of psychologists in order to better service this population. More funds and grants are needed to expand the number of studies on SCD and to provide more comprehensive neuropsychological evaluations that are often expensive to conduct.

The most significant outcome of the current study is the finding that children and adolescents without any known history of a stroke are at risk for cognitive deficits. Neuropsychologists should therefore conduct assessments as early as possible with all children and adolescents; since a true baseline evaluation would be impossible as this is disorder that a child is born with, it is strongly recommended that all children with sickle cell disease have a neuropsychological evaluation when they enter elementary school (i.e., kindergarten or first grade). Assessment at this early age would gauge the child’s
abilities before the educational and executive functioning demands begin to increase and would allow for tracking the learning trajectory of the child.

Conclusion

In conclusion, the results of the current study suggest that specific cognitive measures remain appropriate for identifying cognitive weaknesses in a SCD sample. There are indications that SCD has an impact on the frontal lobes of the brain, even in children with SCD and no stroke. The results fell short in identifying an age-related decrement for processing speed and working memory in a SCD population; however, further investigation is warranted as cross-sectional designs are limited in evaluating cumulative effects on the brain.


Gustafson, K. E., Bonner, M. J., Hardy, K. K., & Thompson, R. J. (2006). Biopsychosocial and developmental issues in sickle cell disease. In R. T. Brown...


literacy levels: Effects of education and reading level in participant characterization.

*Journal of International Neuropsychological Society, 11 (7), 889-898.*


Appendix A

Solicitation Letters
Dear Patient or Parent,

I am inviting you to participate (or to permit your child to participate, if he or she is under 18 years of age) in a research study that will examine children and adolescents across several areas of functioning. You have been asked to take part in this study because you have Sickle Cell Disease.

The study is being conducted by Laura J. Tagliareni, M.A., a doctoral student in the Counseling Psychology Program at Seton Hall University, South Orange, New Jersey and an employee at the medical center where the study is taking place.

The purpose of the study is (1) to see how quickly children are able to complete tasks and how they remember new information (2) to see if older adolescents complete tasks slower than their younger peers (3) to see if older adolescents have more difficulty remembering new information than their younger peers (4) to see if some children and adolescents tire more quickly at tests than others. Estimated time of participation is 1 hour.

Patients 18 years and older or parents interested in having their child participate in this study should contact Laura Tagliareni at 201-996-5332 to schedule an appointment to complete the research battery at the medical center. Once the appointment is scheduled, Ms. Tagliareni will meet with you to complete a form that you will sign only if you decide that you want to do the study. A research assistant will then begin the study with you.

Please note that all names will be kept separate from the data, so that performance on the instruments will remain confidential.
Participation in the study is completely voluntary. Potential participants may choose not to participate in the study after reviewing the forms may stop their participation at any time during the testing session.

Those who choose to participate will complete a short questionnaire focusing on self and family, a computerized attention test, 2 tasks that assess speed of thinking, 2 tasks that look at memory and thinking. Once the information is completed, participants will receive a $25 gift card. Participants will also be given money if needed to cover their trip to and from the hospital, if needed.

Participation in the study is completely voluntary. Potential participants may choose not to participate in the study after reviewing the forms may stop their participation at any time during the testing session.

Please be assured that all participants’ anonymity will be protected in various ways. Although the pages are coded by number in order according to the scheduled appointment, no identifying information will be requested in the study. No part of the study requires that participants provide their names or other information that will reveal their identity. Results of the study will be reported based on group data only.

Please be assured that all participants’ anonymity will be protected in various ways. Although the pages are coded by number in order according to the scheduled appointment, no identifying information will be requested in the study. No part of the study requires that participants provide their names or other information that will reveal their identity. Results of the study will be reported based on group data only.

All protocols will be stored in a locked cabinet maintained at the medical center by Ms. Tagliareni. Data from these forms and the computer responses will be transferred to a computer database, available only by the researchers. Further, the completed pages will be shredded as will the computer scores be erased, once the database has been created and reviewed for accuracy. No one outside the researchers will have access to these questionnaires.
If you have any questions, you may contact the primary researcher, Laura J. Tagliareni, M.A. at (201) 996-5332 or tagliala@shu.edu.

Thank you for your consideration.

Sincerely,

Laura J. Tagliareni, M.A.

Solicitation Letter for Healthy Participants

I am inviting you to participate in a research study that will examine children and adolescents across several areas of functioning. You have been asked to take part in this study because you are an individual without any major health problems.

The study is being conducted by Laura J. Tagliareni, M.A., a doctoral student in the Counseling Psychology Program at Seton Hall University, South Orange, New Jersey and an employee at the medical center where the study is taking place.

The purpose of the study is: (1) to see how quickly children are able to complete tasks and how they remember new information (2) to see if older adolescents complete tasks slower than their younger peers (3) to see if older adolescents have more difficulty remembering new information than their younger peers (4) to see if some children and adolescents tire more quickly at tests than others. Estimated time of participation is 1 hour.

Individuals 18 years and older or parents interested in having their child participate in this study should contact Laura Tagliareni at 201-996-5332 to schedule an appointment to complete the research battery at the medical center. Once the appointment is scheduled, Ms. Tagliareni will meet with you to complete a form that you will sign only if you decide that you want to do the study. A research assistant will then begin the study with you.

Those who choose to participate will complete a short questionnaire focusing on self and family, a computerized attention test, 2 tasks that assess speed of thinking, 2 tasks that look at memory and thinking. Once the information is completed, participants will receive a $25 gift card.
Participants will also be given money if needed to cover their trip to and from the hospital, if needed.

Participation in the study is completely voluntary. Potential participants may choose not to participate in the study after reviewing the forms may stop their participation at any time during the testing session.

Please be assured that all participants’ anonymity will be protected in various ways. Although the pages are coded by number in order according to the scheduled appointment, no identifying information will be requested in the study. No part of the study requires that participants provide their names or other information that will reveal their identity. Results of the study will be reported based on group data only.

All protocols will be stored in a locked cabinet maintained at the medical center by Ms. Tagliareni. Data from these forms and the computer responses will be transferred to a computer database, available only by the researchers. Further, the completed pages will be shredded as will the computer scores be erased, once the database has been created and reviewed for accuracy. No one outside the researchers will have access to these questionnaires.

If you have any questions, you may contact the primary researcher, Laura J. Tagliareni, M.A. at (201) 996-5332 or tagliala@shu.edu. Thank you for your consideration.

Sincerely,

Laura J. Tagliareni, M.A.
Appendix B

Consent and Assent Forms
ORAL ASSENT BY MINOR SUBJECT (UNDER 12 YEARS OF AGE)
(to be read to child)

Hello, (minor's name). My name is (researcher). I'm from the Department of Counseling Psychology at Seton Hall University. My job is to ask you some questions and give you a computer test. I'm here to give you some of these test questions. Your (parent/guardian) has given me permission to talk to you. All of the questions and computer test will take about 1 hour.

You can decide if you want to meet with me or not. You may decide to stop at any time. Whatever you decide to do is okay, and you and your family will not get into any trouble if you decide to stop or not meet with me.

Everything that we do today is confidential. That means that no one will know who took these tests today.

You will be given $25 at the end of our session as a thank you for your time.

Do you have any questions for me?

If it okay with you to begin, I will need you to sign the paper below. I can read the form to you if you need help.

You are being asked to agree to participate in this research study. You have the right to find out what is involved for you if you do the study, and to tell your parent(s) whether you do or do not want to do the study.

Your parents will also be asked to give permission for you to do the study.

Laura Tagliareni, M.A. (or her researcher) and your parent(s) have explained to you the steps that are involved, and you understand them.

Laura Tagliareni, M.A. (or her researcher) and your parent(s) have also explained to you what you will do today in the study.
You have asked any questions you have, and all your questions have been answered.

You understand everything that has been told to you.

Check one:

______ I agree to participate in this study.

______ I do not agree to participate in this study.

*Parents/Guardians must also read and sign the informed consent before child participates.
ASSENT BY MINOR SUBJECT TWELVE YEARS OF AGE OR OLDER

You are being asked to agree to participate in this research study. You have the right to find out what is involved for you if you participate, and to tell your parent or guardian(s) whether you do or do not want to participate. Your parents will also be asked to give permission for you to participate in this study.

The study is being done by Laura Tagliareni, M.A. She is from the Department of Counseling Psychology at Seton Hall University and works at this hospital.

The purpose of the study is to see how children learn.

Ms. Tagliareni and her researchers will ask you some questions and give you a computer test. All of the questions and computer test will take about 1 hour.

You can decide if you want to meet with Ms. Tagliareni and her research assistants or not. You may decide to stop at any time. Whatever you decide to do is okay, and you and your family will not get into any trouble if you decide to stop or if you do not want to begin the study.

Everything that we do today is confidential. That means that no one will know who took these tests today.

You will be given $25 at the end of our session as a thank you for your time.

If you have any questions about today, please ask Ms. Tagliareni.

If you are okay to begin, you will sign the paper below.

Laura Tagliareni, M.A. (or her researcher) and your parent(s) have explained to you the procedures that are involved, and you understand them.

Laura J. Tagliareni, M.A. (or her research assistant) and your parent(s) have explained to you the procedures that are involved, and you understand them.

You have asked any questions you have, and all your questions have been answered.

You understand everything that has been told to you.
Check one:

_____ I agree to participate in this study.

_____ I do not agree to participate in this study.

*Child subjects and their parents/legal guardians will be given a copy of the signed, countersigned and dated Assent Form before their participation begins*

_________________________ ________________ ____________
Child's Name     Child’s Signature    Child's Age

_________________________ ____________
Signature            Date

_________________________ ____________
Parent/Legal Guardian     Date

_________________________ ____________
Researcher            Date

*Parents/Guardians must also read and sign the informed consent before child participates.*
Informed Consent for Parents

You are invited to permit your child to participate in a research study comparing children and adolescents with and without Sickle Cell across several areas.

Researcher's Affiliation

This study is being conducted by Laura J. Tagliareni, M.A., a doctoral student in the Counseling Psychology Program at Seton Hall University, South Orange, New Jersey and an employee at the medical center where the study is taking place.

Purpose and Duration of Study

The purpose of the study is: (1) to see how quickly children are able to complete tasks and how they remember new information (2) to see if older adolescents complete tasks slower than their younger peers (3) to see if older adolescents have more difficulty remembering new information than their younger peers (4) to see if some children and adolescents tire more quickly at tests than others.

Estimated time of participation is 1 hour.

Procedures and Instruments

Participants will meet with the primary researcher to complete an informed consent or assent. A research assistant will then begin the study. Those who choose to participate will complete a short questionnaire focusing on self and family, a computerized attention test, 2 tasks that assess speed of thinking, and 2 tasks that look at memory and thinking.

Once the information is completed, participants will receive a $25 gift card. Participants will also be given money to cover the cost of their trip to and from the hospital if needed.

Voluntary Nature of the Study

Participation in the study is completely voluntary. After reviewing the informed consent participants may stop participating at any time during the testing session.
Anonymity

Please be assured that all participants' anonymity will be protected in various ways. Although pages are coded by number in order according to the scheduled appointment, no identifying information will be requested in the study. No part of the study requires that participants provide their names or other information that will reveal their identity. Results of the study will be reported based on group data only.

Confidentiality of Data

Please note that all names will be kept separate from the data, so that performance on the instruments will remain confidential.

All protocols will be stored in a locked cabinet maintained at Hackensack University Medical Center by Ms. Tagliareni. Data from these forms and the computer responses will be transferred to a computer database which will be stored electronically on a USB memory key, accessible only by the researchers. Further, the completed pages will be shredded as will the computer scores be erased, once the database has been created and reviewed for accuracy. No one outside the researchers will have access to these questionnaires.

Risks and Discomforts

There are no anticipated risks or discomforts.

Benefits

No direct benefits to subjects are expected from this research. The knowledge gained from the study will likely help understand specific aspects of learning. The findings may help psychologists to better understand how children and adolescents with Sickle Cell Disease learn, which will help in educational and academic planning for student accommodations and interventions.

All subjects will receive a copy of the signed and dated Informed Consent form prior to participation in the study.
Contact Information

If you have any questions, you may contact the primary researcher, Laura J. Tagliareni, M.A. at (XXX) XXX-XXXX at XXXXXXXXX Medical Center or her faculty advisor, Laura Palmer, Ph.D., Chair of the Counseling Psychology Ph.D. program at Seton Hall University. This study was approved by the Institutional Review Board at Seton Hall University. Mary Ruzicka, Ph.D., the Director of the IRB, may be contacted by phone at 973-313-6314. The principal investigator, faculty advisor, and/or IRB committee may be contacted at any time to answer questions regarding the research.

Thank you for your consideration.

-----------------------------------------  
Participant or Parent/Guardian   Date

-----------------------------------------  
Researcher   Date
Appendix C

Demographic Form
Please provide the following information about yourself, which will help us to better understand the results of this study. This information is strictly confidential, and will only be reported in group format.

1. Birthdate: _______ (month-day-year)

2. Age: _______

3. Gender: _______

4. Current grade in school. If college, please indicate year. _______

5. Your race/ethnicity: _______

6. Parents’ education:

   - Some high school
   - High school graduate
   - Some college
   - 2 year college
   - Technical school
   - 4 year college
   - Post graduate

7. Approximate annual household income:

   - Less than $10,000
   - $10,000 to $19,999
   - $20,000 to $29,999
   - $30,000 to $39,999
   - $40,000 to $49,000
   - $50,000 to $59,000
   - $60,000 to $69,000
   - $70,000 to $79,000
   - $80,000 to $89,000
   - $90,000 to $99,000
   - Greater than $100,000

8. Please list any prenatal problems: ____________________________

9. Please list any problems at birth: ____________________________

10. Please list all medical conditions/diagnoses: ____________

    If Sickle Cell Disease, please indicate age of diagnosis: _______

11. Please list any form of documented disability, including Learning Disabilities. ____________________________
12. Please list all current medications: __________________________

13. Number of hospitalizations related to SCD in the past year ______________
   Not applicable ____________

14. Number of hospitalizations related to SCD throughout your lifetime_______________
   Not applicable ____________

*15. Have you ever experienced any type of stroke? Please check. Yes _____ No _____

   If history of stroke, you are not eligible for this study.

*16. Have you ever received a bone marrow transplant? ________
   If Yes, please inform the researcher as you are not eligible in the current study.

17. Are you currently experiencing any pain? If so, please circle the extent of your current Pain:

   0 1 2 3 4 5 6 7 8 9 10

   No pain                      Moderate Pain                      Severe Pain

*18. Is your pain greater than 5? Yes or No

* If you responded yes to these questions, please notify the researcher immediately, as you are not eligible for the current study.

    Thank you for your participation.