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Impact of sickle cell disease on executive functioning in an adult population

Christina Wade
cwade001@ucr.edu

Pepperdine University

Graduate School of Education and Psychology

IMPACT OF SICKLE CELL DISEASE ON EXECUTIVE FUNCTIONING IN AN ADULT POPULATION

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of the requirements for the degree of

Doctor of Psychology

by

Christina Wade

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Shelly Harrell, Ph.D. – Dissertation Chairperson

This clinical dissertation, written by

Christina Wade

under the guidance of a Faculty Committee and approved by its members, has been submitted to and accepted by the Graduate Faculty in partial fulfillment of the requirements for the degree of

DOCTOR OF PSYCHOLOGY

Doctoral Committee:

Shelly Harrell, Ph.D., Chairperson
Sharon H. O'Neil, Ph.D., M.H.A.
Ashley M. Whitaker, Ph.D., ABPP-Cn
Robert deMayo, Ph.D., ABPP

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DEDICATION

To my mother, Carla Barillas Wade, and father, Michael Wade, who came to this country with dreams of a brighter future. For the foundations you have built and sacrifices you have made so that I may be privileged with an education. For instilling the value of knowledge and stretching the paths before me. For teaching me the depth of our culture and pride in our people. To those that have come before me and paved the way for what was once impossible.

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VITA

EDUCATION

Expected 2020 *Doctor of Psychology, Clinical Psychology*
Pepperdine University

2015 *Master of Arts with Honors, Psychology*
Pepperdine University

2009 *Bachelor of Arts with Honors, Psychology/Law & Society*
University of California, Riverside

CLINICAL EXPERIENCE

2018-Present *Neuropsychology Extern*
Division of Hematology, Oncology, and Blood and Marrow Transplantation
Children's Center for Cancer and Blood Diseases
Children's Hospital Los Angeles
Supervisor: Ashley M. Whitaker, Ph.D., ABPP-Cn

- Conduct outpatient and inpatient neuropsychological evaluations with children and adolescents (ages 0-21) referred for various hematological and oncological conditions
- Diagnoses include brain tumors (e.g., craniopharyngioma), blood cancers (e.g., acute lymphoblastic leukemia), sickle cell and non-sickle cell anemias, genetic conditions (e.g., severe combined immunodeficiency), metabolic diseases (e.g., adrenoleukodystrophy), treatment-related complications (e.g., stroke), and additional comorbid medical conditions (e.g., epilepsy)
- Responsibilities include clinical intake interviews and feedback sessions with patients and their families; compilation and review of medical and educational records; administration, scoring, and interpretation of measures; integrated report writing; and development of appropriate recommendations
- Presentations during didactics on topics such as clinical cases as well as community supports and resources

2016-Present *Intake Coordinator*
Harbor Regional Center
Supervisor: Denise Godfrey-Pinn, Ph.D.

- Conduct clinical interviews for clients across the lifespan referred due to concern for developmental delay or disability
- Provide interdisciplinary consultation to speech & language pathologists, occupational therapists, physical therapists, geneticists, pharmacists, pediatricians, social workers, school personnel, etc.
- Diagnoses include autism spectrum disorder (ASD), epilepsy, intellectual disability, intrauterine substance exposure, failure to thrive, low incidence impairments, genetic disorders, and extreme prematurity
- Responsibilities include observation of developmental evaluations conducted by pediatric occupational, physical, and speech therapists using the Bayley and the DAYC; administration of the MCHAT; clinical screening for ASD and other developmental disabilities; and documentation via clinical notes and comprehensive psychosocial reports
- Attend seminars on child development, infant mental health, community resources, and developmental disabilities

2017-Present *Assessment Extern*
STAR of CA
Supervisor: Keegan Tangeman, Psy.D.

- Conduct psychodiagnostic evaluations for toddlers, children, adolescents, and adults referred for disruptive behaviors, emotional dysregulation, learning challenges, or suspected developmental disabilities
- Conduct psychoeducational evaluation to determine eligibility for Educationally Related Intensive Counseling Services (ERICS) as part of the Individualized Education Program (IEP) assessment for school-aged children referred for disruptive behaviors and emotional dysregulation impacting their ability to access an integrated school campus
- Provide interdisciplinary consultation to teachers, behaviorists, and school psychologists
- Diagnoses include ASD, intellectual disability, speech delay, epilepsy, cerebral palsy, attention-deficit/hyperactivity disorder (ADHD), specific learning disabilities, personality disorders, and depressive disorders
- Responsibilities include completion of clinical interview; development of assessment battery; administration and scoring of psychometric measures; review and compilation of available records; consultation with treating clinicians; and report writing

2018-Present *Peer Consultant*
Wiseburn School District Program
Pepperdine University
Supervisor: Keegan Tangeman, Psy.D.

- Provide weekly peer consultation services to first year Pepperdine Psy.D. students delivering school-based, culturally and developmentally informed cognitive behavioral and family systems therapy in the elementary, middle, and high school settings
- Diagnoses include anxiety disorders, mood disorders, ASD, ADHD, specific learning disabilities, and trauma
- Responsibilities include review of written materials such as clinical notes and intake reports; review of therapy session audio recordings; provision of didactic instruction on diagnostic criteria, conceptualization, treatment planning, and intervention; and auditing of client charts for required documentation

2017-2018 *Neuropsychology Extern*
Neuropsychology Program
The Saban Research Institute
Children's Hospital Los Angeles
Supervisor: Sharon H. O'Neil, Ph.D., M.H.A.

- Conducted outpatient clinical and research neuropsychological and neurodevelopmental evaluations with infants, children, adolescents, and adults (ages 0-65)
- Diagnoses included brain tumors, sickle cell disease, optic nerve hypoplasia, congenital heart disease (CHD), neurofibromatosis type 1 (NF1), epilepsy syndromes, ASD
- Responsibilities included compilation and review of medical and educational records; administration, scoring, and interpretation of measures; development of appropriate recommendations; and integrated report writing
- Attended weekly neuropsychology program didactics and monthly medical guest lectures on topics such as language and cultural issues in assessment, cognitive late effects of medical treatment (e.g., chemotherapy, cranial irradiation), bone marrow transplant, and neuroanatomy; weekly neurology case conferences and didactics on topics such as imaging techniques, brain tumors, demyelinating disorders, encephalopathy, and seizure disorders; and weekly brain cutting seminars with a neuropathologist

2017-2018 *Therapist*
West Los Angeles Clinic
Pepperdine University
Supervisor: Shelly Harrell, Ph.D.

- Provided individual therapy services to adults utilizing culturally informed cognitive behavioral therapy (CBT)
- Diagnoses included complex trauma as well as mood and anxiety disorders
- Responsibilities included completion of clinical interview; documentation via intake reports and progress notes; and monitoring of progress using empirically validated assessment measures

2016-2018 *Therapist*
Wiseburn School District Program
Pepperdine University
Supervisor: Keegan Tangeman, Psy.D.

- Provided school-based therapy services for children (ages 5-10) utilizing developmentally adapted and culturally informed cognitive behavioral and family systems therapy
- Provided interdisciplinary consultation to teachers, school counselors, school psychologists, and speech and language pathologists
- Responsibilities included completion of Trauma Focused-CBT training program; clinical interviews; participation in IEPs; and documentation
- Attended weekly case conference including case presentations

2012-2016 *Service Coordinator*
Early Childhood Department
Harbor Regional Center
Supervisor: Maria Rivas, MSW

- Provided case management for infants and children (ages 0-7) diagnosed with, or at increased risk for, developmental delays and disabilities
- Participate in interdisciplinary consultation with educational attorneys, pediatricians, geneticists, pharmacists, psychotherapists, special and general education teachers, school psychologists, and social workers
- Diagnoses included ASD, cerebral palsy, epilepsy, intellectual disability, intrauterine substance exposure, failure to thrive, low incidence impairments, genetic disorders, prematurity, and CHD
- Responsibilities included completion of psychosocial assessments; implementation of rehabilitative therapy services and supports; monitoring and evaluation of service delivery; agency representation at outreach events; advocacy for free and appropriate programming through the school district; and facilitation of access to generic and private resources such as social security, medi-cal, and private health insurance
- Attended seminars on topics such as epilepsy, ASD, behavior management, sensory integration, special education, and genetic disorders

2009-2012 *Child & Family Specialist*
Bayfront Youth & Family Services
Supervisor: Cynthia Sarmiento, LMFT

- Provided community-based intervention to children and adolescents (ages 5-18) as well as their families (in the home as well as out-of-home residential placements) referred to facilitate family reunification or decrease risk for out-of-home placement
- Provided interdisciplinary consultation to Department of Child and Family Services social workers, probation officers, general and special education teachers, psychotherapists, and psychiatrists
- Diagnoses included complex trauma, intellectual disability, ASD, ADHD, specific learning disabilities, bipolar disorder, and schizophrenia
- Responsibilities included clinical intake interviews; attendance at criminal and family court proceedings; collaboration with immediate family as well as informal supports; and documentation via clinical progress note and report writing

2009 *Therapeutic Behavioral Services Coach*
C.H.A.R.L.E.E. Family Care
Supervisor: Danielle Benton, LMFT

- Provided intensive behavioral intervention to children and adolescents (ages 5-17) referred for disruptive behaviors and emotional dysregulation in the family home as well as out-of-home residential placements
- Provided interdisciplinary consultation and collaboration with probation officers, social workers, and group home staff
- Diagnoses included complex trauma, ADHD, bipolar disorder, and oppositional defiant disorder
- Responsibilities included provision of parent training on principles of behavior management; data collection; and documentation via progress notes

2008-2009 Volunteer
Riverside County Department of Substance Abuse
Supervisor: Keith Boone

- Co-facilitated court-mandated group therapy sessions with adults referred due to history of substance abuse and legal involvement
- Responsibilities included conducting clinical intake interview; preparation of group curriculum; administration of random drug screening; reporting to parole and probation officers; and documentation via progress notes

COMMUNITY OUTREACH

Wade, C. (2015, November). *Autism: More than a spectrum.* Resource fair at a conference organized by UCLA Center for Autism Research and Treatment and Healthy African American Families hosted at Holman United Methodist Church, Los Angeles, CA.

Wade, C. (2015, October). *Introduction to the Harbor Regional Center*. Community presentation at Dolores Elementary School, Carson, CA.

Wade, C. (2015, June). *Understanding Early Start services at the Harbor Regional Center*. Community presentation at Pepperdine University, Los Angeles, CA.

Wade, C. (2015, January). *Obtaining an Early Start Individual Family Service Plan.* Presentation at Volunteers of America Family Resource Center community partnership meeting, Harbor City, CA.

PROFESSIONAL PRESENTATIONS

Wade, C. (2015, June). *Improving prognosis in children with autism through intensive early intervention*. Poster presentation at Pepperdine University, Los Angeles, CA.

Wade, C. (2018, November). *Cerebral lateralization and cultural considerations in the treatment of acute lymphoblastic leukemia*. American Psychological Association approved for continuing education didactic presentation at Children's Hospital Los Angeles, Los Angeles, CA.

Wade, C. (2019, February). *Impact of sickle cell disease on executive functioning in adults*. Poster presentation at the International Neuropsychological Society 2019 Annual Meeting, New York, NY.

Wade, C. (2019, May). *Accessing regional center services.* American Psychological Association approved for continuing education didactic presentation at Children's Hospital Los Angeles, Los Angeles, CA.

Wade, C. (2019, May). *Executive functioning in adults with sickle cell disease.* Research presentation at the Excellence in Hemoglobinopathies Research Award Retreat at the University of Southern California, Los Angeles, CA.

ABSTRACT

Children diagnosed with sickle cell disease (SCD) struggle with executive functions (EF); however, there is a paucity of research on neuropsychological outcomes in adults with SCD. This study aimed to examine differences in EF between adults with SCD and healthy controls. Thirty-one patients with SCD and 34 healthy controls (ages 18-45) participating in an IRB-approved Children's Hospital Los Angeles (CHLA) study of cerebral blood flow underwent neuropsychological evaluation using the Delis–Kaplan Executive Function System (D-KEFS) Trail Making and Color Word Interference Tests and the Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV) Digit Span subtest to assess various aspects of EF. The Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II) was administered to estimate general intellectual ability. There were no significant differences between groups related to age, gender, race, parental education, or general intellectual ability; however, the control group was estimated to have significantly higher current combined annual family income as compared to patients with SCD, x_2 (6, N = 65) = 10.87, p = .02. Therefore, income was statistically controlled for during analyses. Both groups performed in the solidly average range across EF measures and no significant differences were noted between groups in working memory, $F(1) = .009$, $p = .93$, $\eta_{p2} = .000$; inhibition, $F(1) = .156$, $p = .03$, $\eta_{p2} = .03$; or cognitive flexibility, $F(1) = 3.11$, $p = .08$, $\eta_{p2} = .06$. Adults with SCD in this study performed comparably to healthy controls. Early treatment with hydroxyurea to the maximum tolerated dose may improve prognosis and serve as a protective factor against EF deficits in adults with SCD. However, additional research is needed to better understand how treatment protocols influence neuropsychological outcomes in this population.

Chapter 1: Statement of the Problem

Sickle cell disease (SCD) refers to a group of inherited disorders characterized by two sickle cell genes (one gene is required from each parent) in which misshapen blood cells lead to anemia among other complications (National Heart, Lung, and Blood Institute [NHLBI], n.d.). These disorders result in a range of complications including episodes of intense pain, stroke, susceptibility to infection, academic challenges, and changes in cognitive functioning (Centers for Disease Control and Prevention [CDC], 2016; Manci et al., 2003).

SCD most commonly affects individuals of African ancestry (e.g., African American, Afro-Caribbean); however, there is also occurrence in individuals of Mediterranean, Middle Eastern, Asian Indian, and South or Central American descent (Brousseau, Panepinto, Nimmer, & Hoffmann, 2010; Hassell, 2010; Nelson & Hackman, 2013; Quinn, Rogers, McCavit, & Buchanan, 2010; Rees, Williams, & Gladwin, 2010; Yanni, Grosse, Yang, & Olney, 2009). In the United States (U.S.), approximately 1 in 365 African American children (approximately 8%) are diagnosed with SCD as compared to the next most common community, which is 1 in 16,305 Latinos (approximately 0.00006%; Hassell, 2010; Huttle, Maestre, Lantigua, & Green, 2015; NHLBI, n.d.). The descendants of those most commonly affected hail from regions with a relatively recent history of pervasive malaria infection (Aidoo et al., 2002; Allison, 1954; Gilles et al., 1967). The single sickle cell gene has served an adaptive function in these populations, as it protects those with sickle cell trait (SCT; i.e., one sickle gene as opposed to two) against death from malaria. The malaria parasite lives in the red blood cells of its host; however, due to premature hemolysis (i.e., breakdown) of sickled red blood cells, the parasite is unable to reproduce (Wiesenfeld, 1967). This clearly provides a distinct advantage for those individuals who face potential death due to malaria exposure, although in areas where the disease is rare,

sickled red blood cells provide no benefits to survival for the population as a whole. Unlike their SCT counterparts, those with SCD are generally more susceptible to infection (Platt et al., 1994).

Due to the slave trade's strong tie to our nation's history, there exists a significant population of African Americans in the United States (U.S.). Unfortunately, their health and prosperity have not been an area of great focus since the abolition of slavery (Phillips, 1999) and African Americans have faced alarming health disparities in this nation (CDC, 2005; Landrine & Corral, 2009; Orsi, Margellos-Anast, & Whitman, 2010). During the 1960s and '70s, the sickle cell cause became a focus within the civil rights movement with activists citing the reality that most patients with SCD did not live beyond their teenage years (Scott & Castro, 1979; Wailoo, 2014). In response to calls for action, the Sickle Cell Anemia Control Act was passed into law in 1972 which allocated federal funding for the research, education, screening, and treatment of SCD.

At the time of the Sickle Cell Anemia Control Act, the majority of SCD-related deaths occurred in early childhood, leading the disease to be considered a pediatric condition (Gill et al., 1995; Lee, Thomas, Cupidore, Serjeant, & Serjeant, 1995). However, in the 1990s, the average life expectancy for individuals with SCD jumped to the 40s (Platt et al., 1994). This is attributable to newborn infant screening programs (i.e., state-mandated targeted genetic testing for all newborns) which began to include SCD in the 1960s and '70s, the use of prophylactic antibiotics and vaccinations, as well as the rise of treatments such as blood transfusion and hydroxyurea (Chaturvedi & DeBaun, 2016; El-Haj & Hoppe, 2018; Gaston et al., 1986; Lopes de Castro Lobo et al., 2013; Yanni et al., 2009). As patients with SCD are beginning to live much longer than they have in the past, it is increasingly important to understand the disease in adult populations. Lanzkron, Carroll, and Haywood (2013) found that the adult mortality rate

increased by 1% annually between 1979 to 2005, while the pediatric mortality rate decreased by 3% annually during the same time period (both $p < 0.001$). While these patterns in mortality may be reflective of an increase in life expectancy in SCD patients, the investigators note that it is likely that this at least partially reflects a lack of access to comprehensive adult care. Further, young adults transitioning from pediatric to adult care are at the highest risk for death (Quinn et al., 2010), many of which are related to acute medical events which suggests that these individuals may have not been able to sufficiently establish connections with adult specialists. This has occurred alongside a relative increase in research and comprehensive care in pediatric SCD when compared to adults (Grosse et al., 2011). This disparity in adult SCD care may be ameliorated following an increase in research focused on the needs of patients as they transition from pediatric to adult care.

In addition to medical research, increased life expectancy necessitates a better understanding of the neuropsychological impact of SCD in adults. A growing body of literature has contributed to our understanding of the neuropsychological effects of SCD in the pediatric population, particularly related to executive functions (EF) which are higher order cognitive skills necessary for mental planning, organization, and execution/completion of purposeful, goal-oriented tasks. However, a relative paucity exists when considering the effects in adults. This study aims to inform a greater understanding of the effect of SCD on EFs in the adult population. More specifically, the study will determine whether previous research demonstrating decreased performance among children with SCD will be replicated within an adult SCD sample.

Chapter 2: Review of the Literature

Sickle Cell Disease (SCD) refers to a group of inherited red blood cell disorders whose primary physical feature is abnormally shaped hemoglobin - a protein that carries oxygen through the body via red blood cells (Howard & Telfer, 2015; Ilesanmi, 2010; Kral, Brown, & Hynd, 2001; NHLBI, n.d.). Typical hemoglobin in adults is known as hemoglobin A (HbA). The disc shape of HbA allows the cells to easily move through blood vessels without sticking to vessel walls or becoming obstructed. Sickle hemoglobin, known as hemoglobin S (HbS), is shaped like a crescent, or sickle, as the name implies. This results in cells that stick to vessel walls, particularly fine capillaries and arterioles, causing partial or complete obstruction, and impaired delivery of oxygen throughout the body. Over time, sickled blood cells cause irreversible damage to blood vessel membranes as they attempt to squeeze through the small passageways, which leads to dehydration of the cells.

Genotypes

As SCD refers to a group of disorders, there are various genotypes through which the disease can be manifested (Kral et al., 2001). The most common and severe genotype of SCD is hemoglobin SS (HbSS) which is also known as sickle cell anemia[1] (SCA). Other forms of SCD also have their names derived from the type of hemoglobin inherited (e.g., HbSC, HbSD, HbSE; CDC, 2016). The complications typical of each genotype vary in quality and severity. As of 2006, all states within the U.S., including Puerto Rico and the U.S. Virgin Islands, mandate HbSS testing as part of the standard newborn screening tests (Benson & Therrell, 2010). This early screening allows prompt diagnosis and subsequent medical care at

[1] Some practitioners also include the genotype $S\beta^0$-thalassemia ($HbS\beta^0$-thalassemia) in SCA as the subtypes present similarly (NHLBI, 2014).

specialized treatment centers where available (Raphael, Kavanagh, Wang, Mueller, & Zuckerman, 2011). Screening is particularly important as infants with SCD typically do not initially show signs of the disease due to the protective nature of fetal hemoglobin (HbF), which is in dominant production until approximately 6 months of age (Edoh, Antwi-Bosaiko, & Amuzu, 2006; Watson, Stahman, & Bilello, 1948). While adults retain the capacity to produce HbF, levels of production drop to less than 1% by age 2, which is below clinical significance (Mosca, Paleari, Ivaldi, Galanello, & Giordano, 2009, Thein & Menzel, 2009). There is evidence to suggest that in some cases, elevated levels of HbF continue to be produced into adulthood, which assists in managing pain crises (Edoh et al., 2006; Gardner & Thein, 2016); however, this only occurs in approximately 10% of the general population (Thein & Craig, 1998; Thein & Menzel, 2009).

In addition to the aforementioned SCD genotypes, there are also individuals with Sickle Cell Trait (SCT). In order to acquire SCD, a child must receive two genes for SCD – one from each parent (CDC, 2016). However, individuals with SCT received only one of these genes, and as a result, they are carriers for the disorder although they do not experience the full range of symptoms. Despite this, there are rare, yet serious complications that may occur even with SCT. These include blockages in small blood vessels in very low oxygen conditions (e.g., high altitude, physical exertion), increased susceptibility to infection, kidney cancer, and reduced blood flow to the spleen (American Society of Hematology, n.d.; Eichner, 2007; Thogmartin et al., 2011; Yanamandra, Das, Malhotra, & Varma, 2018). As SCD is an autosomal recessive condition, individuals with SCT may also pass SCD along to their children if that child receives one sickle cell gene from each parent.

Medical Complications

The primary function of hemoglobin is to transport oxygen to organs throughout the body (Kral et al., 2001). One of the most common complications of SCD is poorly oxygenated tissue (i.e., hypoxia) due to the misshapen, inefficient hemoglobin S, which results in vaso-occlusive crises (also known as VOCs, pain crises, and acute painful episodes; NHLBI, n.d.; Serjeant & Serjeant, 1992). This mild to extremely severe pain is caused when blood flow is disrupted in small blood vessels (CDC, 2016). The pain may be described as throbbing, sharp, or gnawing (Rees et al., 2003). These episodes are the most frequent reason for emergency room visits for patients with SCD (CDC, 2016). Additionally, sickled blood cells last only 10 to 20 days as compared to 90 to 120 days for normal cells, requiring increased speed in replenishment. The body has difficulty keeping up with the production of new red blood cells, leading to anemia, which may be manifested as lethargy, slowed growth, or delayed puberty. Other common complications of SCD include hand-foot syndrome (i.e., swelling in the hands and feet as a result of sickled blood cells obstructing blood flow in the extremities), increased risk for infection, acute chest syndrome (i.e., life-threatening chest pain, coughing, difficulty breathing, and fever), splenic sequestration (i.e., life-threatening enlargement of the spleen), ischemic priapism (i.e., painful, prolonged erections), vision loss, and increased risk for blood clots. Over time, significant damage can occur to body organs, tissues, and/or bones due to insufficient blood flow. Infection, heart disease, stroke, and liver disease are leading causes of death in the SCD population (Lanzkron et al., 2013). Despite increased understanding of the disease processes involved with SCD as well as revised treatment recommendations, recent research suggests the rate of SCD related complications has risen which may be attributable to improved survivorship (Perumbeti et al., 2018).

Neurological complications of SCD include symptomatic infarction (i.e., arterial obstruction in the brain which impairs blood/oxygen flow and is accompanied by traditional neurologic symptoms; also known as overt stroke or cerebrovascular accident [CVA]) and intracranial hemorrhage (i.e., rupture of a blood vessel in the brain; Thust, Burke, & Siddiqui, 2014). These are serious complications, which affect approximately 24% of SCA patients by age 45 (Ohene-Frempong et al., 1998). The risk remains significant in the broader SCD population (as compared to SCA specifically), with approximately 10% of individuals experiencing overt stroke in their lifetime (Farooq & Testai, 2019). Unlike their SCD counterparts, a recent meta-analysis found that African Americans with SCT are not at increased risk for ischemic stroke (Hyacinth et al., 2018).

Transcranial doppler (TCD) can be utilized to measure blood flow velocity. Overall, those with an elevated TCD in the absence of blood transfusion are at the highest risk for initial overt stroke although this risk can be reduced with the timely initiation of chronic blood transfusions (Adams & Brambilla, 2005). It is recommended that TCD be utilized routinely in SCD care (every 6 to 12 months) beginning at 24 months of age (Adams, 2005). Despite these recommendations, one single-site study indicated that only 43% of board-certified pediatric hematologists complied with this guideline (Raphael, Shetty, Liu, Mahoney, & Mueller, 2008). The same researchers also found that patients with private insurance were three times more likely to keep scheduled TCD appointments when compared to those with public insurance.

While strokes are often manifested by overt neurological symptoms such as numbness, weakness, confusion, visual changes, or severe headache (National Center for Chronic Disease Prevention and Health Promotion, Division for Heart Disease and Stroke Prevention, 2017), individuals with SCD are also at an increased risk for silent stroke (also known as silent cerebral

infarct; SCI). In such instances, patients do not experience overt neurological symptoms; however, abnormalities are noted on magnetic resonance imaging (MRI; Kinney et al., 1999). On MRI, SCI are typically visible as white matter hyperintensities (WMHs; van der Land, et al., 2016). Although small WMHs are sometimes seen in healthy populations (Debette & Markus, 2010; Hopkins et al., 2006; Sachdev, Chen & Wen, 2008), the quantity and volume are often exceptional in those with SCD, with the prevalence as high as 39.1% by age 18 (DeBaun et al., 2012; Farooq & Testai, 2019; Wang et al., 2001). In both children and adults, SCI increases the patient's risk for subsequent SCI and/or overt stroke (Jordan et al., 2018; Pegelow et al., 2002).

Overt strokes tend to occur in the internal carotid and middle cerebral arteries in patients with SCD (Adams et al., 1988; Pavlakis et al., 1988; Pegelow et al., 2002; Rothman, Fulling, & Nelson, 1986; Schatz, Brown, Pascual, Hsu, & DeBaun, 2001; Switzer et al., 2006; Telfer et al., 2011; Wang et al., 1998; Waterston, Brown, Butler, & Swash, 1990). Overall, the regions of the brain distally served by the anterior and middle cerebral arteries (known as the border zones due to decreased perfusion in these relatively distant areas; Mangla, Kolar, Almast, & Ekholm, 2011) are the most commonly affected, including the deep white matter, basal ganglia, middle and superior frontal gyrus, and dorsal parietal regions (Pavlakis et al., 1988; Powars et al., 1999). SCI in the border zones are associated with low velocity blood flow, suggesting insufficient oxygenation to the affected tissue (Ford et al., 2018). In the SCD population, infarct in the frontal lobe is the most frequently affected location, found in up to 93% of patients with either silent or overt stroke (Brown et al., 2000; Schatz et al., 2001). To date, literature has not examined differences in stroke location in adults as compared to children; however, adults are more likely to have a broader etiology which may include fat embolism or illicit substance use (Calvet et al, 2015). Collectively, overt strokes account for approximately 10% of all SCD deaths (Manci et

al., 2003). Even without evidence of tissue damage, chronic cerebral blood flow dysfunction has also been noted in adult SCD patients (Doepp, Kebelmann-Betzing, Kivi, & Schreiber, 2012).

Medical Treatments

Treatments for SCD include pain management, red blood cell transfusion, hydroxyurea, Endari, and stem cell transplantation (also known as bone marrow transplant; Mayo Clinic Staff, 2019). Each of these treatments are discussed in greater detail below.

Pain management. As mentioned, one of the most common complications of SCD are acute painful episodes which tend to become more frequent with age (Panepinto, Brousseau, Hillery, & Scott, 2005). Similarly, adults with SCD tend to have higher rates of emergency room visits when compared to pediatric samples (Wolfson, Schrager, Khanna, Coates, & Kipke, 2012). The episodes are so common that the American Pain Society, American College of Physicians, NHLBI, and the CDC's National Center on Birth Defects and Developmental Disabilities have each published guidelines for the use of analgesics with the SCD population. They all indicate that SCD requires prompt treatment and recommend the use of opioids for severe pain. The use of oral morphine has even been found to decrease the rate of hospitalization as well as the need for intravenous medication (Paquin et al., 2019). In addition to these acute VOCs, many adults with SCD also experience daily chronic pain (Smith et al., 2008). Alternatives to pharmacology are available and effective to lessen SCD-related chronic pain. Interventions include prayer or spiritual healing, acupuncture, massage therapy, meditation, self-hypnosis, relaxation training, and cognitive behavioral therapy (Anie & Green, 2015; Chen, Cole, & Kato, 2004; Dinges et al., 1997; Sibinga, Shindell, Casella, Duggan, & Wilson, 2006; Thomas, Dixon, Milligan, & Thomas, 1999; Thomas, Wilson-Barnett, & Goodhart, 1998; Williams & Tanabe, 2016).

Transfusions. Red blood cell transfusion increases the number of circulating red bloods cells by removing them from donor blood and transferring them to the recipient intravenously. The benefits of red blood cell transfusion include temporary correction of anemia, improvement of the blood's ability to transport oxygen, reduction or prevention of sickling, and control or prevention of vascular and tissue damage (Howard & Telfer, 2015). Blood transfusion also reduces the risk of overt stroke; however, possible complications include infection and iron overload, among others (Ballas, 2001; Ballas, Zeidan, Duong, DeVeaux, & Heeney, 2018; DeBaun et al., 2014; Garraud et al., 2018; Harmatz et al., 2000; Talahma, Strbian, Sundararajan, 2014; Verduzco & Nathan, 2009). Chronic blood transfusions, every three to four weeks, are common for those with elevated TCD which indicates a high risk for overt stroke. Excessive iron in the blood may be controlled through chelation therapy (i.e., the removal of iron from the body with the use of medication such as Jadenu; Allali, de Montalembert, Brousse, Chalumeau, & Karim, 2017; Cohen & Martin, 2001; Kwiatkowski & Cohen, 2004).

Hydroxyurea. Hydroxyurea is an enteral chemotherapy medication which reduces the occurrence of pain crises, acute chest syndrome, and the need for blood transfusions in patients with SCD primarily by stimulating the production of HbF (Lanzkron, Rand, Haywood & Hassell, 2008; Voskaridou et al., 2010; Wong, Brandow, Lim, & Lottenberg, 2014). Higher rates of HbF predict increased life expectancy in patients with SCA (Platt et al., 1994; Powars, Weiss, Chan, & Schroeder, 1984; Voskaridou et al., 2010; Wong et al., 2014) and at least one study has demonstrated improvement in survival associated with duration of hydroxyurea exposure (Voskaridou et al., 2010). In 2002, the NHLBI issued seminal guidelines encouraging the use of hydroxyurea for those with SCD. Despite these benefits and guidelines, a survey of adult SCD providers indicated that the drug was prescribed for less than half of eligible patients (Lanzkron

et al., 2008). This survey also indicated significant group differences with regard to provider race, as providers who identified as Black had higher rates of eligible patients on hydroxyurea than those identifying as White (94% vs 73%). The most frequent reasons endorsed by providers for not prescribing the medication was related to lack of awareness of the drug and disagreement regarding the benefits. Even when prescribed, adherence is often poor, which may be related to delayed onset of symptoms following a missed dose as well as fear of long-term toxicity (Brandow & Panepinto, 2010; Heeney & Ware, 2010). Current NHLBI (2014) guidelines include the introduction of hydroxyurea as early as 9 months of age and continued use throughout the lifespan regardless of clinical severity.

Endari. In 2017, the U.S. Food & Drug Administration (FDA) announced that a new drug, Endari, was approved to treat the complications of SCD in patients age five years and older. The generic agent is L-glutamine and while the drug's mechanism of action is not completely understood, it is believed to reduce oxidative damage to red blood cells (Niihara et al., 2018). The treatment lowered the incidence of both pain crises and acute chest syndrome in a clinical sample and decreased the number of hospitalization days ($p = 0.005$). Although there is some additive benefit when used in conjunction with hydroxyurea, Endari comes at a much higher cost than its predecessor (approximately $40,515 annually as compared to $1,700; The Medical Letter, Inc., 2018). This is only the second drug approved for the treatment of SCD and the first new treatment in almost 20 years.

Stem cell transplant. Stem cell transplants are the only potential cure for SCD and involve intravenously replacing bone marrow in the recipient with healthy donor bone marrow (NHLBI, n.d.). As part of the treatment, the recipient also receives chemotherapy and/or radiation to destroy their own stem cells so that the donor cells may proliferate. It is difficult to

find an appropriate donor and the potential complications are serious, including graft-versus-host -disease (a complication in which the donor tissue begins to attack the host tissue) and even death. As these risks are increased with older age, transplants are reserved for individuals younger than 16 years old with particularly problematic symptoms. For these reasons, treatment for SCD typically focuses on avoiding pain crises, symptom management, and prevention of complications.

Neuropsychological Effects

In addition to the aforementioned physical symptoms, a range of neuropsychological impairments have also been identified, even in individuals without a history of stroke (Wang et al., 2001). Given the historically shortened lifespan in SCD, the literature has primarily focused on pediatrics and limited research is available with adult participants. Therefore, the following review will focus on the pediatric literature with a briefer discussion on the available adult literature. Prior research has generally identified deficits in the following domains: cognition, processing speed, learning and memory, academic achievement, visual motor integration, attention, and EFs. The current literature review places a particular emphasis on EFs, which are the primary area of consideration in this study.

Cognition. In the most commonly used measures of intellectual functioning, the Full Scale Intelligence Quotient (FSIQ) is a composite score based on performance on multiple tasks which measure various subskills (typically inclusive of verbal and nonverbal reasoning, processing speed, and working memory)[2]. Due to the integration of these subskills into a single

[2] Relevant findings related to processing speed and working memory, along with other aspects of neuropsychological functioning, are discussed further in the subsequent sections.

estimate of intellectual functioning (i.e., FSIQ), impaired performance in any of these areas will reduce the broader FSIQ.

IQ testing has commonly been used as an overall measure of cognition in SCD research and children with SCA have historically demonstrated significantly lower IQ scores when compared to healthy controls (Armstrong et al., 1996; Brown, Armstrong, & Eckman, 1993; Schatz et al., 2001; Schatz, Finke, Kellett, & Kramer, 2002). Children with SCA and history of overt stroke demonstrated the greatest level of impairment, followed by children with history of SCI, and then by children with no history of stroke (Cohen, Branch, McKie, & Adams, 1994; DeBaun et al., 2012; Hogan, Pit-ten, Vargha-Khadem, Prengler, & Kirkham, 2006). Performance on measures of IQ is negatively correlated with volume of WMHs (Schatz et al., 2002); however, even in the absence of stroke, children with SCA continue to perform significantly below healthy race, age, sex, and education matched controls (Berkelhammer et al., 2007; Kawadler, Clayden, Clark, & Kirkham, 2016; Schatz et al., 2002), which is likely attributable to their chronic hypoxic state as discussed above (Armstrong, Pavlakis, Goldman, Thompson, & Cuadra, 2010; Kawadler et al., 2015). Further, the progression of WMHs was related to general cognitive decline. Taken together, these results suggest that neuroanatomical changes in individuals with SCD contribute to neuropsychological functioning.

Although the number of studies with adult patients is far smaller than those in pediatrics, there is also evidence to suggest poorer general intellectual functioning in adults with SCA regardless of history of stroke (Kugler et al., 1993). Vichinsky and colleagues (2010) conducted the only large-scale study examining general cognitive functioning in adults with SCA. They found that the mean FSIQ for patients with SCA was 90.47, as compared to 95.66 for age, sex, and education matched healthy controls (p = .008). This reflects a difference of approximately 5

IQ points, or 1/3 standard deviation, although some of these differences may be due to slower processing speed (Crawford & Jonassaint, 2016). Mackin and colleagues (2014) utilized data from Vichinsky's research to examine the relationship between neuropsychological functioning and frontal lobe cortical thickness and basal ganglia volumes. They found that participants with SCA had thinner frontal lobe cortex as well as reduced basal ganglia and thalamus volumes when compared to healthy controls. As a result, they adjusted data from Vichinsky et al., (2010) for intracranial volume and found significant differences between those with SCA and healthy controls based on Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) FSIQ after controlling for age, sex, and education level (adjusted mean, standard score of 91.2 for patients vs 96.0 for controls [mean difference, −4.8]; $p = .04$)**.** Lower IQ in the SCD population is also consistent with findings of a meta-analysis which found that insults to white matter (which are comprised of myelinated axons that facilitate quick communication between neurons) are inversely associated with general cognitive functioning in non-SCD adult populations (Debette & Markus, 2010; Vasquez & Zakzanis, 2015).

Processing speed. Processing speed refers to the time it takes to perceive and respond to a stimulus or demand. Most processing speed tasks used in the SCD literature have utilized psychomotor processing speed in particular (e.g., quickly matching numbers with symbols or quickly scanning/marking complex arrays for specified targets). Some tests of processing speed also measure accuracy by deducting points for errors. Overall, children with SCD tend to demonstrate slower processing speed when compared to a normative population, with those with SCA demonstrating the greatest impairment as compared to both SCD and healthy samples (Smith & Schatz, 2016). Armstrong et al. (1996) also found significant differences on the Wechsler Intelligence Scale for Children – Revised (WISC-R) Coding subtest (Wechsler, 1974;

i.e., a measure that requires children to quickly pair numbers with geometric figures) when comparing pediatric SCD patients with history of overt (p = .003) and silent stroke (p = .01), to those with normal MRI. Van der land et al. (2016) found that higher volume of WMHs in pediatric SCD patients was associated with reduced processing speed (as well as lower FSIQ; however, as discussed, processing speed is a component of FSIQ).

With regard to research on processing speed in adults, Vichinsky et al. (2010) and Crawford and Jonassaint (2016) both reported significantly lower (approximately 2/3 standard deviation) processing speed in adults with SCA without history of CVA when compared to age, sex, and education matched healthy controls - 11.46 (p < .001) and 10.77 (p = 0.02) points respectively.[3] This reflects the largest area of significant group difference (adjusted mean standard score of 86.5 for patients vs 97.9 for controls [mean difference, -11.4]; p < .001; Vichinsky et al., 2010). Again, when Mackin et al. (2014) adjusted data from Vichinsky et al. (2010) for intracranial volume, results also documented significantly lower processing speed in a patient sample when compared to healthy controls (adjusted mean, standard score of 87.2 for patients vs 95.4 for controls [mean difference, −8.2]; p < .001). When these clinically and statistically significant differences are accounted for, individuals with SCD see improved performance in FSIQ scores, 3 points higher than those same controls (Crawford & Jonassaint, 2016; Stotesbury et al., 2018). Further, Vichinsky et al. (2010) did not find significant group differences with regard to verbal (adjusted mean standard score of 92.14 for patients vs 96.04 for controls [mean difference, -3.90]; p = .06) or nonverbal reasoning (adjusted mean standard score

[3] Vichinsky et al. (2010) utilized a sample of SCA patients whereas Crawford and Jonassaint (2016) utilized a more general sample of SCD patients. It should also be noted that different measures were utilized to obtain these scores, Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) and CNS Vital Signs scores, respectively.

of 90.75 for patients vs 95.10 for controls [mean difference, -3.96]; $p = .06$). These results corroborate deficits in processing speed performance in adults with SCD, while suggesting that lower FSIQ scores are best accounted for by slower processing speed. Jorgensen and colleagues (2017) also published a study evaluating processing speed in an adult population. Participants with genotypes typically associated with the most severe complications (e.g., HbSS) obtained a mean T-score of 47.6 (*SD* = 14.5) on a measure of processing speed as compared to those with moderate complications (e.g., HbSC), who obtained a mean T-score of 51.0 *(SD* = 13.4; both $p = .004$). Again, this is consistent with findings of a meta-analysis of a general adult population which found that WMHs are inversely associated with performance on measures of processing speed (Debette & Markus, 2010); and that insult to subcortical white matter tracts is associated with slower processing speed (Vasquez & Zakzanis, 2015). These differences in processing speed have important implications for other aspects of neuropsychological functioning such as academic achievement, EF, adaptive behaviors, as well as learning and memory.

Learning and memory. In simplest terms, learning and memory refers to the ability to acquire and recall new information. The neuroanatomy of memory is complex and involves various structures; however, memory involves two primary circuits. The first is the Papez circuit (also known as the medial limbic circuit) which has been implicated in autobiographical and explicit memory (Bauer, 2008; Preston & Eichenbaum, 2013; Schoenberg & Scott, 2011; Stucky, Kirkwood, & Donders, 2014). The hippocampus is a central structure (where the circuit begins and ends) that acts in coordination with the mammillary bodies, anterior thalamic nuclei, and cingulate gyrus (Catani, Dell'Acqua & de Schotten, 2013). A second circuit, the lateral limbic circuit, utilizes the amygdala as the central structure and has been implicated in emotional memory and assigning emotional significance to stimuli. The lateral limbic circuit acts in

coordination with the dorsomedial nucleus of the thalamus, orbitofrontal cortex, and uncinate fasciculus (Stucky et al., 2014). Damage to either structure can result in memory impairment; however, if damaged, each of these systems can accommodate one another to a large extent. In addition, the dorsolateral prefrontal cortex (PFC) plays a role in memory consolidation and organization while the cerebellum contributes to nondeclarative (also known as implicit) memory (Preston & Eichenbaum, 2013; Schoenberg & Scott, 2011).

Deficits in learning and memory have been noted in the pediatric SCD population. On a measure of rote verbal list learning, children with diffuse cerebral infarcts retained approximately 20% less information than their healthy sibling controls despite several repetitions (Schatz et al., 1999). Brandling-Bennett, White, Armstrong, Christ, and DeBaun (2003) found similar challenges in list learning, while Watkins et al. (1998) noted significant group differences on measures of visual memory and paired associate learning when children with SCD and a history of frontal lobe infarct (either SCI or CVA) where compared to children with SCD without stroke history and healthy controls.

Conversely, impairments in learning and memory have not been documented in neurologically asymptomatic adults with SCA as compared to healthy demographically matched controls (Vichinsky et al., 2010); however, this domain is understudied and only relatively recently evaluated. Further, studies examining functioning in a more general SCD population were not available. As such, continued research is necessary.

Academic achievement. Children with SCD face academic challenges and are more likely to be retained (i.e., held back to repeat a grade), receive special education services, and have a higher rate of absences when compared to peers (Dyson, Atkin, Culley, & Dyson, 2007; Epping et al., 2013; Schatz, 2004). Fatigue and medical complications (e.g., infection, pain

episodes) may account for at least a portion of these absences and subsequent loss of instruction time. Learning difficulties in children with SCD include deficits in reading and mathematics (Brown et al., 1993; Schatz et al., 2001). More specifically, left hemispheric overt stroke has been associated with more global academic delays while those in the right hemisphere have a stronger association with deficits in mathematics (Cohen et al., 1994). One longitudinal study found a progressive annual decline in math achievement, with reading achievement deficits remaining constant, even in pediatric patients with no neuroimaging abnormalities (Wang et al., 2001). It has been hypothesized that these learning difficulties may be attributed to poor sustained attention, organization, and problem-solving skills in both pediatric and adult patients (Grattan & Eslinger, 1991). Some of these academic impairments may be buffered in individuals from higher socioeconomic status (SES; i.e., social standing of an individual based on access to resources) or with parents of higher educational attainment (Brown et al., 1993; Smith, Patterson, Szabo, Tarazi, & Barakat, 2013). This may be attributed to factors such adequacy of school district funding, familial access to private tutoring, learning materials or environments, educator experience level, among other contributors (Aikens & Barbarin, 2008; Bradley, Corwyn, McAdoo, & García Coll, 2001; Clotfelter, Ladd, & Vigdor, 2006; Orr, 2003).

Additional research on academic achievement such as rates of high school graduation and completion of higher education in adults with SCD has not been published. Herron, Bacak, King, and DeBaun. (2003) completed a brief analysis of high risk (due to frequent pain episodes and history of overt stroke) 17-, 18-, and 19-year-olds receiving treatment at St. Louis Children's Hospital and found that only 15% were on target to complete high school. Further research is needed to better understand the factors influencing academic achievement in adults with SCD.

Attention. Attention refers to a collection of skills, which constitute the ability to selectively maintain concentration on salient aspects of an experience while filtering out distracters. Difficulties with attention have been noted in children with SCD and history of either silent or overt stroke (Brown et al., 1993; Craft, Schatz, Glauser, Lee, & DeBaun, 1993; DeBaun et al., 1998; Hijmans et al., 2011); similar to EFs, these difficulties are strongly associated with overt stroke in the frontal lobe (Brown et al., 2000; Cohen et al., 1994; Schatz et al., 2001). As silent strokes in those with SCD frequently occur in the frontal and parietal lobes, measures of attention (and EFs) are commonly included in neuropsychological research for this population. DeBaun et al. (1998) found that impaired performance on a measure of sustained attention, the Test of Variables of Attention (TOVA), most strongly correlated with the presence of SCI. Performance on the TOVA appropriately identified the presence of SCI in 86% of children with SCA. In the educational setting, children with SCD often experience deficits with basic sustained attention and concentration (Brown et al., 1993). Craft and her colleagues (1993) found attentional deficits to be significantly more prominent in SCA pediatric patients when compared to both those with diffuse lesions and their healthy sibling controls.

Research on attention in an adult SCD population is relatively limited; however, Vichinsky et al. (2010) also found significant differences between healthy controls and adults with SCA without history of neurological insult, on performance on a measure of visual attention and scanning, (Test of Everyday Attention [TEA] 2-minute Map Search subtest) as well as the TOVA.

Executive functions. EFs are a complex set of skills that allow individuals to deliberately plan, direct, and monitor their own behavior (Stuss, 1992). The earliest research on EFs arose from the study of patients with brain damage, particularly in the frontal lobe (Harlow,

1868; Luria, 1972). Phineas Gage is a notable example, as he evidenced difficulty with behavioral regulation following a severe workplace accident damaging his orbitofrontal brain structures (Harlow, 1868). Through continued research, we have come to understand that EFs are primarily orchestrated in the PFC, in coordination with many other brain regions (Alvarez & Emory, 2006; Buchsbaum, Greer, Chang, & Berman, 2005; Damasio, Graff-Radford, Eslinger, Damasio & Kassell, 1985; Stuss, 1992; Stuss et al., 1986). One meta-analysis found a moderate positive correlation between EFs and both the volume and thickness of the PFC in a healthy adult sample (Yuan & Raz, 2014). In addition to reduction in gray matter, the integrity of white matter tracts linking the PFC and other regions also influences EF. Brinkman and colleagues (2012) found a positive correlation between damage to the white matter of the frontal lobes bilaterally and impaired performance on various measures of shifting attention, planning/organization, working memory, and cognitive flexibility. Results from these and similar studies, have converged to support EFs as orchestrated in the frontal lobe, and most often the PFC specifically. A meta-analysis found a significant inverse relationship between WMHs and performance on measures of EF (Debette & Markus, 2010). As such, it is reasonable to anticipate deficits in EF in patients who both chronically and acutely experience insufficient blood flow to the primary orchestrating regions.

EF is an umbrella term for many distinct yet complementary skills (Miyake et al., 2000). In considering the diverse, yet related, nature of EFs, it becomes necessary to identify the particular EFs examined in this study. From the larger study on cerebral blood flow in SCD, data from several key EFs were available: inhibition (i.e., the ability to inhibit prepotent responses or to refrain from an impulsive response in favor of another), working memory (i.e., the ability to

mentally hold and manipulate information), and cognitive flexibility (i.e., the ability to switch one's attention between and within tasks).

Working memory. Working memory refers to the ability to mentally hold and manipulate information (Blumenfeld, 2010). The neuroanatomy of working memory remains debated; however, it appears to encompass several different brain regions which vary based on the type of information processed (Eriksson, Vogel, Lansner, Bergström, & Nyberg, 2015). Barbey, Koenigs, & Grafman (2013) studied patients with brain lesion and results indicated that the left dorsolateral PFC is primarily implicated in manipulating both verbal and spatial sequencing information (e.g., WAIS-III Letter-Number Sequencing subtest, Wechsler Memory Scale - Third Edition [WMS-III] Spatial Span Backward subtest) while the right dorsolateral PFC was implicated in verbally mediated quantitative reasoning (e.g., WAIS-III Arithmetic subtest)[4]. Meta-analyses have also documented lateralized findings with the left PFC implicated in verbal working memory tasks and the right PFC implicated in spatial tasks (Nee et al., 2012; Wager & Smith, 2003). In addition to the PFC, the bilateral parietal lobes (right greater than left) play a role in spatial working memory and are believed to assist with directing attention (Awh, Vogel, & Oh, 2006; Nee et al., 2012). Cerebellar involvement has also been documented, which further elucidates the communication that would be necessary in order to integrate these various brain regions (Nee et al., 2012). Contributing to this support for working memory as a highly collaborative process, disruption to the white matter pathways as part of normal aging has been associated with working memory impairment (Charlton, Barrick, Lawes, Markus, & Morris, 2010).

[4] Significant differences were not observed with regard to measures of auditory (WAIS-III Digit Span Forward) and visual attention span (WMS-III Spatial Span Forward) suggesting that these abilities are mediated by different neuroanatomical processes.

Consistent with the complex neuroanatomical networks involved with working memory, Baddeley's model of working memory proposes interdependence of four components: the phonological loop, the visuospatial sketchpad, the episodic buffer, and the central executive (1996a; 2000; 2003; 2007).

The phonological loop is responsible for holding speech-based information and operates most predominantly in the left hemisphere, especially the temporoparietal region and Broca's area (Paulesu, Frith, & Frackowiak, 1993; Jonides et al., 1998). Unless rehearsed, this information will fade within seconds, and increased rehearsal improves the likelihood that the information is accurately retained. The presence of the phonological loop is supported by an increase in errors for phonetically similar letters and words, as well as denotatively similar words, even in stimuli presented *visually* (Baddeley, 1996a; Conrad, 1964; Conrad & Hull, 1964).

The visuospatial sketchpad is the complementary component for visual and spatial information (Baddeley, 2007). It operates in much the same way as the phonological loop with rehearsal leading to memory storage; however, it is predominantly located in the right hemisphere of the brain.

The episodic buffer integrates information across various sensory inputs including phonological, visual, and spatial (Baddeley, 2000). The term episodic is utilized to denote that these various pieces of information are integrated into a unitary representation and that for many experiences, neither visual/spatial nor phonological data alone are sufficient to encapsulate the memory.

The central executive refers to general processing capacity and is purely attentional, incapable of storage (Baddeley, 2007). Baddeley utilizes Norman and Shallice's model of the

Supervisory Attentional System (SAS) to account for the central executive (1986). They propose that behavior is controlled at two different levels. On the first are automatic behaviors, which occur due to familiar habits. The other, the SAS, is a mechanism for overriding habitual behaviors in situations that require it. In the model, individuals with damage to the frontal lobe are assumed to also have damage to the SAS. They are able to act in familiar and habitual ways, however, lack the ability to appropriately modulate their behaviors to the demands of the context.

The concept of the phonological loop has been the basis of many evaluations of working memory in the pediatric SCD population (e.g., digit span), while the visuospatial sketchpad has been less studied. In one study that evaluated both systems, children with SCD demonstrated impairment in both verbal and visuospatial working memory (Smith & Schatz, 2016). The same study found that although processing speed is decreased in patients with SCD, which limits the rate of rehearsal, it does not appear to contribute to the observed deficits in working memory. Hijmans and colleagues (2011) found significant deficits in visuospatial working memory, although no such differences were found with verbal working memory when comparing a pediatric SCD population to healthy SES-matched controls.

Vichinsky and colleagues (2010) provided the first study on working memory in an adult SCA population. They did not include scores for each subtest; however, reported overall performance on the WAIS-III Working Memory Index (WMI) to be significantly lower in SCA patients without history of neurological insult when compared to demographically matched controls (adjusted mean, standard score of 90.75 for patients vs 95.25 for controls [mean difference, −4.5]; $p = .03$). Mackin and colleagues (2014) reported similar results when adjusting data from Vichinsky et al. (2010) for intracranial volume (WAIS-III WMI adjusted mean, standard score of 91.5 for patients vs 96.0 for controls [mean difference, −4.5]; $p = .03$).

Inhibition. Inhibition, also known as inhibitory control, refers to the ability to resist a prepotent response in favor of another (Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010). The right anterior insula has been implicated in detecting cues to suppress a response while the right inferior frontal cortex (also known as the ventrolateral PFC) has been implicated as the area of primary activation while enacting the necessary inhibitory control (Aron, Robbins, & Poldrack, 2004; Cai, Ryali, Chen, Li, & Menon, 2014; Levy & Wagner, 2011). Performance on inhibitory tasks is reduced following prefrontal insults (e.g., overt stroke) in the general population (Floden & Stuss, 2006), as well in the pediatric SCD population (Craft et al., 1993; Christ, Moinuddin, McKinstry, DeBaun, & White, 2007). Even without apparent medical complications, children with SCD show impaired inhibitory control (Hijmans et al., 2011).

Vichinsky et al. (2010) provides the only known assessment of inhibition in adults with SCA and reports significant differences between neurologically asymptomatic patients and healthy demographically matched controls (adjusted mean scaled score of 6.61 for patients vs 9.06 for controls [mean difference, −2.45]; $p < .001$) on the Delis–Kaplan Executive Function System (D-KEFS) Color Word Interference Task, Trial 3[5]. Studies examining functioning in a more general SCD population were not available.

Cognitive flexibility. Cognitive flexibility refers to the ability to quickly and accurately switch between rules or task demands (Dajani & Uddin, 2015). There is support for the primary activation of the lateral PFC during tasks of cognitive flexibility (i.e., the Wisconsin Card Sorting Test [WCST], D-KEFS; Blumenfeld, 2010; Buchsbaum et al., 2005; Yochim, Baldo, Nelson, & Delis, 2007). Functional MRI (fMRI) studies have indicated more specific activation of the ventrolateral PFC while participants are performing tasks measuring cognitive flexibility

[5] See Methods section for a detailed discussion of this measure.

(Dajani & Uddin, 2015). These findings are often reliable enough to differentiate healthy controls from patients with frontal lobe lesions (Yochim et al., 2007).

Cognitive flexibility is comprised of two complementary subsystems: set shifting and task shifting (Dajani & Uddin, 2015). Set shifting refers to the ability to process information based on different rules within a task whereas task shifting refers to the ability to quickly shift between tasks with different instructions (Dajani & Uddin, 2015; Konishi et al., 1998; Monsell, 2003). Task switching is conceptualized by Bunge and Zelazo (2006) as the most complex form of cognitive flexibility. Although distinct concepts, task switching places greater demands on one's capacity for working memory as it requires that the individual remember separate rules for each task (Dajani & Uddin, 2015). Aspects of inhibition are also implicated in cognitive flexibility as the individual must possess the capacity to control more immediate, or habitual, responses in favor of responses that would be consistent with the task demands (Davidson, Amso, Anderson, & Diamond, 2006).

Research on cognitive flexibility in this population is less bountiful than other EFs. Watkins and colleagues (1998) found that children with SCD and history of overt stroke had significantly more perseverations when administered the WCST when compared to children without history of overt stroke and healthy sibling controls. Brown et al. (2000) found that children without history of overt stroke worked more quickly on a Trail Making task than did children with either SCI or overt stroke history**.**

Adults with SCA and demographically matched controls performed similarly on the WCST; however, significant differences were noted based on performance on the D-KEFS Trail Making

Test Trial 4[6] (a test of visual attention, processing speed, and cognitive flexibility; Vichinsky et al., 2010). Studies examining functioning in a more general SCD population were not available.

Sociopolitical Considerations

Historical Context. As has been the case for other diseases (e.g., syphilis, Tay Sachs), research, treatment, and even acknowledgement of the SCD process are all reflective of social and political climate. While the African people had long spoken of a debilitating disease marked by intense pain episodes (Konotey-Ahulu, 1974), attention in the U.S. focused more on the disease's impact to productivity for slave owners (Phillips, 1999). This occurs alongside the development of pseudoscience promoting the fallacy that Black individuals are resistant to pain and thus require harsher beatings to gain compliance (Cartwright, 1851). Such behaviors were representative of the normative social values of the time.

A demand for medical parity gained traction during the 1960s and '70's when, civil rights advocates brought SCD to the forefront and highlighted the significant health disparities. Indeed, SCD became a focus within the civil rights movement. Activists of the time cited the reality that most patients with SCA did not live beyond their teenage years (Scott & Castro, 1979; Wailoo, 2014). Despite the obvious toll on Black health and the disease's early identification as molecular in nature (Herrick, 1910), little research had been conducted to advance treatment for these patients. This lack of research contributed to a life expectancy in the teenage years for individuals with SCD (Scott & Castro, 1979; Wailoo, 2014); however, the Sickle Cell Anemia Control Act of 1972 allocated federal funding toward the research, treatment and education of SCD. While critical advancements were made in the years following this action, support soon faded (Scott & Castro, 1979).

[6] See Methods section for a detailed discussion of this measure.

Health Disparities. To this day, individuals with SCD continue to face significant disparities with regard to access to quality medical care as well as systemic racism. Despite their chronic and debilitating pain, individuals with SCD are often viewed by hospital personnel as time-consuming, illegitimate users of health care resources who are seeking prescription drugs for illicit purposes (Aisiku et al., 2009; Alao, Westmoreland & Jindal, 2003; Jacob, 2001). These perceptions contribute to negative provider attitudes, and ultimately negative healthcare experiences for the patient (Carroll, Haywood, & Lanzkron, 2011; Shapiro, Benjamin, Payne, & Heidrich, 1997). Although the prevalence of prescription drug abuse is almost doubled in White individuals, opioids are more cautiously, more slowly, and less frequently prescribed for Black patients (Armstrong, Pegelow, Gonzalez, & Martinez, 1992; Lazio et al., 2010; Vaughn, Nelson, Salas-Wright, Qian, & Schootman, 2016). Remnants of Cartwright's teachings smolder in the field as a relatively recent study indicated one-third of physicians and medical students surveyed believed that Black patients inherently experience less pain than their White counterparts (Hoffman et al., 2016). When seeking emergency medical services, patients with SCD may wait 25 to 50% longer for treatment when compared to other patients and these results were also significantly associated with identification as African American (Haywood, Tanabe, Naik, Beach, & Lanzkron, 2013).

There exists a clear parallel between these modern experiences and the long-standing inequity and even cruelty in healthcare for ethnic minorities in the U.S. (Baker et al., 2008; Byrd & Clayton, 2001; CDC, 2015; Reverby, 2012; Gamble, 1997). A recent poll conducted by National Public Radio (NPR), found that almost one-third of African Americans reported experiences of discrimination in a healthcare setting (Neel, 2017). Similar studies have also cited significant perceptions of racism when seeking medical treatment (Hatzfeld, Cody-Connor,

Whitaker, & Gaston-Johansson, 2008; Nelson & Hackman, 2013; Strickland, Jackson, Gilead, McGuire, & Quarles, 2001). African American patients have shared that, among other factors, the expectation of racism during health care provision reduces trust in their physician and subsequent help-seeking (Benkert, Peters, Clark, & Keves-Foster, 2006; Cuevas & O'Brien, 2017; Jacobs, Rolle, Ferrans, Whitaker, & Warnecke, 2006; Kennedy, Mathis & Woods, 2007), and also contributes to increased subjective stress ratings, depression, and decreased quality of sleep (Anderson, 2013; Grandner et al., 2012; Mezuk et al., 2010). Furthermore, this lowered trust is associated with nonadherence - a challenge consistently documented in the SCD population (Brandow & Panepinto, 2010; Reeves, Tribble, Madden, Freed, & Dombkowski, 2018; Teach, Lillis, & Grossi, 1998).

Critique and Need for Further Study

In comparison to the number of studies completed in the pediatric population, relatively little research has focused on adult patients. This may be partially because of SCD's history as a pediatric condition due to the significantly shortened life spans of previous generations. As individuals with SCD are now expected to live into their fourth and fifth decades, it is increasingly important to expand upon the literature to reflect the needs of those afflicted by the condition. Such data are necessary in order to accurately anticipate, prevent, or remediate any neuropsychological deficits in this population.

Further, of those studies that have examined SCD in adults, much of this research has rightly focused on understanding the biomedical underpinnings of the disorder (Vichinsky et al., 2010). As the literature expands, it is also important to balance this increased knowledge by examining the relationship between SCD and neuropsychological functioning. Of particular importance to the daily functioning of these patients is an examination of the relationship

between EFs and SCD in adults. As such, the current study was guided by the following research questions and hypotheses:

Research Questions and Hypotheses

Consistent with the aforementioned significant group differences between healthy controls and SCD patients observed in the pediatric literature, as well as data from the only available study examining EFs in an adult SCA population, it is anticipated that analyses of the data from the current study will also yield significant group differences on measures of EFs when comparing an adult patient sample to healthy controls. The following research question and hypotheses are offered:

Research Question: Are there differences in EFs when comparing adults with SCD to a sample of healthy controls?

a. *Hypothesis 1a.* Patients with SCD will demonstrate significantly lower performance on a task of working memory when compared to healthy controls.
b. *Hypothesis 1b.* Patients with SCD will demonstrate significantly lower performance on an inhibition task when compared to healthy controls.
c. *Hypothesis 1c.* Patients with SCD will demonstrate significantly lower performance on a task of cognitive flexibility when compared to healthy controls.

Chapter 3: Methodology

Study Aim

Given previously identified deficits in EFs in children with SCD (Christ et al., 2007; Craft et al., 1993; Hijmans et al., 2011), the primary aim of the current study was to examine the EFs of working memory, inhibition, and cognitive flexibility in a population of adults with SCD in comparison to healthy controls. The following section presents the specific procedures of the current study. The research design, sample, recruitment, data collection, and data analyses for the study are described.

Research Design

This quantitative, pre-experimental study utilized a cross-sectional, static group comparison design and is part of a larger project being conducted at Children's Hospital Los Angeles (CHLA) on cerebral blood flow response to perturbations in oxygen tension in individuals with and without SCD[7]. Investigators in the larger study primarily examined:

1. Whether resting cerebral blood flow and oxygen are within the normal range in SCD patients,
2. Whether patients with SCD compensate appropriately for brief changes in inhaled oxygen tension, and
3. Whether cerebral blood flow and responses to change in oxygenation correlate with neurovascular and brain parenchymal changes on MRI.

Participants were identified from the CHLA patient population and their family members and divided into three groups: those with SCD, those with non-sickle cell anemia, and healthy controls. Inclusion criteria consisted of:

[7] The primary investigator on this larger study was Dr. John C. Wood. Data collection for the study began in 2013.

1. At least 13 years of age to cooperate with blood draw and MRI,
2. Either gender,
3. Competent to follow instructions,
4. Informed consent obtained from participants over 18 years of age, or parent/legal guardian for those under 18 years of age,
5. Assent obtained from participants under 18 years of age, and
6. HbSS, HbSC, or HbSβ_0 thalassemia genotypes for those in the SCD group.

Exclusion criteria included:

1. Clinically documented prior overt stroke,
2. Any known illness that might compromise subject safety or data integrity, and
3. Known pregnancy.

In addition to a medical workup including MRI and blood draw, the participants underwent neuropsychological evaluation to examine profiles of patients with SCD. Consistent with the aforementioned areas of identified dysfunction in the SCD population, a standardized battery was developed to assess these areas (see Table 1). The neuropsychological assessment battery was administered in an outpatient setting by a neuropsychologist or students under her supervision. Demographic data (e.g., birth history, education level, income, academic achievement, etc.) were collected through a questionnaire as well as review of CHLA medical records, if available.

Table 1

Neuropsychological battery for larger study

Measure	Subtests/Trials	Acronym	Domain
Wechsler Abbreviated Scale of Intelligence - Second Edition		**WASI-II**	General Intellectual Functioning
National Institutes of Health Toolbox	Pattern Comparison Processing Speed	**NIH Toolbox**	Processing Speed
Wechsler Adult Intelligence Scale – Fourth Edition	Coding, Symbol Search	**WAIS-IV**	
Rey Complex Figure Test and Recognition Trial	Copy	**RCFT**	Visual Motor Integration
California Verbal Learning Test - Second Edition & Children's Version		**CVLT-II & CVLT-C**	Learning & Memory
Rey Complex Figure Test and Recognition Trial	Immediate, Delay	RCFT	
Wechsler Adult Intelligence Scale – Fourth Edition	Digit Span Forward	WAIS-IV	Auditory Attention Span
Behavior Rating Inventory of Executive Function		**BRIEF**	Executive Functions
Delis-Kaplan Executive Function System	Color-Word Interference Test, Trail Making Test, Verbal Fluency	**D-KEFS**	
National Institutes of Health Toolbox	Dimensional Change Card Sort, Flanker Inhibitory Control	NIH Toolbox	
Wechsler Adult Intelligence Scale – Fourth Edition	Digit Span Backward	WAIS-IV	
Behavior Assessment System for Children - Second Edition		**BASC-2**	Social-Emotional
PROMIS Fatigue Scale			Health

Note. that many psychometric measures assess more than one aspect of functioning. As such, the primary domain is indicated; however, particular subtests and/or trials are delineated as appropriate. The overall measure is bolded the first time it appears in the table. Detailed information regarding the measures selected for the current study is discussed in the Neuropsychological Protocol and Data Collection section of this paper.

Participants

The sample for the current study was obtained from data collected as part of the aforementioned larger study. As the purpose of the current study was to expand upon the

literature for adult patients, a subset of the larger study's SCD patients were identified for inclusion based on their age (18-45 years old). A subset of healthy controls 18- to 45-years of age was also selected. Individuals above the age of 45 were excluded to be consistent with the general life expectancy of SCD patients and to account for the increased likelihood of cognitive changes due to confounding disease processes. (e.g., increased likelihood of CVA/SCI, increased rates of both chronic and acute pain). The final sample consisted of 65 individuals (31 SCD and 34 control).

Recruitment

Recruitment and data collection were consistent with an application approved by the Institutional Review Board (IRB) of Children's Hospital Los Angeles (CHLA; IRB Application/Protocol #11-00083) as well as the IRB of Pepperdine University Graduate School of Education and Psychology, Psychology Division (IRB Application/Protocol #18-12-951). Participants were recruited from the CHLA SCD patient population and invitations to participate were also extended to their friends and family members. Letters explaining the study and requesting both healthy and SCD subjects were either given to patients during their routine examinations or mailed to the address in the electronic medical record. Participants were paid a total of $200 for 2 days ($100 after completion of the neuropsychological testing and $100 after completion of the medical workup which included a brain MRI, oxygen manipulation, and a oxygen saturation sensor worn overnight).

Data Collection

Neuropsychological Protocol. As part of the larger study, participants completed a battery of assessments in the areas of general cognition, attention, language, verbal and non-verbal learning and memory, processing speed, visuomotor construction, and social-emotional

functioning. Given the aims of this study, scores from measures assessing working memory, inhibition, and cognitive flexibility were analyzed (see Table 2).

Table 2

Neuropsychological trials and subtests analyzed

Measure	**Domain**	
WASI-II	General Cognition	
Measure	**Trial**	**Executive Function**
WAIS-IV	Digit Span (Backward)	Working Memory
D-KEFS	Color-Word Interference Test (Trial 3)	Inhibition
D-KEFS	Trail Making Test (Trial 4)	Cognitive Flexibility

Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II). The WASI-II is a brief screening measure of general intelligence. It is comprised of four subtests – Vocabulary, Similarities, Block Design, and Matrix Reasoning – which are very similar to the subtests of the same names on the full-length Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV) and the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV). The WASI-II was normed on a sample of 2,300 examinees ranging in age from 6 to 90 years including 201 children and 182 adults who were administered both the WASI-II and either the WISC-IV or WAIS-IV. General intellectual functioning is estimated as an FSIQ using these 4 subtests (FSIQ-4) on the WASI-II. Unlike the WAIS-IV, the WASI-II FSIQ-4 does not integrate processing speed as a component of intellectual functioning and as a result is less impacted by processing speed. For this study, the WASI-II was used to examine group differences with regard to general intellectual functioning.

Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV). The WAIS-IV as a whole is designed to measure intellectual ability. The test was normed on a sample of 2,200

individuals ranging in age from 16 to 90 years. These individuals were stratified by age, gender, education level, ethnicity, and region. From the WAIS-IV, our study utilized the Digit Span, Coding, and Symbol Search subtests.

Digit Span. Digit Span has been used widely in research to assess working memory. Digit Span is comprised of three trials. During the first trial, the examinee is asked to repeat strings of numbers of increasing length. This provides a measure of immediate auditory attention span. During the second and third trials, the examinee is asked to repeat strings of numbers of increasing length either in reverse order or sequentially (smallest to largest), respectively. Both of these trials are measures of working memory, as they require that the examinee not only briefly hold this information in mind, but also mentally manipulate the information based on the demands of the task. The sequencing task adds the potential confound of number sequencing and other cognitive processes, so the Digit Span Backward (DSb) task was selected to provide the purest overall measure of working memory.

Delis-Kaplan Executive Function System (D-KEFS). The D-KEFS is comprised of 9 stand-alone tests, evaluating various EFs. The D-KEFS was standardized on a sample of 1,700 individuals, ages 8 to 89 years, who were selected to represent the U.S. population with regard to demographic profiles. For this study, the D-KEFS provides data on the EFs of response inhibition and cognitive flexibility. More specifically, the Color-Word Interference Test (CW) and Trail Making Test (TMT) were selected for this purpose.

Color-Word Interference Test. To allow for greater differentiation between EFs and other confounding variables, CW is comprised of four trials, which are largely modeled after the classic Stroop test (Golden, 1978). The first trial requires the examinee to quickly identify the color of an organized array of squares and primarily provides a measure of rapid naming. The

second trial requires that the examinee quickly read the names of colors printed in black ink and primarily provides a measure of word reading speed. The third trial requires that the examinee inhibit the automatic response of reading a color name and instead name the color of ink the word was printed in (e.g., the word orange printed in purple ink) and primarily provides a measure of response inhibition in addition to the above-mentioned foundational skills. Performance on this third trial was examined in data analyses. In the final trial, examinees are asked to switch between identifying the ink color and reading the name of a color printed in a contrasting color, which provides a measure of cognitive flexibility in addition to response inhibition, rapid naming, and word reading speed.

Trail Making Test. Similar to CW, the TMT consists of five trials, which allow for a greater degree of discernibility between EFs and other confounds. The first trial screens visual scanning ability by asking the examinee to quickly mark only a select number in a large, scattered array. The second and third trials evaluate letter and number sequencing, respectively, by asking the examinee to sequentially connect either letters or numbers among a field both characters. The fourth trial provides an estimate of cognitive flexibility by requiring the examinee to quickly alternate or "switch" between connecting numbers and letters in sequential order. Performance on this fourth trial was utilized for data analyses as a measure of cognitive flexibility. The final trial is a measure of graphomotor speed and asks that the examinee quickly connect a series of open circles by tracing along a dashed line as fast as possible while marking each circle along the track.

Preliminary Analysis

All of the continuous independent, covariate, and dependent variables were examined by assessing means, medians, standard deviations, and minimum and maximum scores. The data

were examined for the presence of any outliers using the interquartile rule (IQR) with a 2.2 multiplier (Hoaglin & Iglewicz, 1987). There were no significant outliers found in the data set.

Categorical variables (i.e., age, gender, race) and ordinal variables (i.e., parental educational levels and both childhood and current annual combined family income) were examined by assessing frequencies.

Data Analyses

SPSS (Version 24) was employed to analyze the data collected. Data analyses included descriptive, correlational, and inferential analyses. In order to determine potential significant differences in estimated intelligence and demographic factors between SCD and control groups, the groups were compared using either independent samples *t*-tests for continuous variables (i.e., age, FSIQ-4) or chi-square tests for categorical variables (i.e., gender, ethnicity, level of parental education, income category)[8]. Given significant group differences related to current annual combined family income (described in results), this variable was then incorporated as a covariate during subsequent hypothesis testing. More specifically, in order to test hypotheses, a multiple analysis of covariance (MANCOVA) was performed with group (SCD or control group) as an independent variable, current annual combined family income as a covariate, and performance on WAIS-IV DSb (Working Memory), D-KEFS CW Trial 3 (Inhibition), and D-KEFS TMT Trial 4 (Cognitive Flexibility) as dependent variables.

[8] While parental education and income can be considered continuous variables, the data collection method utilized in the original study was based on reporting brackets of educational achievement and income that were not equal across levels; therefore, these variables were treated as ordinal.

Chapter 4: Results

Description of Participants

The 65 total participants included 40 females (61.5%) and 25 males (38.5%). Their ages ranged from 18 to 45 years ($\bar{x}$ = 28.11) and average intellectual functioning was within normal limits ($\bar{x}$ = 95.65; see *Table 3* for demographic characteristics of the combined groups*)*. While participants were not asked to identify their own race, they were asked to identify each of their parents as either African American or Other. The majority of the participants indicated that at least one of their parents identified as African American (87.3%).

Various SES factors were considered. Regarding maternal education level, the majority of the sample indicated that their mother completed some college (27.4%), while others reported less than 8 years (8.1%), less than 12 years (3.2%), high school (19.4%), associate degree (4.8%), bachelor's degree (17.7%), some graduate school (4.3%), or a graduate degree (14.5%). Regarding paternal education level, equal numbers of participants indicated that their father completed high school or some college (26.8%), while others reported less than 8 years (3.6%), less than 12 years (3.6%), associate degree (3.6%), bachelor's degree (7.1%), some graduate school (5.4%), or a graduate degree (14.3%). The majority of the sample reported a childhood annual combined family income of below $20K (35%), while smaller portions of the sample indicated incomes of $20K-39K (25%), $40K-59K (22.5%), $60K-79K (12.5%), $80K-99K (12.5%), and $100K or above (17.5%). Similarly, the majority of the sample reported a current annual combined family income of $20-39K (29.1%), while smaller portions of the sample indicated incomes of less than $20K (27.3%), $40-59K (16.4%), $60-79K (9.1%), $80-99K (9.1%), and $100K or above (9.1%).

Table 3

Demographic characteristics of the combined groups

Demographic	$\bar{x}$ **(*SD*)**	
Age	28.11 (*7.84*)	
FSIQ-4	95.65 (*11.33*)	
Demographic	***N***	**Frequency**
Gender		
Female	40	61.5%
Male	25	38.5%
Parent Race		
At least one parent identified as African American	55	87.3%
Neither parent identified as African American	8	13.7%
Maternal Education		
Less than 8 years	5	8.1%
Less than 12 years	2	3.2%
High school degree	12	19.4%
Some college	17	27.4%
Associate degree	3	4.8%
Bachelor's degree	11	17.7%
Some graduate school	3	4.3%
Graduate degree	9	14.5%
Paternal Education		
Less than 8 years	2	3.6%
Less than 12 years	2	3.6%
High school degree	15	26.8%
Some college	15	26.8%
Associate degree	2	3.6%
Bachelor's degree	4	7.1%
Some graduate school	3	5.4%
Graduate degree	8	14.3%
Childhood Combined Annual Family Income		
Less than $20,000	14	35%

(continued)

Demographic	*N*	Frequency
$20-39,000	10	25%
Childhood Combined Annual Family Income		
$40-59,000	9	22.5%
$60-79,000	5	12.5%
$80-99,000	5	12.5%
$100,000 or above	7	17.5%
Current Combined Annual Family Income		
Less than $20,000	15	27.3%
$20-39,000	16	29.1%
$40-59,000	9	16.4%
$60-79,000	5	9.1%
$80-99,000	5	9.1%
$100,000 or above	5	9.1%

Preliminary Descriptive Analyses

Data were initially assessed for frequencies (categorical variables), as well as means, standard deviations, and minimum and maximum scores (continuous variables). Means and standard deviations were computed for continuous variables (see *Table 4* for between group sample characteristics). There were no outliers identified using the IQR for outliers with a 2.2 multiplier.

Demographic Differences and Relationships

Independent samples *t*-tests were computed to determine whether there were significant group differences with regard to age or FSIQ-4.

Age. Age was similar between the control ($\bar{x}$ = 28.74, *SD* = 8.07) and SCD groups ($\bar{x}$ = 27.42, *SD* = 7.67) and independent samples *t*-test revealed no significant differences between groups with regard to age ($t(63) = .67$, $p = .50$). Levene's Test was utilized to assess the assumption of homogeneity of variance and was nonsignificant ($F = .02$, $p = .90$).

FSIQ-4. Similarly, there were no significant differences with regard to FSIQ-4 between the control ($\bar{x}$ = 96.62, *SD* = 13.07, *p* = .47) and SCD groups ($\bar{x}$ = 94.58, *SD* = 9.15), *t*(63) = .72, *p* = .08. Levene's Test was utilized to assess the assumption of homogeneity of variance and results indicated nonsignificant differences in variance (*F* = 3.25, *p* = .08).

Chi square tests were utilized to assess whether there were significant group differences with regard to categorical demographic variables (i.e., gender, race, parental education levels, and both childhood and current annual combined family income).

Gender. Binary gender was utilized and coded as either female or male. The control group was 61.8% female and 38.2% male while the SCD group was 61.3% female and 38.7% male. There were no significant differences between groups with regard to gender, x^2 (1, *N* = 65) = .002, *p* = .97.

Race. While seven options for race (African American/Black, American Indian/Alaska Native, Asian/Pacific Islander, Caucasian, Hispanic/Latino, Multiracial, Other) were included within the questionnaire, reported race was then collapsed into two general options during analyses for ease of computation and retention of power. Data were coded as either African American or Other given the aforementioned overwhelming prevalence of the disease in the African American population. Further, data were extrapolated based on the participants' report of their parents' racial identity such that a participant was categorized as African American if they endorsed having at least one parent who is African American (87.3%). Conversely, the participant was coded as Other if they endorsed Other for both parents (12.7%)[9]. There were no significant differences between groups with regard to binary race, x^2 (1, *N* = 63) = .38, *p* = .54.

[9] Data were not available for 2 participants.

Maternal Education Level. The majority of the control group indicated maternal education level of high school (28.1%), while less than 8 years (9.4%), less than 12 years (3.1%), some college (25%), bachelor's degree (15.6%), some graduate school (3.1%), and a graduate degree (15.6%) were endorsed to a lesser degree[10]. The majority of the SCD group indicated maternal education level of some college (30%) while less than 8 years (6.7%), less than 12 years (3.3%), high school (10%), associate degree (10%), bachelor's degree (20%), some graduate school (6.7%), and a graduate degree (15.6%) were endorsed to a lesser degree[11]. There were no significant differences between groups with regard to maternal education level, x_2 (7, N = 62) = 6.74, p = .46.

Paternal Education Level. The majority of the control group indicated paternal education level of some college (29%), while less than 8 years (16.1%), less than 12 years (3.2%), high school (22.6%), bachelor's degree (9.7%), some graduate school (3.2%), and a graduate degree (9.7%) were endorsed to a lesser degree[12]. The majority of the SCD group indicated paternal education level of high school (32%) while less than 8 years (8%), less than 12 years (4%), some college (24%), bachelor's degree (20%), some graduate school (6.7%), and a graduate degree (13.3%) were endorsed to a lesser degree[13]. There were no significant differences between groups with regard to paternal education level, x_2 (7, N = 56) = 5.20, p = .64.

Childhood Combined Annual Family Income. The majority of those in the control group endorsed a childhood annual combined family income of less than $20K (36.7%), while $20-39K (16.7%), $40-59K (10%), $60K-79K (13.3%), $80-99K (10%), and $100K and above

[10] Data were not available for 2 participants.
[11] A data point was not available for 1 participant.
[12] Data were not available for 3 participants.
[13] Data were not available for 6 participants.

(13.3%) were endorsed to a lesser degree[14]. The majority of those in the SCD group endorsed a childhood annual combined family income between $40-59K (30%), while less than $20K (15%) $20-39K (25%), $60K-79K (5%), $80-99K (10%), and $100K and above (15%) were endorsed to a lesser degree[15]. However, there were no significant differences between groups overall with regard to childhood combined annual family income, x_2 (6, N = 65) = 10. 87, p = .09.

Current Combined Annual Family Income. The majority of control participants endorsed a current annual combined family income of between $20-39K (33.3%),[16] while the majority of those in the SCD group endorsed a current annual combined family income of less than $20K (28%; see *Figure 1*). Additionally, only one participant in the SCD group endorsed income between $80K-99K (4%),[17] with none endorsing income at or above $100K as compared to 4 participants in the control group endorsing income between $80K-99K (13.3%) and 5 endorsing income at or above $100K (16.7%). This resulted in statistically significant differences between groups with regard to current combined annual family income, x_2 (5, N = 55) = 13.52, p = .02. Therefore, these differences were considered during subsequent analyses.

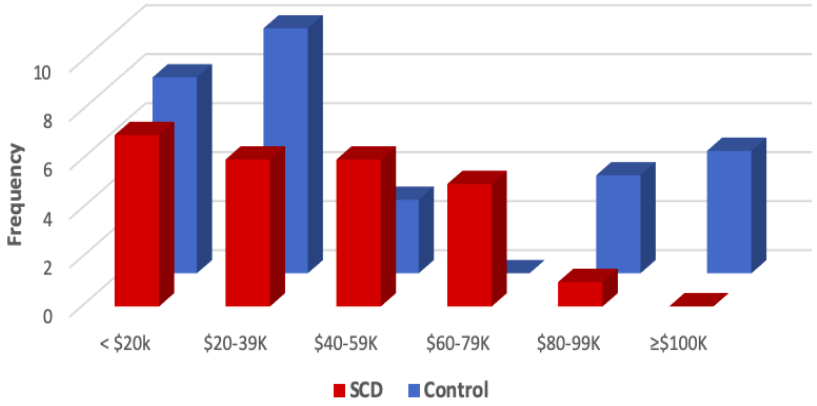

Figure 1

Current combined annual family income

[14] Data were not available for 4 participants.
[15] Data were not available for 11 participants.
[16] Data were not available for 9 participants.
[17] A data point was not available for 1 participant.

Table 4

Between group demographic characteristics

Demographic	**Control** $\bar{x}$ **(*SD*)**		**SCD** $\bar{x}$ **(*SD*)**		***p***
Age	28.74 (*8.1*)		27.42 (*7.7*)		.50
FSIQ-4	96.62 (*13.1*)		94.58 (*9.1*)		.47
Demographic	***N***	**Frequency**	***N***	**Frequency**	***p***
Gender					. 97
Female	21	61.8%	19	61.3%	
Male	13	38.2%	12	38.7%	
Race					. 54
At least one parent identified as African American	28	84.8%	27	90%	
Neither parent identified as African American	5	15.2%	3	10%	
Maternal Education					.47
Less than 8 years	3	9.4%	2	6.7%	
Less than 12 years	1	3.1%	1	3.3%	
High school degree	9	28.1%	3	10%	
Some college	8	25%	9	30%	
Associates degree	0	0%	3	10%	
Bachelor's degree	5	15.6%	6	20%	
Some graduate school	1	3.1%	2	6.7%	
Graduate degree	5	15.6%	4	13.3%	
Paternal Education					. 64
Less than 8 years	5	16.1%	2	8%	
Less than 12 years	1	3.2%	1	4%	
High school degree	7	22.6%	8	32%	
Some college	9	29.0%	6	24%	

(Continued)

Paternal Education					. 64
Associate degree	2	6.5%	0	0%	
Bachelor's degree	3	9.7%	1	4%	
Some graduate school	1	3.2%	2	8%	
Demographic	***N***	**Frequency**	***N***	**Frequency**	***p***
Childhood Combined Annual Family Income					.09
$0-19,000	11	36.7%	3	15%	
$20-39,000	5	16.7%	5	25%	
$40-59,000	3	10%	6	30%	
$60-79,000	4	13.3%	1	5%	
$80-99,000	3	10%	2	10%	
$100,000 or above	4	13.3%	3	15%	
Current Combined Annual Family Income					. 02
$0-19,000	8	26.7%	7	28%	
$20-39,000	10	33.3%	6	24%	
$40-59,000	3	10%	6	24%	
$60-79,000	0	0%	5	20%	
$80-99,000	4	13.3%	1	4%	
$100,000 or above	5	16.7%	0	0%	

Testing Assumptions

Data were analyzed to ensure all assumptions necessary for MANCOVA. The groups are categorical and by definition independent of one another while the dependent variables are continuous. Box's Test of Equality of Covariance Matrices indicated homogeneity of covariance (see *Table 5*). Kolmogorov-Smirnov's Test of Normality indicated that the data regarding working memory, $D(61) = .16$, $p = .001$, inhibition, $D(61) = .15$, $p = .002$, and cognitive flexibility, $D(61) = .16$, $p = .001$ were not normally distributed. All three dependent variables were transformed into a normal distribution by taking the logarithm with a base of 10 (Bland,

Altman, & Rohlf, 2013). Analyses were computed utilizing both the original and transformed variables (with the latter using a more cautious *p* value of .01; Manikandan, 2010). Levene's Test indicated nonsignificant differences in variance for working memory ($F = .09$, $p = .77$), inhibition ($F = .38$, $p = .54$), and cognitive flexibility ($F = .16$, $p = .69$). Pearson's correlation did not indicate a statistical relationship between the covariate (current combined annual family income) and the dependent variables (working memory, inhibition, cognitive flexibility); however, there were moderate positive correlations between the dependent variables themselves (see *Table 6;* Evans, 1996). More specifically, there were moderate positive correlations between working memory and inhibition, $r = .41$, p = .001, working memory and cognitive flexibility, $r = .47$, $p < .001$, and inhibition and cognitive flexibility, $r = .51$, $p < .001$. Tabachnick and Fidell (2012) suggest that no correlation be above $r = .90$; therefore, this assumption has been met.

Table 5

Box's Test of Equality of Covariance Matrices

Box's *M*	6.64
F	1.03
*df*1	6
*df*2	16720.03
Sig.	0.402

Table 6

Pearson correlations for covariate and dependent variables

Variable	Current Combined Annual Family Income		Working Memory		Inhibition	
	r	***p***	***r***	***p***	***r***	***p***
Current Combined Annual Family Income						
Working Memory	-.03	.85				
Inhibition	-.06	.65	.41	.001		
Cognitive Flexibility	.20	.18	.47	< .001	.51	< .001

Dependent Variables

Performance on the measures of EF are reported as scaled scores which have a mean of 10 and a standard deviation of 3. Broadly average scores range from 7 to 13 with lower scores indicating poorer performance and higher scores indicating better performance. Scores have the potential to range from 1 to 19.

Working Memory. The control group performed in the average range with a mean score of 10.85, standard deviation of 3.44, and range from 6 to 19 (see *Figure 2*). Of note, there were two individuals in the control group who obtained a scaled score of 19 which placed their performance at the 99.9th percentile, one individual who obtained a scaled score of 16 (98th percentile), and one individual who obtained a scaled score of 15 (95th percentile.) The SCD group also performed in the average range on the measure of working memory with a mean score of 10.88, standard deviation of 3.19, and range from 6 to 18. There was one individual in the SCD group who obtained a scaled score of 18 (99.6th percentile), one individual who obtained a scaled score of 17 (99th percentile), one individual who obtained a scaled score of 16 (98th percentile), and one individual who obtained a scaled score of 15 (95th percentile). Despite

these above average scores, neither group contained statistically significant outliers. Overall, the combined groups performed in the average range with a mean score of 10.86, standard deviation of 3.29, and range from 6 to 19. As a result of the aforementioned distribution of scores, the data were negatively skewed.

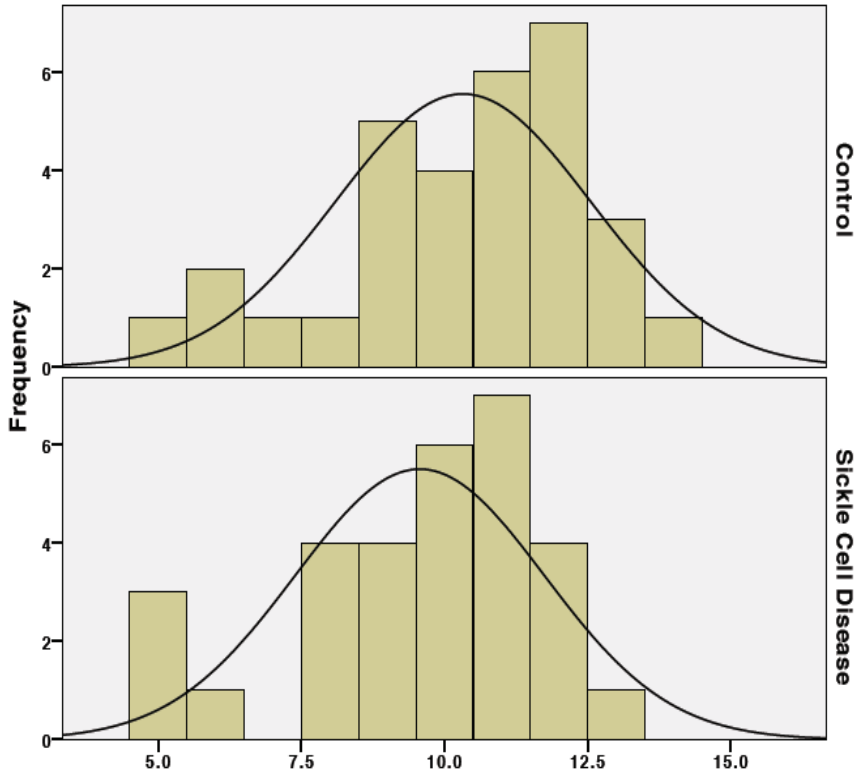

Figure 2

Working memory scaled score histogram

Inhibition. The control group performed in the average range with a mean score of 10.44, standard deviation of 2.36, and range from 3 to 13 (see *Figure 3*). The SCD group also performed in the average range on the measure of inhibition with a mean score of 9.71, standard deviation of 2.37, and range from 4 to 13. Overall, the combined groups performed in the average range with a mean score of 10.10, standard deviation of 2.37, and range from 3 to 13.

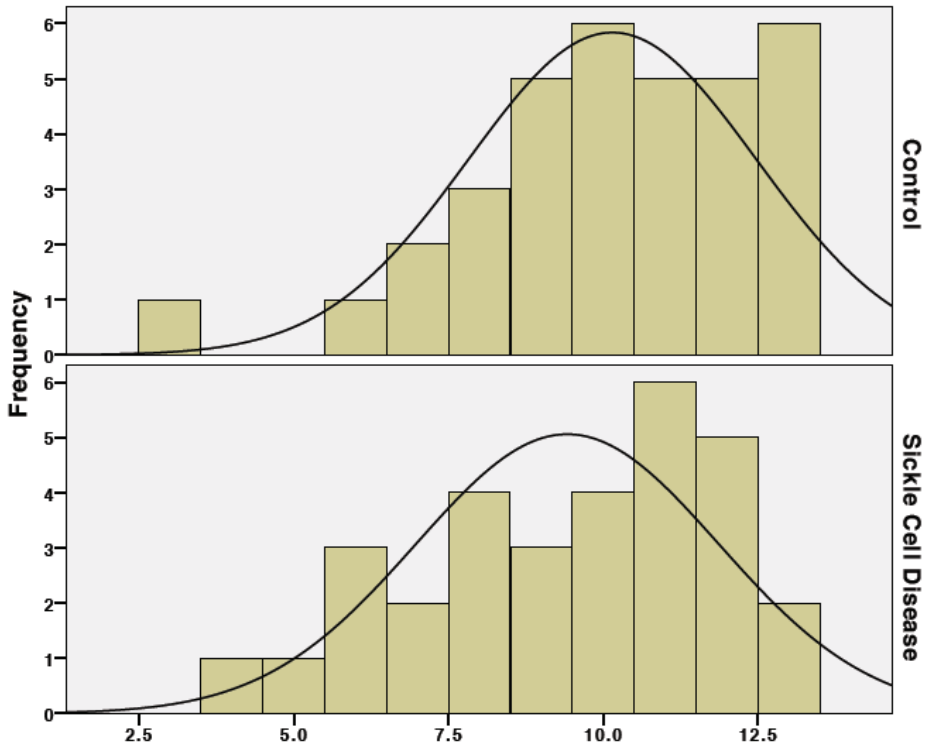

Figure 3

Inhibition scaled score histogram

Cognitive Flexibility. The control group performed in the average range with a mean score of 10.44, standard deviation of 2.33, and range from 5 to 14 (see *Figure 4*). The SCD group also performed in the average range on the measure of cognitive flexibility with a mean score of 9.46, standard deviation of 2.30, and range from 5 to 13. Overall, the combined groups performed in the average range with a mean score of 9.98, standard deviation of 2.35, and range from 5 to 14.

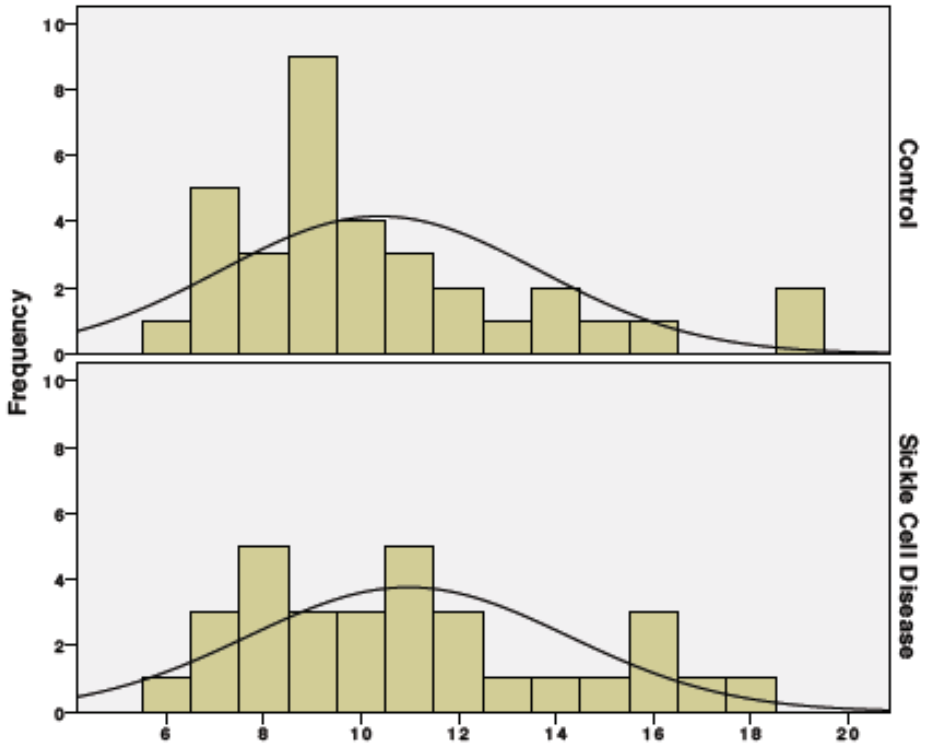

Figure 4

Cognitive flexibility scaled score histogram

Hypothesis Testing

The aim of the current study was to examine EFs in an adult SCD population in comparison to a sample of healthy controls. Hypotheses were tested using a MANCOVA to determine statistically significant differences between groups (SCD or control) on each of the three EF outcome measures, while controlling for current annual combined family income (see *Table 7)*. Additionally, post-hoc analyses were used to also examine potential group differences in EFs without controlling for income.

Working Memory. The first hypothesis postulated that there would be significant group differences on the measure of working memory (hypothesis 1a), with the SCD group performing lower than the SCD group. MANCOVA revealed no significant group differences

with regard to performance on WAIS-IV DSb when accounting for current annual combined family income, $F(2, 48) = .20$, $p = .82$, $\eta_{p2} = .01$. Additionally, no significant group differences were found even when current annual combined family income was not accounted for, $F(2, 49) = .002$, $p = .82$, $\eta_{p2} = .008$.

Inhibition. The second research hypothesis was that there would be significant group differences on the measure of inhibition (hypothesis 1b), with the SCD group performing lower than the SCD group. MANCOVA revealed no significant group differences with regard to performance on D-KEFS CW Trial 3 when accounting for current annual combined family income, $F(2, 48) = .53$, $p = .60$, $\eta_{p2} = .02$. Additionally, no significant group differences were found even when current annual combined family income was not accounted for, $F(2, 49) = .68$, $p = .51$, $\eta_{p2} = .03$.

Cognitive Flexibility. The third hypothesis postulated that there would be significant group differences on the measure of cognitive flexibility (hypothesis 1c), with the SCD group performing lower than the SCD group. MANCOVA revealed no significant group differences with regard to performance on D-KEFS TMT Trial 4 when accounting for current annual combined family income, $F(2, 48) = 3.04$, $p = .06$, $\eta_{p2} = .12$. Additionally, no significant group differences were found even when current annual combined family income was not accounted for, $F(2, 49) = 1.98$, $p = .15$, $\eta_{p2} = .08$.

Table 7

Adjusted and unadjusted means for dependent variables

Domain	Subtest	Adjusted $\bar{x}$ (*SD*)			Unadjusted $\bar{x}$ (*SD*)		
		Control	**SCD**	***p***	**Control**	**SCD**	***p***
Working Memory	WAIS-IV DSb	10.96 (*3.11*)	11.19 (*3.17*)	.82	10.85 (*3.44*)	10.88 (*3.20*)	.99
Inhibition	D-KEFS CW Trial 3	10.71 (*2.27*)	10.05 (*2.20*)	.60	10.44 (*2.36*)	9.71 (*2.37*)	.51
Cognitive Flexibility	D-KEFS TMT Trial 4	10.51 (*2.29*)	9.51 (*2.07*)	.06	10.44 (*2.33*)	9.46 (*2.30*)	.15

Main Effect. In addition to analyzing group differences for each of the three EF outcome measures, MANCOVA was also used to examine associations between the groups and three EF outcome measures together. It showed no significant multivariate effect for working memory, inhibition, and cognitive flexibility as a whole in relation to whether participants were SCD patients or healthy controls, Wilks' $\lambda = .91$, $F(3, 46) = 1.52$, $p = .22$, $\eta_{p2} = .09$.

Chapter 5: Discussion

The purpose of the current study was to examine EF in a sample of adults with SCD. More specifically, this study examined the EFs of working memory, inhibition, and cognitive flexibility in a patient sample compared to healthy controls. Given the relatively small body of literature examining EFs in adults with SCD, this study aimed to contribute to a better understanding of the neuropsychological profile of this population. Methodological limitations are considered and suggestions for future directions are offered.

Summary of Results

In the current study, both the SCD and control groups performed in the solidly average range across measures of EF. Further, there were no significant differences in performance on measures of working memory, inhibition, or cognitive flexibility between individuals with SCD and healthy controls, both with and without controlling for current combined annual family income. Consistent with earlier research (Vichinsky et al., 2010), the SCD group also performed within the average range with regard to general intellectual functioning, at approximately 1/3 standard deviation below the mean, which was not statistically significant when compared to the control group, which performed approximately 2 IQ points higher.

Interpretation of Findings

To date, there have been very few studies examining neuropsychological outcomes in an adult SCD population. This lapse comes alongside a tremendous increase in the life expectancy of those with SCD, such that the group of disorders are no longer considered pediatric conditions (Platt et al., 1994). Despite undeniable advancements in life-preserving medical treatments, brain-behavior relationships warrant further examination in this population. The current study sought to contribute to this need by examining EF in an adult SCD population;

however, findings regarding general intellectual functioning are also notable with important implications for treatment.

Executive Functions. Earlier literature has demonstrated significant differences in EF functioning of children with SCD when compared to both healthy controls and normative data (Brown et al., 2000; Hijmans et al., 2011; Smith & Schatz, 2016). More specifically, these studies indicate that children with SCD function significantly below their typical peers in various aspects of EF including working memory and inhibition (with cognitive flexibility being less studied). While the deficits are more pronounced in children with history of CVA, they may also be present in the absence of CVA, either with or without SCI (Brown et al., 2000).

Limited literature has documented clinically and statistically significant differences with regard to EF when comparing adults with SCA to a sample of healthy controls (Vichinsky et al., 2010; Mackin et al., 2014). When comparing the participant characteristics of the study conducted by Vichinsky and colleagues with the current study, there are some limitations. While Vichinsky does not report the mean age of participants, the majority of both patients and healthy controls in the study conducted were over the age of 30. In the current study, the average age of those in the SCD group was 27.42 years and 28.74 years for those in the control group. This suggests a potentially younger cohort in the current study. With regard to sex (binarily defined), in Vichinsky's study, the control group was 63% female as compared to the control group which was 49% female. Approximately 61% of participants across either group were female in the current study. Due to differences in data collection methods, SES factors are more challenging to compare. For example, education levels for the participant were not collected (although data was collected regarding parental education level), while Vichinsky reported that the majority of the patient sample completed more than a 12th grade education (64%) while 36%

obtained less than a 12th grade education, which was similar to that observed in the control group (68% vs 32%). All individuals enrolled in Vichinsky's study self-reported their race as "African American," which is compared to 84.8% of controls and 90% of those in the SCD group in the current study. Vichinsky et al (2010) did not provide detailed information regarding treatment histories of participants. When administered at least two of the same subtests as were analyzed in this current study (D-KEFS CW Trial 3 and TMT Trial 4 which measure inhibition and cognitive flexibility, respectively), adults with SCD performed in the low average range, which was significantly below their healthy counterparts (Vichinsky et al., 2010). With regard to working memory, data were not published on WAIS-III[18] DSb performance specifically; however, Vichinsky et al. (2010) reported that adults with SCD performed marginally in the broadly average range and approximately 1/3 standard deviation below healthy controls on the more general WAIS-III WMI. These findings diverge from those obtained in the current study which suggest that performance on measures of working memory, inhibition, and cognitive flexibility are within the normative range in an adult SCD sample. However, the current sample represents the broader SCD population (as compared to SCA specifically) which may account for some of the differences in findings. Additionally, participants in the prior study utilized a sample with a broader age range than the current study (19-55 vs 18-45 years) and recruitment also occurred from 12 sites across the U.S. (rather than the single site recruitment in the current study). These results appear to provide evidence that at least some aspects of EFs may remain intact in adults with SCD although understanding of protective factors warrants further research as they may reflect site-specific practices or benefits from more recent treatment protocols.

[18] The current study utilized the more recently published WAIS-IV; however, earlier literature utilized the WAIS-III.

General Intellectual Functioning. With regard to general cognition, earlier studies have documented significantly lower functioning in children with SCD when compared to healthy controls (Armstrong et al., 1996; Bernaudin et al., 2000; Brown et al., 1993; Schatz et al., 2001; Schatz et al., 2002). Typically, those with SCA (as compared to other forms of SCD) present with the most pronounced impairment (Berkelhammer et al., 2007; Kawadler et al., 2016; Schatz et al., 2002), especially in the presence of CVA although SCI may also have significant deleterious effects (Cohen et al., 1994; DeBaun et al., 2012; Hogan et al., 2006). Pediatric SCD studies support an inverse relationship between the volume of SCI and IQ - a finding which has also been found in non-SCD adult populations (Debette & Markus, 2010; Schatz et al., 2002). While the available literature is limited, the relationship between general intellectual functioning and SCD come alongside research documenting increased risk of SCI with age (Kassim et al., 2016). As a significant portion of individuals with SCD will experience stroke of either variety, and even in the absence of neuroradiological findings adults with SCD may demonstrate performance significantly below a healthy population, concern arises for the neuropsychological functioning of the aging SCD population (Farooq & Testai, 2019; Kugler et al., 1993; Ohene-Frempong et al., 1998) who are more susceptible to stroke in general and as a result are at increased risk for cognitive decline.

While it was not intended as a primary analysis, the current study also contributed information toward understanding general cognitive functioning in adults with SCD. Participants were initially screened for general intellectual functioning and results indicated that performance was within the average range for both the SCD and control groups. Significant group differences were not found. A likely explanation for the observed similarities between groups with regard to general intellectual functioning relates to the selection of the test battery. Many studies

examining neuropsychological functioning utilize measures of FSIQ which is partially comprised of processing speed (Armstrong et al., 1996; Bernaudin et al., 2000; Brown et al., 2000; Mackin et al., 2014; Vichinsky et al., 2010). The current study measured intellectual functioning utilizing the WASI-II FSIQ-4 which provides an estimate based on verbal and nonverbal reasoning, without incorporating processing speed. As many cognitive abilities are interdependent, slower processing speed may also impact performance in other domains although to a lesser degree (e.g., timing out on perceptual reasoning tasks). Slowed processing speed in adults with SCD has been documented and there is evidence to suggest that controlling for processing speed accounts for SCD versus healthy control group differences with regard to general intellectual functioning (Crawford & Jonassaint, 2016). Vichinsky et al. (2010) noted several significant group differences when comparing those with SCA to healthy controls (including an adjusted mean FSIQ of 92.14 for their SCD group and 96.04 for controls); however, the largest discrepancy was with regard to processing speed. As a result of data suggesting processing speed was the greatest area of discrepancy between SCA and control groups in the prior study (Vichinsky et al., 2010) and research suggesting that significant groups differences are not found with regard to general cognition when processing speed is accounted for (Crawford & Jonassaint, 2016), findings documenting significant differences may underestimate intellectual functioning. Consistent with this notion, Vichinsky et al. (2010) did not find significant group differences with regard to verbal or nonverbal reasoning.

Treatment Implications. Taken together, these findings indicate that what is known regarding the pediatric neuropsychological profile of SCD may not directly apply to adults. The understanding of the biological basis of SCD, and in turn, best practices for managing symptoms, has developed considerably over the past several decades. Of note, the current study arrives

nearly a decade later than the only known study examining EFs in adults with SCA - Vichinsky and colleagues' 2010 publication. It is possible that younger cohorts have been able to benefit from earlier implementation of these best practices, which likely influences neuropsychological outcomes by reducing the incidence of SCI, CVA, and hypoxia. While explanatory factors remain unclear, there are likely treatment implications which are considered below.

In 1998, hydroxyurea became the first medication approved by the FDA for the treatment of SCD, and at least one limited study has demonstrated improvement in survival associated with duration of hydroxyurea use (Ault, 1998; Voskaridou et al., 2010). Along with decreasing mortality, hydroxyurea reduces many of the most common complications associated with SCD, including need for transfusions to prevent CVA (Voskaridou et al., 2010). Hydroxyurea has been effective in reducing the risk of overt stroke in the SCD population and strokes of either variety, in turn, have been associated with poorer cognitive functioning (Cohen et al., 1994; DeBaun et al., 2012; Hogan et al., 2006; NHLBI, n.d.). Puffer, Schatz, & Roberts (2007) more directly examined the relationship between hydroxyurea and cognitive functioning. Pediatric patients with SCD who utilized hydroxyurea for at least one year were found to have significantly higher general intellectual functioning when compared to those who were not using the medication. Recent literature has demonstrated a direct correlation between processing speed and loss of white matter integrity (Stotesbury et al., 2018). There is evidence in the pediatric SCD literature to suggest that the use of hydroxyurea preserves the integrity of white matter, although additional research in an adult population is necessary (Nottage, 2014). Despite these benefits, hydroxyurea is underutilized in many settings, and estimates indicate that hydroxyurea is only prescribed for less than half of eligible patients (Lanzkron et al., 2008). When prescribed, adherence is often poor (Arjunan, Moss, Burns, & De Castro, 2018; Heeney & Ware, 2010).

While younger adults are more likely to both understand the purpose of hydroxyurea and report use of the medication, this is not true of older individuals who may also benefit (Sinha, Bakshi, Ross, & Krishnamurti, 2017). Taken collectively, these findings suggest the cognitive deficits documented in previous literature may be prevented through timely and consistent use of hydroxyurea. CHLA utilizes early and aggressive hydroxyurea to the maximum tolerated dose beginning at 9 months of age, which is consistent with the current guidelines issued by the NHLBI. As noted above, these treatment guidelines have not been routinely adopted across providers and the treatment protocols utilized at outside institutions, where earlier studies were predominantly conducted, is unknown. As the current SCD sample was taken from the CHLA patient population, the observed results suggest an early and aggressive treatment protocol likely protects against EF deficits. Data regarding length of hydroxyurea use and adherence were not collected in the current study which limits our ability to draw conclusions as to whether this explanation accounts for the current findings. Additional research should examine relationships between use of hydroxyurea, as well as the more recent Endari, and neuropsychological functioning.

Limitations & Future Directions

Despite best efforts, there are limitations with the current study which should be addressed in future research. To be consistent with literature documenting the average life expectancy of an individual with SCD, participants in this current study were limited in age range from 18 to 45 years. In addition to the health-related needs of the general older adult population, individuals with SCD face significant damage to the body organs, tissues, and/or bones due to insufficient blood flow (Thein, Igbineweka, & Thein, 2017). Most notably, overt stroke remains a leading cause of both morbidity and mortality with recent estimates at 10% the

SCD population and 24% of the SCA population experiencing CVA by the age of 45, which is approximately three times higher than same-aged African Americans without SCD (Farooq & Testai, 2019; Ohene-Frempong et al., 1998; Strouse et al., 2009). The risk of CVA increases dramatically with age (with one estimate at 360/100,000 in individuals ages 13-34, 1,160/100,000 in patients age 35-64, and 4,700/100,000 in individuals age 65 and older; (Kassim et al., 2016; Strouse, Jordan, Lanzkron, & Casella, 2009). Additionally, by the fifth decade, 73% of patients in a cohort study had at least one form of irreversible organ damage which was attributed to vasculopathy (Powars, Chan, Hiti, Ramicone, & Johnson, 2005). As a result of these disease-related processes, it is possible that an older sample would yield significant group differences.

Similarly, the current sample excluded patients with a history of CVA to avoid confounding the SCD neuropsychological data with results more attributable to CVA itself. In addition to CVA, 38% of children with SCD have experienced SCI by the time they reach adulthood (Farooq & Testai, 2019). Although SCI may go undetected due to the lack of traditional neurological symptoms, significant neuropsychological changes in non-SCD populations have been documented (Debette & Markus, 2010). Previous research on SCD documenting significant deficits in general intellectual functioning as well as various aspects of EF may at least partially reflect slower processing speed as well as disrupted cognitive processes reflective of CVA or SCI localization. Additionally, as knowledge regarding the clinical management of SCD has grown over recent decades, it is possible that a younger cohort's demonstration of cognitive functioning more consistent with healthy peers reflects the benefits of newer treatment approaches (such as the early and aggressive use of hydroxyurea to the maximum tolerated dose). However, without continued research, results from the current sample

may be misleading given the relatively high prevalence of both SCI and overt stroke in the SCD population. Further, there is a need to more closely examine the role of SCI on neuropsychological functioning in this population utilizing imaging (e.g., MRI) data.

While this study utilized racial/ethnic data for each participant's parents, data were not coded for the racial/ethnic identity of the participant themselves and as a result participant race was determined by whether either parent identified as African American. The vast majority of the sample had at least one parent who identified as African American. Given the stated disparities in medical care often faced by the SCD population, allowing opportunities for the patient to report their own ethnic and/or racial identity preferences may also be an avenue to demonstrate provider cultural awareness and interest, which may aid in engaging a population with continuing healthcare disparities (Aisiku et al., 2009; Alao et al., 2003; Armstrong et al., 1992; Lazio et al., 2010; Vaughn et al., 2016).

The current study did not indicate current income to be contributory with regard to EF, and other factors of SES assessed were similar across groups (e.g., parental income, parental education level, childhood combined annual income); however, EF has a well-documented association with SES (Ardila, Rosselli, Matute, & Guajardo, 2005; Sarsour et al., 2011). As a result, future studies should consider controlling for broader aspects of SES (particularly aspects present during childhood which have a greater likelihood of interacting with brain maturation processes, such as access to an adequate and nutritious diet, availability of books and other stimulating developmental materials, or time spent caring for younger siblings outside of school hours; Hackman, Gallop, Evans, & Farah, 2015; Lawson, Hook, Hackman, & Farah, 2016). Additionally, data regarding parental education levels and income brackets were coded across a high number of categories which resulted in many cells with fewer than five participants. As a

result, the ability to draw statistical inferences may be limited by the small cell sizes within each of these categories. Future studies with larger sample sizes or alternative coding methods may be considered.

Similarly, the current sample was selected from the CHLA patient population and their friends and family and, as a result, there may be site-specific confounds. More specifically, by selecting participants from an active patient population, there is an inherent bias toward individuals with access to healthcare and/or insurance coverage. As discussed above, individuals without adequate access to healthcare are more likely to experience complications which may make the current sample unrepresentative of those without access to healthcare (Wolfson et al., 2012). In the absence of routine comprehensive care, adults with SCD may utilize emergency services when symptoms become most pronounced without adequate preventative care. Wolfson et al., (2012) cited support for this pattern of healthcare utilization as there was a lower likelihood of inpatient hospitalization which indicated that needs may be better addressed in a less acute setting. Access to, and utilization of, comprehensive care and the relationship to neuropsychological functioning should be further evaluated in future studies.

There are also inherent challenges in evaluating EFs (particularly in medical populations who may experience high levels of pain, fatigue, or stress). First, task impurity must be considered. By definition, EFs are a network of cognitive skills that rely on one another (Baddeley, 1996a; Baddeley, 1996b; Baddeley, 1998; Miyake, Emerson, & Friedman, 2000). Given the interconnectivity, many tasks will place demands across EFs, as well as other abilities. For example, basic attention, visual processing, motor speed, and numerical awareness have the potential to confound results.

If EFs are able to be isolated, there remains the question of whether or not the findings of standardized assessment are ecologically valid (Barkley & Murphy, 2011). In the clinical setting, test administration generally occurs in a quiet, one-to-one, non-distracting room. Seldom does this accurately reflect the challenges an individual is likely to face in their natural environments. This raises the question of whether performance on these tasks provide meaningful information about everyday functioning. Further, prior research indicates that the performance-based measures commonly utilized to evaluate EF in the clinical setting (e.g. WCST, Stroop test, Tower of London) may not correlate with standardized report of symptoms in other settings, suggesting that different constructs may be reflected with each measurement (Toplak, West, & Stanovich, 2013). In a clinical setting, performance on measures of EF can be supplemented with collateral information (e.g., the BRIEF) for comprehensiveness (Isquit, Roth, & Gioia, 2013). In addition to their utility in providing a more wide-ranging account of symptoms, these report-based measures also provide opportunities to measure aspects of EF that are less amenable to performance-based testing (e.g., organization, initiation).

Despite these limitations, prior research on EFs in adults with SCD has been sparse and this study is among the first to examine neuropsychological functioning in an adult SCD sample. Additional research is necessary to critically examine whether profiles are similar across geographic sites and across patient presentations (e.g., age groups, genotypes, treatment histories). Understanding the neuropsychological profile of SCD, including differences in care needs for pediatric and adult samples, will allow more informed treatment planning, prevention efforts, and remediation as necessary. Further, expanding on this literature provides an opportunity to begin to adjust the long-standing history of disparities in medical care often faced by African Americans.

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Appendix A

Literature Table

Author(s)	Year	Title	Methodology & Sample	Psychometric Measures	Outcomes	Relevant Findings
Allen, Anderson, Rothman, & Bonner	2017	Executive functioning and health-related quality of life in pediatric sickle cell disease	Cross-sectional study in which 45 children with SCD aged 8 to 16 years old as well as their caregivers completed measures of quality of life as well as executive and psychosocial functioning.	Pediatric Quality of Life Inventory (PedsQL), Behavior Rating Inventory of Executive Functioning (BRIEF), Wechsler Abbreviated Scale of Intelligence (WASI), Parent Experience of Child Illness (PECI), Visual Analog Pain Scale, Hollingshead Two-Factor Index of Socioeconomic Status	Quality of life	Controlling for age, pain, and SES, EF was found to be positively correlated with child- and parent-reported quality of life among children with SCD.
Anie & Green	2005	Psychological complications in sickle cell disease	Literature review with a focus on psychological coping, quality of life, and neuropsychology.	N/A	Psychological complications	With regard to the neuropsychological profile, SCD is associated with impaired verbal reasoning, visual-motor integration, attention, and EFs which are dependent on location of both overt and silent stroke (although to a lesser degree in the latter).
Armstrong Pavlakis, Goldman, Thompson, & Cuadra	2010	Neurocognitive function in sickle cell disease: Have we been missing something?	Editorial	N/A	Neurocognitive function	The author provides a very brief and general overview of the neurocognitive outcomes for those with SCD and calls for action to consider the role of SCD related complications when evaluating academic and vocational achievement (as compared to attributing any impaired performance to SES factors).

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Author(s)	Year	Title	Methodology & Sample	Psychometric Measures	Outcomes	Relevant Findings
Baker et al.	2008	African American physicians and organized medicine 1846-1968	Literature review based on the American Medical Association (AMA)'s invitation to a panel of experts to review and analyze the historical roots of the black-white divide in U.S. medicine.	N/A	Segregation, bias, and exclusion against African American physicians and their patients.	There is a history of discrimination and exclusion against Black physicians which continues to impact Black physicians and their patients.
Brown et al.	2000	Neurocognitive functioning and magnetic resonance imaging in children with sickle cell disease	Cross-sectional study in which 63 children and adolescents with SCD underwent neuropsychological assessment after referral by investigators due to concern for learning problems and adjustment difficulties.	Wechsler Intelligence Scale for Children-III (WISC-III), Woodcock-Johnson Psychoeducational Test Battery: Tests of Achievement-Revised (WJ-R), Cancellation A's Task, Trail Making Test, Boston Naming Test, Rapid Automized Naming (RAN), Purdue Pegboard, Child Behavior Checklist (CBCL), Vineland Adaptive Behavior Scales	Neurocognitive function	Children with history of either overt or silent stroke demonstrate differences from their peers with regard to attention and EF. These deficits are attributed to frontal lobe dysfunction.
Cahill et al.	2019	Sickle cell trait and cognitive function in African Americans: The reasons for geographic and racial differences in stroke (REGARDS) cohort	Longitudinal study in which 7,743 Black and White individuals (583 with SCT) with a mean age of 63 underwent psychological assessment.	Six-Item-Screener (SIS)	Neurocognitive function	Individuals with SCT are more likely to have hypertension. In regard to the neuropsychological screening, those with SCT showed little change over time in word list learning and recall, however, processing time slowed with age and this affected performance on timed tasks.

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Author(s)	Year	Title	Methodology & Sample	Psychometric Measures	Outcomes	Relevant Findings
Christ, Moinuddin, McKinstry, DeBaun, & White	2007	Inhibitory control in children with frontal infarcts related to sickle cell disease	Cross-sectional study in which 52 children ages 6 to 18 years underwent neuropsychological assessment. Those in the clinical group were diagnosed with SCD.	Stimulus-response reversal inhibitory task	Inhibitory control	Children with SCA and frontal infarcts made significantly more errors in an inhibitory control task than children with SCA without history of infarct.
Crawford & Jonassaint	2016	Adults with sickle cell disease may perform cognitive tests as well as controls when processing speed is taken into account: A preliminary case-control study	Cross-sectional study in which 31 patients with SCD (mean age of 33) and 17 controls (mean age of 36) underwent neuropsychological assessment.	CNS Vital Signs, Stroop test and unspecified measures of memory, finger tapping, symbol digit coding, shifting attention, and continuous performance	Processing speed	Results corroborated earlier studies which found that there is at least a 10-point deficit in processing speed among SCD patients, however, when differences in processing speed are accounted for, those in the SCD group performed as well as controls on various cognitive tasks.
DeBaun et al.	2012	Silent cerebral infarcts: A review on a prevalent and progressive cause of neurological injury in sickle cell anemia	Literature review	N/A	Neurological injury	Risk for silent stroke is greatest in childhood. Individuals with overt stroke generally have the most impaired cognitive skills, followed by individuals with silent stroke, then individuals with no stroke history.
DeBaun et al.	1998	Cognitive screening examinations for silent cerebral infarcts in sickle cell disease	Cross-sectional study in which 28 individuals with SCD ages 7 to 21 years underwent neuropsychological evaluation.	TOVA, WCST, CVLT-C	Attention & EF	Screening for attention and EF were the most reliable in identifying patients with history of silent stroke.
El-Haj & Hoppe	2018	Newborn screening for SCD in the USA and Canada	Literature review	N/A	Newborn screening	Newborn screening for SCD has been in place across all 50 states since 2006. This has improved the prognosis for individuals with SCD through timely access to early intervention services and prophylactic treatment. The authors note that there are few studies that have evaluated the long-term health outcomes in adults with SCD.

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Author(s)	Year	Title	Methodology & Sample	Psychometric Measures	Outcomes	Relevant Findings
Gaston et al.	1986	Prophylaxis with oral penicillin in children with sickle cell anemia: A randomized trial	Randomized, double-blind, placebo-controlled clinical trial examined whether administration of oral penicillin would reduce the incidence of septicemia in children with SCA under the age of 3. 105 children received the drug while 110 children received a placebo.	N/A	Septicemia	Children with SCA have an increased susceptibility to bacterial infections. Prophylactic oral penicillin was effective in reducing the incidence of infection by 84%. The authors concluded that those screened for SCD during the neonatal period should begin prophylactic penicillin by 4 months of age.
Hijmans et al.	2011	Neurocognitive deficits in children with sickle cell disease: A comprehensive profile	Cross-sectional study in which 41 children with SCD and 38 SES-matched controls underwent neuropsychological evaluation.	WAIS-III, WISC-III, Stop task, Tower of London, N-back task, Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI)	Neurocognitive function	SCD was associated with lower IQ scores and more than 1 in 3 children with SCD had a FSIQ below 75. Deficits were also noted in visuo-motor functioning and EF.
Jacobs, Rolle, Ferrans, Whitaker, & Warnecke	2006	Understanding African Americans' views of the trustworthiness of physicians	Focus groups were conducted at 2 sites (a hospital and a community advocacy organization). Participants were all African American and included 32 women and 34 men.	N/A	African Americans' distrust in healthcare	Factors contributing to African Americans' distrust in physicians include a lack of interpersonal and technical competence, perceived quest for profit and expectations of racism and experimentation during routine provision of health care. Distrust inhibits care-seeking and may lead to nonadherence.
Jorgensen et al.	2017	Disease severity and slower psychomotor speed in adults with sickle cell disease	Cross-sectional study in which 88 adults with SCD underwent neuropsychological screening as well as a blood draw.	Digit Symbol Substitution Test (DSST)	Processing speed	Impairment in psychomotor speed was indicated with no significant correlation related to history of stroke or severity of anemia. Those with more severe genotypes had more slowing than those with moderate genotypes. *Note: The authors state that there is impairment although the T-scores are in the average range.
Kassim et al.	2016	Silent cerebral infarcts and cerebral aneurysms are prevalent in adults with sickle cell anemia	Cross-sectional study in which 60 adults with SCA underwent neuroimaging using MRI as well as magnetic resonance angiography (MRA).	N/A	SCI, aneurysm	SCI was found in 53% of the participants. Adults with SCA also have a higher prevalence of cerebral aneurysm than would be expected in healthy individuals (9% observed).

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Author(s)	Year	Title	Methodology & Sample	Psychometric Measures	Outcomes	Relevant Findings
Kawadler et al.	2016	Intelligence quotient in paediatric sickle cell disease: A systematic review and meta-analysis	A meta-analysis was conducted utilizing articles with a pediatric SCD population, MRI information, and a Weschler IQ. Ultimately, 19 articles were included and compared 3 groups: stroke vs SCI, SCI vs no SCI, and no SCI vs healthy controls.	Any Weschler intelligence scale (e.g., WASI, WISC, or WAIS)	Full-Scale IQ	Children with stroke had an IQ of approximately 10 points lower than those with SCI, those with SCI had an IQ approximately 6 points lower than those with no SCI, and patients with no SCI had an IQ approximately 7 points lower than healthy controls. Children with SCD and no apparent MRI abnormality have significantly lower IQ than healthy controls.
Kawadler et al.	2015	White matter damage relates to oxygen saturation in children with sickle cell anemia without silent cerebral infarcts	Cross-sectional study in which 25 children with SCA and 14 age- and race-matched controls underwent MRI.	N/A	White matter abnormalities	There are significant white matter abnormalities even in asymptomatic children diagnosed with SCA. These abnormalities are taken as evidence for the effects of chronic hypoxia on the central nervous system.
Kennedy, Mathis, & Woods	2007	African Americans and their distrust of the healthcare system: Healthcare for diverse populations	Historical perspective on African Americas' distrust of the healthcare system.	N/A	African Americans' distrust in healthcare	African Americans are often hesitant to participate in biomedical research due to historically rooted mistrust.
Kinney et al.	1999	Silent cerebral infarcts in sickle cell anemia: A risk factor analysis	Longitudinal study in which 42 children with SCD and no known history of CVA underwent medical workup.	N/A	SCI	Children with history of seizures were 15x more likely to have SCI. Lower hemoglobin level was among other medical factors associated with higher rates of SC. Elevated WBC were also associated with SCD.
Mackin et al.	2014	Neuroimaging abnormalities in adults with SCA	Cross-sectional study in which 120patients with SCA and 33 healthy controls underwent neuropsychological assessment and medical workup.	WAIS-III	Neurocognitive function, neuroimaging findings	Individuals with SCA have thinner frontal lobe cortex and reduced basal ganglia and thalamus volumes compared to healthy controls. Reduced volume of the basal ganglia and thalamus were significantly associated with lower performance IQ, perceptual organization, and working memory scores; however, frontal lobe cortex thickness was not significantly associated with any cognitive measures.

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Author(s)	Year	Title	Methodology & Sample	Psychometric Measures	Outcomes	Relevant Findings
Niihara et al.	2018	A phase 3 trial of L-glutamine in sickle cell disease	230 patients with SCA participated in a randomized, placebo-controlled, double-blind, phase 3 trial,	N/A	Pain crises	L-glutamine (brand name Endari) was effective in reducing pain crises, acute chest syndrome, and hospitalization days.
Ohene-Frempong et al.	1998	Cerebrovascular accidents in sickle cell disease	Longitudinal study in which 4,082 patients with SCD were followed for an average of 5.2 years to assess age-related prevalence and incidence of CVA.	N/A	CVA	Overall, individuals with SCD have higher rates of CVA. More specifically, those with SCA had the highest rates followed by other forms of SCD.
Paquin et al.	2019	Oral morphine protocol evaluation for the treatment of vaso-occlusive crisis in paediatric sickle cell disease	Retrospective chart review of patients with SCD who sought medical care due to pain crises.	N/A	Hospitalization rate	The use of oral morphine was effective in decreasing the need for hospitalization and intravenous medication.
Paulukonis et al.	2016	Emergency department utilization by Californians with sickle cell disease, 2005-2014	Retrospective chart review of patients with SCD who presented to the emergency department.	N/A	Emergency department utilization rates	The study examined emergency department utilization in California with SCD. 9/10 patients were treated and released during the span of the study; The average number of ED visits was 2.1 visits per year.
Pegelow et al.	2002	Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease	Longitudinal study in which 266 children and adolescents with SCD underwent MRI.	N/A	Neuroimaging findings	Researchers report that most lesions in girls occurred before age 6, whereas boys remained at risk until age 10. Overt stroke was less likely to be found in the frontal or parietal cortex than silent strokes. Children with SCI had an increased incidence of new overt stroke and new or more extensive silent stroke.
Rees et al.	2003	Guidelines for the management of the acute painful crisis in sickle cell disease	Medline was searched via PubMed from 1965 to 2001 to identify hematologists with a known interest in SCD. They were then contacted and invited to submit guidelines for the management of sickle cell pain.	N/A	Pain	Guidelines were established to provide a basic, minimum standard of care for patients with SCD experiencing pain crises. Suggestions include rapid admission to the hospital, analgesics within 30 minutes of arrival, and ruling out serious complications such as infection, acute chest syndrome, or neurological events.

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Author(s)	Year	Title	Methodology & Sample	Psychometric Measures	Outcomes	Relevant Findings
Routhieaux, Sarcone, & Stegenga	2005	Neurocognitive sequelae of sickle cell disease: Current issues and future directions	Literature review to identify areas for future research	N/A	Neurocognitive function	Overt stroke and SCI are both major complications of SCD. Stroke, including silent stroke, is associated with decreased IQ, math achievement, verbal abilities, and visual-motor integration. While the author believes care is commonly sought for the physical symptoms of SCD, they argue that this is not the case when it comes to neurocognitive effects.
Schatz, Brown, Pascual, Hsu, & DeBaun	2001	Poor school and cognitive functioning with silent cerebral infarcts and sickle cell disease	Cross-sectional study in which 19 children with SCA and history of SCI, 45 children with SWCD and no history of SCI, and 18 healthy sibling controls underwent neuropsychological screening battery as well as medical workup.	Boston Naming Test, Cancellation of A's, CVLT-C, Differential Abilities Scale (DAS), Judgment of Line Orientation, Rapid Automized Naming, Peabody Picture Vocabulary Test (PPVT), Purdue Pegboard, TOVA, Trail Making Test, Wide Range Assessment of memory and Learning (WRAML), WJ-R, Word Fluency	Neurocognitive function	Children with SCI had twice the rate of school difficulties as children without them. Eighty percent of SCI cases had clinically significant cognitive deficits, whereas 35% had deficits in academic skills. Children with SCI show high rates of poor educational attainment, cognitive deficits, and frontal lobe injury. Poor school performance in SCD is one indicator of SCI.
Schatz, Finke, Kellett, & Kramer	2002	Cognitive functioning in children with sickle cell disease: A meta-analysis	Meta-analysis of studies of cognition in SCD to determine the size of any statistical difference between children with SCD and controls.	British Abilities Scale (BAS), Cancellation of Recurring Figures Test, DAS, Detroit Test of Learning Aptitude-2, Goodenough-Harris Drawing Test, Kaufman Assessment Battery for Children (K-ABC), Luria Nebraska Neuropsychological Battery for Children, Matching Familiar Figures Test, Stanford-Binet Intelligence Test (S-B), VMI, WAIS, WCST, WISC, WISC-R, WISC-III, WMS	Neurocognitive function	Results were small, however, there was a 4.3 difference in IQ when comparing children with SCD to healthy controls. *Note: Analysis consolidated various measures of intelligence.

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Author(s)	Year	Title	Methodology & Sample	Psychometric Measures	Outcomes	Relevant Findings
Silva et al.	2009	Brain magnetic resonance imaging abnormalities in adult patients with sickle cell disease: Correlation with transcranial doppler findings	Cross-sectional study in which 50 adult patients with SCD underwent MRI.	N/A	Neuroimaging findings	MRI abnormalities were noted in 60% of adult patients with SCD which is higher than the incidence seen in healthy children.
Smith et al.	2008	Daily assessment of pain in adults with sickle cell disease	Prospective cohort study in which 232 patients with SCD age 16 and older completed a daily pain diary for up to 6 months.	N/A	Pain	Pain in patients with SCD is primarily managed at home; however, pain episodes should be considered the rule rather than the exception. Previous studies likely underestimate the prevalence of pain in the SCD population.
Switzer, Hess, Nichols, & Adams	2006	Pathophysiology and treatment of stroke in sickle-cell disease: present and future	Literature review of the epidemiology, clinical spectrum, and pathophysiology of stroke in SCD to identify potential therapeutic targets.	N/A	Therapeutic targets	Overt strokes are associated with occlusion of the larger arteries while silent stroke is associated with occlusion of the smaller arteries and more commonly affect white matter.
Thogmartin et al	2011	Sickle cell trait-associated deaths: A case series with a review of the literature	Case study and literature review of 16 expired individuals with SCT.	N/A	Mortality	An analysis of SCT fatality indicated that despite seeking medical treatment, SCT-related micro-occlusive crisis (often associated with exertion) was inadequately considered in the differential diagnosis. Several of these cases were associated with sudden death.
Thust, Burke, & Siddiqui	2014	Neuroimaging findings in sickle cell disease	Literature review of the neuroradiological findings in patients with SCD.	N/A	Neuroimaging findings	Neuroradiological findings in patients with SCD are common and are typically, but not always, due to vasculopathy. Coexisting acute and chronic pathology may pose challenges to interpretation.
van der Land et al.	2016	Risk factor analysis of cerebral white matter hyperintensities in children with sickle cell disease	Cross-sectional study in which 40 children with SCD underwent medical workup including MRI.	N/A	Neuroimaging findings	Several key points were made. Firstly, boys are at an increased risk for WMH. Secondly, lower HbF was associated with larger WMH volume. This suggests that HbF may be protective for WMHs and endothelial dysfunction may contribute to the development of WMHs by reducing cerebral blood flow.

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Author(s)	Year	Title	Methodology & Sample	Psychometric Measures	Outcomes	Relevant Findings
Vichinsky et al.	2010	Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia	Cross-sectional study in which 149 adult participants with SCA underwent neuropsychological screening and MRI.	D-KEFS, TEA, WAIS-III	Neurocognitive function, Neuroimaging findings	This study was the first to evaluate neuropsychological outcomes in an adult SCD population. Although there were no significant group differences with regard to total gray matter or hippocampal volume, participants with SCD demonstrated significantly lower FSIQ and processing speed when compared to healthy demographically matched controls.
Wang et al.	2001	Neuropsychologic performance in school-aged children with sickle cell disease: A report from the Cooperative Study of Sickle Cell Disease	Longitudinal study in which 373 children with SCD underwent neuropsychological screening battery as well as MRI	WJ-R, WISC-R, WISC-III	Neurocognitive function	Researchers evaluated neuropsychological functioning in a SCD population with history of SCI (in the absence of overt stroke). Overall, participants with history of SCI demonstrated poorer performance than healthy controls on various measures.
Webb & Kwiatkowski	2013	Stroke in patients with sickle cell disease	Literature review which discusses the current understanding of the epidemiology, risk factors, and pathophysiology of small and large vessel disease, primarily in pediatrics.	N/A	Overt stroke	This article reviews current understanding of the epidemiology, risk factors and pathophysiology of stroke with a focus on pediatrics.
Yanamandra et al.	2018	A case of autosplenectomy in sickle cell trait following an exposure to high altitude	Case study of a 24-year-old man with SCT who experienced autosplenectomy following exposure to high altitude.	N/A	Autosplenectomy	Individuals with SCT can be asymptomatic until exposure to severe hypoxia at which time they can manifest clinically with sickle cell syndrome.

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Appendix B

IRB Approval

PEPPERDINE

Pepperdine University
24255 Pacific Coast Highway
Malibu, CA 90263
TEL: 310-506-4000

NOTICE OF APPROVAL FOR HUMAN RESEARCH

Date: February 12, 2019

Protocol Investigator Name: Christina Wade

Protocol #: 18-12-951

Project Title: IMPACT OF SICKLE CELL DISEASE ON EXECUTIVE FUNCTIONING IN AN ADULT POPULATION

School: Graduate School of Education and Psychology

Dear Christina Wade:

Thank you for submitting your application for exempt review to Pepperdine University's Institutional Review Board (IRB). We appreciate the work you have done on your proposal. The IRB has reviewed your submitted IRB application and all ancillary materials. Upon review, the IRB has determined that the above entitled project meets the requirements for exemption under the federal regulations 45 CFR 46.101 that govern the protections of human subjects.

Your research must be conducted according to the proposal that was submitted to the IRB. If changes to the approved protocol occur, a revised protocol must be reviewed and approved by the IRB before implementation. For any proposed changes in your research protocol, please submit an amendment to the IRB. Since your study falls under exemption, there is no requirement for continuing IRB review of your project. Please be aware that changes to your protocol may prevent the research from qualifying for exemption from 45 CFR 46.101 and require submission of a new IRB application or other materials to the IRB.

A goal of the IRB is to prevent negative occurrences during any research study. However, despite the best intent, unforeseen circumstances or events may arise during the research. If an unexpected situation or adverse event happens during your investigation, please notify the IRB as soon as possible. We will ask for a complete written explanation of the event and your written response. Other actions also may be required depending on the nature of the event. Details regarding the timeframe in which adverse events must be reported to the IRB and documenting the adverse event can be found in the *Pepperdine University Protection of Human Participants in Research: Policies and Procedures Manual* at community.pepperdine.edu/irb.

Please refer to the protocol number denoted above in all communication or correspondence related to your application and this approval. Should you have additional questions or require clarification of the contents of this letter, please contact the IRB Office. On behalf of the IRB, I wish you success in this scholarly pursuit.

Sincerely,

Judy Ho, Ph.D., IRB Chair

cc: Mrs. Katy Carr, Assistant Provost for Research