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Neuropsychological implications of nocturnal hypoxemia in sickle cell disease

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Graduate School of Education and Psychology

NEUROPSYCHOLOGICAL IMPLICATIONS OF NOCTURNAL HYPOXEMIA IN SICKLE CELL DISEASE

A dissertation submitted in partial satisfaction

of the requirements for the degree of

Doctor of Psychology

by

Sheena Ram

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Louis Cozolino, Ph.D. – Dissertation Chairperson

This clinical dissertation, written by

Sheena Ram

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:

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EDUCATION

2017 – 2021 (*expected*) Doctor of Psychology in Clinical Psychology
Graduate School of Education and Psychology
Pepperdine University

2011 – 2013 Master of Arts in Psychology
Graduate School of Education and Psychology
Pepperdine University

2006 - 2010 Bachelor of Science, Psychology with an emphasis in Biology
University of California, Davis

CLINICAL EXPERIENCE

August 2020 – Present *Pediatric Neuropsychology & Psychology Intern*
Primary Children's Hospital
Pediatric Behavioral Health
Training Director: Natalie Sergent, Psy.D.
Primary Supervisors: John Fulton, Ph.D., ABPP-CN
Laura Bennett-Murphy, Ph.D.

Neuropsychology Rotation – 50%

- Provide neuropsychological assessment services to children ages 2 to 18 years in both outpatient and inpatient settings. Patient populations include a wide range of medical diagnoses that impact central nervous system functioning including congenital heart disease, stroke, cerebral palsy, hydrocephalus, and traumatic brain injury
- Assessment services include review of pertinent historical data (including electronic medical record and previous evaluations), consultation with the medical teams, family and school, designing a test battery to best address the referral question, administration of neuropsychological assessment measures, scoring and interpretation, provision of feedback and psychoeducation, and delivery of a comprehensive integrated report. Assessments completed in two separate settings
    - Outpatient Pediatric Behavioral Health Clinic: Includes patients referred by both medical teams within the hospital setting and community providers. Patients generally have a medical diagnosis that may impact central nervous system functioning
    - Neuroscience Trauma Unit: Includes assessment of pediatric patients with recent acquired brain injury during their hospitalization. Consultation is provided to both patients and their families, as well as the rehabilitation medical team regarding the

patient's acute neurocognitive functioning to assist with inpatient treatment plans, post-discharge services, and school reentry
- Recruit participants for the Teen Online Problem Solving (TOPS) program, which is a national, multi-site, evidenced-based online treatment program shown to be effective in improving behavioral outcomes after pediatric traumatic brain injury

Consultation & Liaison Rotation – 30%
- Provide psychological consultation and services to pediatric patients hospitalized on medical-surgical services where emotional and behavioral concerns impact medical care and treatment adherence
- Work collaboratively with interprofessional care teams including Cardiac Intensive Care Unit, Cardiology and Heart Transplant Team, Gastroenterology, Hematology/Oncology, Hospitalist Teams, Neonatal Intensive Care Unit, Neurology, Neuroscience Trauma Unit, and Pediatric Intensive Care Unit
- Populations served include infants, children, and young adults with a range of medical and/or psychiatric presentations including congenital heart disease, cancer and leukemia, gastrointestinal disorders, traumatic brain injury, somatic symptom and functional neurologic disorder, eating disorders, and epilepsy
- Common referral questions include assessing for and addressing anxiety and depression, suicidal ideation/risk assessment, delirium, noncompliance with treatment, pain management, and somatic symptom/functional neurological disorder
- Provide inpatient evidence-based short-term psychological interventions to address acute psychological concerns associated with hospitalization, treatment, and adjustment to medical conditions and assist with disposition planning following discharge
- Attend and participate in rounds and treatment team meetings within medical specialty teams

Outpatient Behavioral Health Rotation – 20%
- Provide evidence-based psychotherapy for children and adolescents experiencing mental health difficulties due to or impact of a medical condition
- Specific areas of intervention include adapting to acute and chronic medical conditions, complying with medical regimens, chronic pain management, reducing tic behaviors, and returning to baseline functioning secondary to functional neurologic disorder diagnosis

July 2019 – March 2020 *Pediatric Psychology Extern*
Loma Linda University Children's Hospital

Consultation & Liaison Service
Supervisors: Veronica Regueiro, Psy.D. &
Sharis Rostamian, Psy.D.

- Conduct pediatric inpatient consultation and liaison services to assess psychological, cognitive, and behavioral functioning in infants, children, and adolescents with a range of medical diagnoses (e.g., diabetes, cystic fibrosis, seizure disorder, cancer, traumatic brain injury, heart disease) and psychiatric problems (e.g., conversion disorders, psychogenic seizures, depression, suicidal ideation, anxiety disorders)
- Provide evidence-based interventions, psychoeducation, risk assessment and crisis intervention for children, adolescents, and their families while admitted to inpatient Pediatric Intensive Care, Hematology/Oncology & Stem Cell Transplant, Bone Marrow Transplant, Acute Adolescent, and General Pediatric units
- Collaborate with multidisciplinary team including physicians, psychiatrists, nurses, social workers, child life services, and patient care assistants to provide patient-centered holistic care through biopsychosocial integrative framework
- Complete medical chart review, intake interviews, and electronic medical record clinical note writing
- Attend weekly multidisciplinary didactic seminars focused on psychiatric and medical conditions common in pediatric populations
- Provide evidence-based psychological and cognitive rehabilitation interventions at *Totally Kids Rehabilitation Hospital*, an acute/subacute rehabilitation facility

July 2018 – June 2020

Neuropsychology Extern
Clinical Translational Science Institute
Children's Hospital Los Angeles
Supervisor: Sharon H. O'Neil, Ph.D., M.H.A., ABPP-CN, ABPdN

- Conduct outpatient clinical and research neurodevelopmental and neuropsychological evaluations with infants, children, adolescents, and young adults (ages 0-24)
- Diagnoses include brain tumors, sickle and non-sickle cell anemias, congenital heart disease, neurofibromatosis type 1, seizure disorders, craniosynostosis and preterm birth
- Responsibilities include review of medical and educational records; administration, scoring, and interpretation of measures; development of appropriate recommendations; and integrated report writing
- Attend weekly multidisciplinary team meetings with oncologist, nurse care practitioner, psychologist,

neuropsychologist, pharmacist, radiation oncologist within the Pediatric Hematology-Oncology and Pediatric Neurology departments
- Attend weekly brain-cutting seminars with neuropathologist
- Participated in an 8-week self-empowerment support group for 15 girls with cranio-facial differences through the Division of Plastic Surgery under the supervision Alessia Johns, Ph.D.

September 2017 – June 2020

Clinical Psychology Extern
Pepperdine University, Encino Community Clinic
Supervisor: Anat Cohen, Ph.D.

- Conduct individual and family therapy with children, adolescents, and adults
- Complete intake evaluation reports, including initial diagnostic and cultural case conceptualizations and weekly case progress notes and maintain current and accurate clinical documentation
- Participate in school observations and consultation with school personnel to assess child clients' academic and social functioning in school environment
- Participate in outreach presentations focused on bullying prevention at local elementary and middle schools

January 2018 – June 2018

Clinical Psychology Extern
Wiseburn Unified School District
Supervisor: Keegan Tangeman, Psy.D.

- Conducted individual and family therapy with children in elementary school environment
- Completed intake evaluation reports, weekly case progress notes, and maintained current and accurate clinical documentation
- Collaborated with teachers and school counselor
- Co-led social skills group with school counselor for 5 children

July 2018

Camp Counselor
Intensive Outpatient Summer Program
Rich & Associates
Supervisor: Erika C. Rich, Ph.D. & Seth Shaffer, Psy.D.

- Trained in behavioral management for intensive outpatient program for children and adolescents presenting with social and emotional difficulties
- Duties included monitoring behavioral plans for youngest age group (ages 5-7), which incorporated conversation skills, conflict negotiation, emotional regulation, social

communication, organization for play, collaboration, peer problem-solving, and group self-inclusion
- Assisted with providing individualized interventions and camp curriculum

August 2013 – January 2015 *Behavior Specialist*
Center for Behavioral, Educational, and Social Therapies (C.B.E.S.T.)
Supervisor: Shah Bahador, Psy.D.

- Provided Applied Behavioral Analysis to children ages 4-12 focusing on behavior management, emotional regulation, language and communication, socialization, academic, and independent daily living skills in school and home environments
- Monitored and updated short and long-term behavioral plans with case manager, supervisor, and families to optimize intervention

November 2010 - June 2011 *Co-Clinician*
Social Skills Program
UC Davis MIND Institute
Supervisors: Marjorie Solomon, Ph.D. & Erika Frieze, Psy.D.

- Served as co-clinician in group-based social skills intervention program for school-aged children diagnosed with autism spectrum disorders
- Focused on teaching strategies such as emotion recognition and regulation, empathy development, and coping skills

RESEARCH EXPERIENCE

June 2015 – June 2017 *Staff Research Associate*
Pregnancy Experiences & Infant Development Study
University of California, Irvine Conte Center & Chapman University
Principle Investigators: Laura Glynn, Ph.D. & Curt Sandman, Ph.D.

- Aided in lab coordination for NIH-funded study following women during and after pregnancy to examine the relationship between fetal exposure to fragmented maternal emotional states and subsequent emotional and cognitive development of children
- Collected data including health and psychosocial history, developmental and IQ performance, biosamples, anthropometric measures, and maternal/fetal heart rate
- Involved in recruiting pregnant women, consenting participants, scheduling appointments

June 2010 – August 2011 *Junior Specialist*
Infants at Risk of Autism: A Longitudinal Study

Neuroimaging for Infants at Risk of Autism: A Longitudinal Study
UC Davis MIND Institute
Principle Investigators: Sally Ozonoff, Ph.D. & David Amaral, Ph.D.

- Aided in lab coordination of NIH-funded study examining early behavioral markers in infants at risk for autism, beginning at 6 months of age
- Acquired data on attention, speech processing, motion understanding, and visual tracking data using Tobii eye-tracking technology
- Assisted magnetic resonance imaging technologists in acquiring research sequences
- Responsible for recruiting and consenting families, scheduling visits, and obtaining height, weight, and head circumference of infants

December 2009 – June 2010 *Research Assistant*
Infants at Risk of Autism: A Longitudinal Study
UC Davis MIND Institute, Undergraduate training
Supervisor: A.J. Schwichtenberg, Ph.D.

- Video recorded behavior of typically-developing infants, as well as those at risk of developing an autism spectrum disorder
- Coded behavior via video data using Noldus Behavioral Coding Suite
- Entered data for Autism Diagnostic Observation Schedule (ADOS) and Mullen Scales of Early Learning (MSEL)
- Provided childcare for participant siblings

SUPERVISING & TEACHING EXPERIENCE

July 2019 – June 2020 *Assessment Peer Supervisor*
Clinical Translational Science Institute
Children's Hospital Los Angeles
Supervisor: Sharon H. O'Neil, Ph.D., M.H.A.

- Participate in training incoming externs on the administration and scoring of psychometric measures
- Co-administer Bayley Scales of Infant Development, 3rd Edition
- Provide supervised supervision to one trainee through co-review of live video and video recording and of patient sessions

September 2019 – June 2020 *Clinical Peer Supervisor*
Pepperdine University, Encino Community Clinic
Supervisor: Anat Cohen, Ph.D.

- Selected to provide supervised weekly individual peer supervision for three beginning and intermediate doctoral-

level psychology trainees offering treatment to individuals in the community
- Utilize a competency-based consultation approach to foster the development of clinical skills, including comprehensive feedback on intake reports, case notes, and video recorded therapy sessions
- Review legal and ethical concerns, crisis management, professional development, maintaining appropriate boundaries, managing countertransference, and therapeutic techniques
- Participate in weekly supervision-of-supervision meetings
- Participate in weekly didactics of clinical supervision theory to enhance competencies

September 2019 – June 2020 *Teaching Assistant*
Pepperdine University
PSY 713: Advanced Psychological Assessment
Supervisor: Susan Himelstein, Ph.D.

- Grade exams for doctoral psychology students in advanced integrated assessment courses
- Facilitate assessment labs where students are trained and evaluated on assessment administration skills
- Check accuracy of students' scoring on the WAIS-IV, MMSE, Bender-II, MMPI-2, MCMI-IV, NEO PI-R, TAT, RISB, and Rorschach
- Provide written and oral feedback to assessment students

PUBLICATIONS

Ram, S., Howland, M. A., Sandman, C. A., Davis, E. P., & Glynn, L. M. (2018). Prenatal Risk for ASD: Fetal Cortisol Exposure Predicts Child Autism-Spectrum-Disorder Symptoms. *Clinical Psychological Science*, 2167702618811079.

PROFESSIONAL PRESENTATIONS

Ram, S., *Updates on Congenital Heart Disease and Neuropsychological Functioning*. APA-approved continuing education lecture presented at Children's Hospital Los Angeles, Los Angeles, CA. April 5, 2019.

Ram, S., Howland, M., Sandman, C., Davis, E., Glynn, L. (2017, April). *Prenatal Cortisol Exposures Predict Risk of Autism Spectrum Disorder Symptoms at 5-years of Age*. Poster presented at the Society for Research in Child Development (SRCD), April 6-8, 2017. Austin, TX.

Shen, M.D., Nordahl, C.W., Liston, S.E., DiNino, M., **Ram, S.**, Wootton-Gorges, S.L., Young, G.S., Ozonoff, S., Amaral, D.G. (2011, May). *Incidental MRI Findings in Infants at Risk for Autism*. Program No. 116.072. Poster presented at the International Meeting for Autism Research, San Diego, CA.

COMMUNITY OUTREACH PRESENTATIONS

March 1, 2019 &
November 27, 2018

Mindful Parenting
Presented at Alfred B. Nobel Charter Middle School
Northridge, CA

- Community outreach project targeting parents of local middle school students. Provided psychoeducation on responsive versus reactive parenting techniques, suggesting ways for parents to connect with their adolescent children in healthy, mindful ways

October 13, 2017 &
November 30, 2018

Join the Resistance and Stand Up to Bullying
Presented at Gaspar de Portola Middle School
Tarzana, CA

- Annual community outreach project targeting local middle school students. Provided psychoeducation about the prevalence and effects of bullying in schools, suggesting ways for students to get involved to stop its occurrence

January 26, 2018

Stand Up to Bullying: Parent Presentation
Presented at Nevada Avenue Elementary School,
Canoga Park, CA

- Community outreach project targeting parents of local middle school students. Provided psychoeducation about the prevalence and effects of bullying in schools, suggesting ways for parents to notice effects in their children as victims, bullies, and bystanders

ABSTRACT

Neuropsychological impairments have been observed in both individuals with sleep-disordered breathing and in individuals with sickle cell disease (SCD), but there has been little research on the potential effect of sleep-disordered breathing on neuropsychological function in individuals with SCD. This study aims to examine the effect nocturnal oxygen desaturations have on neuropsychological functioning in individuals with sickle cell disease when compared to those with non-sickle anemia and healthy controls. Thirty-four participants with SCD, 18 non-sickle anemia controls (ACTL), and 29 healthy controls (CTL), ages 9 to 63 years, participating in an IRB-approved Children's Hospital Los Angeles study of cerebral blood flow underwent neuropsychological evaluation examining general intelligence (WASI-II FSIQ), processing speed (WISC-IV/WAIS-IV Coding), inhibition (D-KEFS Color-Word Interference Inhibition), and cognitive flexibility (D-KEFS Color-Word Interference Inhibition/Switching). Oxygen saturation via finger plethysmography was recorded for 24 hours. When comparing the SCD group with the ACTL group, the ACTL group performed better on measures of processing speed, inhibition, and cognitive flexibility. With regard to an interaction between oxygen desaturations and disease status impacting processing speed, significant differences were found when comparing the SCD group with the CTL group. Significant differences were also found when comparing the SCD group with the ACTL group. Simple slope analysis revealed that in both cases, higher values of nocturnal oxygen desaturations predicted lower processing speed scores for the SCD group when compared to both the ACTL and CTL groups, suggesting a moderating effect of oxygen desaturations on processing. Participants with SCD in this study performed more poorly on measures of processing speed, inhibition, and cognitive flexibility when compared to those with non-sickle anemia. Further, individuals with SCD with higher nocturnal oxygen desaturations had a slower speed of processing when compared to healthy controls and those with non-sickle anemia. Neuropsychological assessment may identify those at risk and

early rehabilitation efforts restoring oxygen may lead to a greater recovery of function and a higher quality of life for this vulnerable population.

Chapter 1: Statement of the Problem

Sickle cell disease (SCD) refers to a group of inherited hemoglobin disorders and is one of the most common severe monogenetic disorders in the world (Rees et al., 2010). The incidence is estimated to be approximately 300,000 neonates globally each year, with the majority in sub-Saharan Africa and numbers predicted to increase over the next 40 years (Kato et al., 2018; Piel et al., 2013). Due to historic slave trading and contemporary population movements, the distribution of SCD has spread beyond its origins, particularly in North America and Western Europe (Kato et al., 2018; Piel et al., 2013, 2017). In the United States, SCD affects approximately 100,000 individuals, with 1 in 356 African Americans and 1 in 16,300 Hispanic Americans affected (Centers for Disease Control and Prevention [CDC], 2020). SCD also affects people from southern European, Middle Eastern, and Asian Indian backgrounds (National Heart, Lung, and Blood Institute, n.d.c).

Most of the literature to date has focused solely on the pediatric SCD population. With the advent of newborn screening, penicillin prophylaxis, pneumococcal immunization, and education about disease complications, early childhood death rates in individuals with SCD have improved significantly, particularly in high-income countries (Kato et al., 2018). The survival of children with SCD in high-income countries is approaching that of unaffected children. However, in sub-Saharan Africa, where there is a lack of newborn screening and routine childhood vaccinations and where malaria, malnutrition, and poverty remain important challenges, the mortality among children with SCD who are younger than 5 years of age can be as high as 90% (Grosse et al., 2011; Makani et al., 2010; Piel et al., 2017; Telfer et al., 2007).

In 1973, it was estimated that the median survival age of SCD individuals in the United States was 14.3 years, with 20% of deaths occurring before the fifth year of life, half between 5 and 30 years of age, and one sixth after the age of 30. By the late 1980s, the Cooperative Study

of Sickle Cell Disease (CSSCD) reported approximately 85% of children and adolescents with sickle cell anemia survived to 20 years of age (Leikin et al., 1989). Platt and colleagues (1994) followed 3764 patients with SCD and found about 50% of patients survived beyond the fifth decade (Platt et al., 1994). Life expectancy has remained at 50 years and while research on adults with SCD is emerging, continued efforts are necessary to examine longer-term outcomes in this population.

While life expectancy has increased, implications of the disease continue to have overwhelming effects on the quality of life for these individuals. Medical complications linked to hypoxemia[1] and occlusion, like pain episodes, splenic infarctions, infections, and acute chest syndrome continue to be a concern and a large reason for frequent hospitalizations. Similarly, as blood supply and oxygen to the brain is decreased, there can be significant neurological effects, including silent cerebral infarcts and stroke. As a potential consequence of oxygen deprivation, neuropsychological dysfunction has also been observed in individuals with SCD. Neuropsychological dysfunction may be the most important and least studied problem affecting this population (Vichinsky et al., 2010). Hypoxia[2] in the brain directly related to the disease is thought to be an underlying mechanism for neuropsychological impairments. Similarly, a growing body of evidence has linked disordered breathing during sleep with SCD, and it has been suggested that these two diseases share common pathophysiological pathways, including hypoxia. Neuropsychological impairments have been observed in both individuals with sleep-disordered breathing and in individuals with SCD, but there has been little research on the potential effect of sleep-disordered breathing on neuropsychological function in individuals with SCD. While medical research on older individuals with SCD continues to expand, a better

[1] Hypoxemia is a low level of oxygen in arterial blood.
[2] Hypoxia is when an area of the body is deprived of oxygen.

understanding of the neuropsychological impact of SCD is crucial. This study aims to examine the effect nocturnal oxygen desaturations have on neuropsychological functioning in individuals with sickle cell disease.

Chapter 2: Review of the Literature

According to the National Heart, Lung, and Blood Institute (NHLBI), anemia is the most prevalent blood disorder and it affects more than 3 million Americans (NHLBI, n.d.a). The most common cause of anemia is a deficiency of iron, which is needed to produce hemoglobin. Red blood cells carry hemoglobin, an iron-rich protein that attaches to oxygen in the lungs and carries it to tissues throughout the body. Anemia occurs when an individual does not have enough red blood cells or when these cells do not function properly. As a result, there is a lack of oxygen which can lead to fatigue, shortness of breath, dizziness, irregular heartbeat, chest pain, and headaches (American Society of Hematology, n.d.). Common types of anemia include iron-deficiency anemia, vitamin-deficiency anemia, aplastic anemia, and hemolytic anemia. Hemolytic anemias develop when red blood cells are destroyed in the bloodstream or spleen faster than bone marrow can replace them. Anemia can also occur during the course of pregnancy and as a result of other diseases, such as kidney disease, and from treatments like chemotherapy. Thalassemia, characterized by less hemoglobin and fewer red blood cells than normal, can also cause anemia. Sickle cell anemia, also referred to as sickle cell disease, is a common, inherited type of hemolytic anemia where abnormal hemoglobin changes the shape of blood cells, which causes cell death earlier than normal red blood cells. This leads to a deficiency of red blood cells in the body. Sickle cell disease affects thousands of individuals worldwide, and rates are predicted to increase. This disease causes significant medical and neuropsychological complications which impact the daily functioning and quality of life of these individuals (American Society of Hematology, n.d.). Sickle cell disease is a genetic condition that is present at birth and defines a group of diseases characterized by gene mutations that create abnormal proteins in red blood cells, called hemoglobin S (HbS; Kato et al., 2018). Once oxygen is unloaded to the tissues, the abnormal HbS allele causes rigid, non-liquid protein strands to form

within the red blood cell. These rigid protein strands distort the shape of the cell, causing the sickled red blood cell that gives the disease its name (NHLBI, n.d.c). Repeated deoxygenation cycles cause permanent red-cell damage (Ilesanmi, 2010). Sickle-shaped cells are inflexible and can stick to vessel walls, causing blockages that can slow or stop the flow of blood. As a result, oxygen is prevented from reaching nearby tissues, leading to sudden pain attacks, called vaso-occlusive crises, which often lead to hospitalization (NHLBI, n.d.c). Recurrent episodes of vaso-occlusion and inflammation result in progressive damage to most organs, including the brain, kidneys, lungs, bones, and cardiovascular system, which become more apparent with increasing age (Rees et al., 2010). Along with organ damage, other common complications in SCD include infection, acute chest syndrome, and stroke (CDC, 2020; Kato et al., 2018). Chronic complications fall into two main groups: those related to large vessel vasculopathy, such as cerebrovascular disease, pulmonary hypertension, priapism, and retinopathy and those caused by progressive ischemic organ damage, namely, hyposplenism, as well as renal failure, bone disease, and liver damage (Piel et al., 2017). Hyposplenism, or diminished functioning of the spleen, is particularly important as a cause of illness and death in young children due to increased risk of infection (Piel et al., 2017). Additionally, sickled cells cannot change shape easily which eventually leads to early cell death, or apoptosis (Fadok et al., 2001; Kato et al., 2018).

Normal red blood cells live about 90 to 120 days, but sickled cells last only 10 to 20 days. Due to this increased rate of cell death, the body may have trouble generating new blood cells as quickly as cells being destroyed. This leads to a constant shortage of red blood cells, causing anemia (CDC, 2020; National Heart, Lung, and Blood Institute [NHLBI], n.d.c).

Genotypes

The term sickle cell disease is an umbrella term used to refer to different genotypes that cause the characteristic clinical syndrome. SCD is caused by the inheritance of abnormal beta-globin alleles carrying the sickle mutation on the HBB gene (Rees et al., 2010). When an individual inherits this abnormal allele from both parents, the most common and most severe form of the disease is expressed, called HbSS, or more commonly, sickle cell anemia (SCA; Ware et al., 2017). Other forms of sickle cell disease include compound heterozygous conditions. A milder form of SCD occurs when a child inherits a sickle cell HbS gene from one parent and a gene for abnormal hemoglobin called HbC from the other parent. HbS beta thalassemia (HbS/β^0-thalassaemia or HbS/β^+-thalassemia) occurs when an HbS gene is inherited from one parent and one gene for beta (β**)** thalassemia, another type of anemia, from the other parent. There are two types of β thalassemia: "0" and "+". Those with HbS/β^0-thalassemia usually have a severe form of SCD, while people with HbS/β^+-thalassemia tend to have a milder form of the disease (NHLBI, 2014).[3] Rarely, HbS may combine with other beta-globin variants resulting in HbS, HbSE, HbSO, all of which express sufficient HbS to cause intracellular sickling (Ware et al., 2017). The severity of these rarer types of SCD varies (see Table 1).

Individuals who inherit one HbS gene and one normal hemoglobin gene have sickle cell trait and usually do not have any signs of the disease (HbAS). The amount of HbS present is insufficient to produce sickling manifestations under most circumstances. However, HbAS individuals are at risk for several complications, as extremes of physical exertion, dehydration, and high altitudes can induce sickle cell vaso-occlusive events (Bender, 2017; Key & Derebail,

[3] The genotype Sβ^0-thalassemia (HbS/β^0-thalassemia) is often included in SCA as the subtypes present similarly (NHLBI, 2014).

2010; Mitchell, 2007). Notably, HbAS individuals are carriers and can pass the trait on to their children (CDC, 2020; National Heart, Lung, and Blood Institute [NHLBI], n.d.c)[4].

Table 1

Genotypes and Clinical Presentations of Sickle Cell Disease

Diagnosis	Gene Type	Cardinal Symptoms
Sickle Cell Disease	HbSS	Sickle-cell crises/pain crises Acute organ syndromes Chronic hemolytic anemia
HbS heterozygosity	HbAS	No apparent illness
Sickle-cell β^{+} - Thalassemia	HbS β^{+} - thalassemia	Variable, mild SCD
Sickle-cell β^{0} - thalassemia	HbS β^{0} - thalassemia	Severe SCD
HbSC disease	HbSC	Weak symptoms of SCD Chronic hemolytic anemia
HbC disease	HbCC	Pain crises Organ events Chronic hemolytic anemia
HbC heterozygosity	HbAC	No apparent disease

Malaria Hypothesis

The geographical distribution of the β^{s} allele is thought to be driven both by the malaria endemic and population movements over time (Kato et al., 2018). The sickle cell trait (HbAS) provides a remarkable level of protection against *Plasmodium falciparum* malaria, and while exact mechanisms of protection are still being debated, the malaria hypothesis, proposed in the early 1950s by Haldane and Allison, offer an explanation of how the proliferation of sickle cell disease is a result of natural selection and balanced polymorphism (Allison, 1954; Haldane, 1949, 1990; Kato et al., 2018; Piel et al., 2010, 2017). Individuals with the sickle cell trait (heterozygotes, HbAS) have the biological advantage, and are thought to be malaria-resistant. While individuals with the sickle cell trait can still get malaria, they tend to have lower levels of

[4] Historically, the term "sickle cell anemia (SCA)" was used to describe individuals homozygous for HbS. There has been a shift to use the umbrella term "sickle cell disease (SCD)," and should be followed by a detailed genotypic description for the individual (e.g., HbSS, HbSC, or HbS/β^{+}-thalassemia; Bender, 2017). SCD will be used throughout this document for consistency.

parasitized red cells in their blood and it is theorized that as these cells become sickled (likely as a result of deoxygenation and lowering pH caused by the parasite), they get removed by macrophages and the spleen which interrupts reproduction of the parasite (Luzzatto, 2012; Luzzatto & Pinching, 1990). Interestingly, it is estimated that individuals with HbAS are up to 90% less likely to experience severe malaria than individuals with normal Hb, which explains the frequency of the β^s allele throughout sub-Saharan Africa, parts of the Mediterranean, the Middle East, and India (Kato et al., 2018; Piel et al., 2010).

On the other hand, homozygotic individuals suffering from SCA (HbSS) are highly susceptible to the lethal effects of malaria. These individuals are at an extreme disadvantage in areas of high malaria transmission as malaria will make the anemia worse, and potentially life-threatening. Notably, impaired splenic functioning, common in individuals with SCA, may not effectively filter and remove parasitized red cells. Also, malaria, like any other acute infection, can trigger pain crises in these individuals (Luzzatto, 2012). It is estimated that 50-90% of children with SCA who live in sub-Saharan Africa die by 5 years of age, mostly due to infections like pneumococcal disease and malaria (Grosse et al., 2011; Kato et al., 2018; McAuley et al., 2010; Williams et al., 2009).

Medical Complications

Signs and symptoms of anemia in general can vary depending on the form and the severity. Some people may have no symptoms, while others may experience several complications due to the lack of oxygen in the body. Fatigue is considered the most common symptom, while weakness, shortness of breath, dizziness, chest pain, irregular heartbeat, headaches, cold extremities, and pale or yellowing skin may also be experienced (American Society of Hematology, n.d.). Individuals with sickle cell disease may experience these signs and symptoms, in addition to disease specific complications.

A number of complications occur in sickle cell disease reflecting the complexity of its pathophysiology. While the severity of disease manifestation varies, several clinical manifestations of SCD result from intermittent episodes of microvascular occlusion leading to tissue ischemia (restriction in blood supply to tissues) and reperfusion (a restoring of blood flow) injury and chronic hemolysis, both contributing to multiorgan dysfunction (Bender, 2017). Reperfusion injury is the tissue damage caused when blood supply returns to tissue after a period of ischemia. The lack of oxygen and nutrients from blood during the ischemic period creates a condition in which the restoration of circulation results in inflammation and oxidative damage through the induction of oxidative stress along with restoration of normal function (Carden & Granger, 2000). In higher-income countries, acute complications are rarely fatal for children, but can be lethal for adults due to chronic organ dysfunction (Couque et al., 2016; Ware et al., 2017).

Vaso-occlusive Events

Ischemia and reperfusion damage to tissues lead to pain and acute or chronic injury affecting organ systems. The bone marrow, spleen, liver, brain, lungs, kidneys, and joints are usually affected (Almeida & Roberts, 2005; Bender, 2017; Darbari et al., 2012; Wood et al., 2012).

Vaso-occlusive pain episodes. Acute pain is the hallmark clinical feature of sickle cell disease, reflecting vaso-occlusion and impaired oxygen supply (Ware et al., 2017). These episodes account for the majority of SCD-related hospital admissions as well as school or work absences (Gill et al., 1995). Vaso-occlusion is caused by blocked blood flow in small blood vessels, depriving downstream tissues of nutrients and oxygen. This results in tissue ischemia and tissue death causing severe pain (Bender, 2017).

Splenic sequestration and infarction. The spleen is an organ that has several functions. It produces white blood cells (lymphocytes), which create specialized proteins called antibodies

that protect against invasion by foreign substances. The spleen also filters blood and removes unwanted material by ingesting microorganisms (i.e., bacteria, fungi, and viruses). Additionally, the spleen monitors red blood cells, destroying those that are abnormal or too old or damaged to function properly (Brender et al., 2005; Jacob, 2018). Impaired splenic functioning contributes to an increased risk of sepsis and infection (Bender, 2017). In individuals with SCD, sickled red blood cells can become trapped in the spleen, referred to as splenic sequestration. Splenic sequestration is characterized by an acutely enlarging spleen and occurs in 10-30% of children with SCD. Severe splenic sequestration may progress rapidly, and blood transfusions may be required to prevent shock and death. Historically, most children with HbSS or HbS/β^0-thalassemia had a dysfunctional spleen within the first year of life and complete atrophy due to ischemia by age five (Bender, 2017).

Acute chest syndrome. Acute chest syndrome is a process that can arise in multiple ways. It is a major cause of mortality and diagnosis is typically made by the presence of a new pulmonary infiltrate on chest radiography. Respiratory tract symptoms, chest pain, hypoxemia, and fever are common clinical manifestations. Acute chest syndrome frequently develops during a vaso-occlusive crisis. Additionally, fat emboli from bone marrow infarcts, pneumonia, pulmonary infarction, and pulmonary embolus lead to acute chest syndrome in many instances (Bender, 2017; Dessap et al., 2011). Acute chest syndrome can progress rapidly, requiring intubation and mechanical ventilatory support.

Infection. As a result of splenic dysfunction, children with SCD are at a high risk for septicemia and meningitis due to encapsulated bacteria. Vaccination and prophylactic penicillin have decreased the incidence of these infections (Adamkiewicz et al., 2003; Bender, 2017). Viral infections also pose a large threat, with human parvovirus B19 remaining a major cause of aplastic crisis (temporary interruption of red blood cell production), resulting in acute anemia

(Bender, 2017). Parvovirus B19 infection can interrupt red blood cell production for eight to ten days, causing a dangerously low hemoglobin level. These life-threatening levels may require red blood cell transfusion.

SARS-CoV-2 coronavirus. The recent spread of the novel SARS-CoV-2 coronavirus (COVID-19) has resulted in global lockdowns and serious health complications for many individuals, leading to hospitalizations and death. COVID-19 is an acute infectious disease and may confer greater risk to the SCD population (Menapace & Thein, 2020). Emerging research to date is mixed, with some sources claiming that it is unclear if there is an increased risk of SARS-CoV-2 in the SCD population, while others reporting that patients with SCD and COVID-19 display a broad range of severity, with a higher case fatality than the non-SCD population (10.9% vs. 3.3%; Menapace & Thein, 2020; Minniti et al., 2021). A recent report from France indicated that SCD patients who were hospitalized due to COVID-19 did not appear markedly worse than the general population, though this might have been a reflection of a younger patient population, as most affected patients in this study were under the age of 45 (Arlet et al., 2020; Minniti et al., 2021). Research also suggests that significant pre-existing comorbidities appear to increase risk for more serious complications from COVID-19 in this population (McCloskey et al., 2020). Older individuals with SCD who have end organ damage and present with acute kidney injury, who are also not being treated with hydroxyurea appear to be at higher risk of death (Minniti et al., 2021). Findings also indicate that acute pain and acute chest syndrome are common presentations in SCD individuals who contract COVID-19, though patients have been shown to recover with adequate care. Despite inconsistencies in emerging data, researchers remain concerned about the impact of social determinants of health care disparities on observed outcomes. Evidence has shown that African American and Hispanic individuals face increased risk for COVID-19 infection, though the etiology remains unclear (Minniti et al., 2021).

Underlying health conditions, dense living conditions, vocation, access to healthcare, and racism have been cited as contributors to the greater impact of COVID-19 on people of color (Marshall, 2020).

Other serious medical complications in the SCD population include pulmonary hypertension, priapism, avascular necrosis, nephropathy, restrictive lung disease, cholelithiasis, retinopathy, cardiomyopathy, and delayed growth and sexual maturation. Additionally, frequent blood transfusions as treatment can lead to iron overload which can be damaging to the liver, lungs, and heart (Kushner et al., 2001). Dactylitis, or pain and/or swelling in the hands or feet, can be the earliest manifestation of SCD in infants and children (Miller et al., 2000). The main causes of death are infection, acute chest syndrome, pulmonary artery hypertension, and cerebrovascular events (Bakanay et al., 2005; Bender, 2017). Children tend to have higher rates of death from infection and splenic sequestration crises, while adult mortality is secondary to chronic end-organ dysfunction, thrombotic disease, and treatment-related complications (Bender, 2017; Manci et al., 2003).

Neurological Complications

In a typically functioning brain, blood is supplied from the internal carotid and vertebral arteries. The anterior and middle cerebral arteries branch out from the internal carotid arteries, while the right and left vertebral arteries come together at the brainstem to form the midline basilar artery. This artery joins the blood supply from the internal carotids in an arterial ring at the base of the brain, creating an anastomotic polygon called the Circle of Willis (Blumenfeld, 2010; Iqbal, 2013). The posterior cerebral arteries arise from the circle, as well as small bridging arteries. The anterior communicating artery connects the anterior cerebral arteries, and two posterior communicating arteries connect internal carotids to the posterior cerebral arteries, thereby joining the anterior and posterior circulations (Blumenfeld, 2010). The anterior cerebral

artery (ACA) supplies blood to most of the cortex on the anterior medial surface of the brain, from the frontal to the anterior parietal lobes, including the medial sensorimotor cortex. The middle cerebral artery (MCA) supplies most of the cortex on the dorsolateral convexity of the brain, and the posterior cerebral artery (PCA) serves to supply the inferior and medial temporal and occipital cortex (Blumenfeld, 2010). The Circle of Willis forms an important collateral network to maintain adequate cerebral perfusion (Iqbal, 2013). Anatomical variations in the Circle of Willis are common, with approximately 34% of individuals having the complete six components (Blumenfeld, 2010). Nevertheless, it improves the chances of any part of the brain to continue to receive blood if one of the major arteries becomes compromised (Purves et al., 2001). Watershed locations are border zone regions in the brain supplied by the major cerebral arteries where blood supply is decreased (Porth & Litwack, 2009). These regions are defined as the ACA-MCA and the MCA-PCA watershed zones and are particularly vulnerable in cerebrovascular events. In SCD, neurological complications include stroke, silent cerebral infarcts, cerebral hemorrhage, cerebral blood flow abnormalities and cerebral microvascular disease. In a population study, SCD was the most common cause of childhood stroke, up to 39% (Earley et al., 1998; Prengler et al., 2002). It is estimated that up to 50% of individuals with SCD will manifest some degree of cerebrovascular disease by age 14 (Bender, 2017; Bernaudin et al., 2011). Increased red cell adhesions, oxidative injury of the vessel wall, and chronic and acute anemia have been identified as the causes of stroke in SCD (DeBaun et al., 2006).

Ischemic Strokes

Stroke is a devastating clinical complication of sickle cell disease that may leave permanent motor, cognitive, and psychological deficits (Bender, 2017; Ware et al., 2017). Ischemic strokes are most commonly seen in SCD children and older adults. The Cooperative Study of Sickle Cell Disease found that 24% of individuals with SCD experienced an overt

stroke with clinically recognizable symptoms by 45 years of age (Ohene-Frempong et al., 1998). Hemiparesis (weakness of one entire side of the body), monoparesis (weakness of one limb), seizures, aphasia or dysphasia, cranial nerve palsies, and mental status change are common presenting signs and symptoms of stroke. Overt strokes occur in as many as 11% of children with SCD, with the majority occurring between ages two and nine years (Ohene-Frempong et al., 1998). Recurring strokes occur in 50-70% of affected individuals within three years after the first event (Bender, 2017; Pavlakis et al., 1989; Powars et al., 1978; Vichinsky et al., 2010). Strokes can be predicted by high velocities in the internal carotid or middle cerebral arteries on transcranial doppler ultrasonography (TCD), and the pathology typically involves the large arteries supplying ACA-MCA watershed zones (Kirkham et al., 2001; Rothman et al., 1986). In children with HbSS and HbS/β^0-thalassaemia, TCD screening for increased risk of overt stroke is performed yearly starting at 2 years of age until at least 16 years of age. TCD can detect high risk of overt stroke and direct the initiation of chronic transfusion programs for primary prevention of stroke (Chonat & Quinn, 2017). The randomized Stroke Prevention Trial in Sickle Cell Anemia (STOP Trial) demonstrated that chronic transfusions reduced the rate of overt stroke by 92% in patients with abnormal TCDs (Adams et al., 1998; Chonat & Quinn, 2017).

Silent Cerebral Infarcts

Silent cerebral infarcts, or silent strokes, are lesions identified on cerebral imaging studies without accompanying neurologic symptoms. Silent cerebral infarctions have a prevalence of 50% at 30 years of age in the SCD population, and individuals with evidence of silent cerebral infarcts are at a higher risk for an overt ischemic stroke, (Kassim et al., 2016; Miller et al., 2001). The brain has two different types of tissue. Grey matter contains the cell bodies, dendrites, axon terminals of neurons, and all synapses. It includes regions of the brain involved in muscle control, memory, emotions, speech, decision-making, self-control, and sensory perception

(Miller et al., 1980; Purves et al., 2001). White matter is made of axons and is considered the "subway" of the brain, connecting different regions of grey matter in the cerebrum to others (Balm, 2014). Silent infarcts frequently occur in frontal lobe white matter, within the watershed zone between the middle and anterior cerebral arteries (Buchanan et al., 2004; DeBaun et al., 2012; Hijmans et al., 2011; Prengler et al., 2002). A study comparing SCD children who were shown to have silent white matter infarct lesions on MRI and healthy controls found widespread bilateral white matter abnormalities in the arterial watershed zones in those affected by SCD (Baldeweg et al., 2006). Another recent study found oxygen delivery is preserved in grey matter of SCD patients but is insufficient to maintain oxygen delivery to the white matter, which may explain the distribution and progressive evolution of silent cerebral infarcts in this population (Chai et al., 2019). White matter hyperintensities[5] occur in watershed areas, where cerebral blood flow and oxygen delivery are intrinsically low, but oxygen delivery in these regions was found to be even lower than predicted by watershed effects (Chai et al., 2019).

Moyamoya Disease

The high incidence of cerebral infarction and intracranial hemorrhage in the SCD population has been attributed to many factors, including large vessel vasculopathy (Merkel et al., 1978; Stockman et al., 1972). In some patients with SCD, this large vessel vasculopathy is accompanied by a fragile network of vessels at the base of the brain in an angiographic pattern resembling moyamoya disease (Fryer et al., 2003). Moyamoya disease is a rare, chronic occlusive cerebrovascular disorder characterized by stenosis of the arteries of the Circle of Willis and the formation of small capillary-sized vessels that provide collateral blood flow. These

[5] White matter hyperintensities are bright white areas that show up on magnetic resonance imaging and are associated with ischemic cerebrovascular disease and loss of vascular integrity (Silbert et al., 2012; Young et al., 2008).

abnormal vessels look like a puff of smoke, which resembles a hazy, or *moyamoya* ("misty" in Japanese) appearance. They commonly result in ischemic strokes in children and cerebral hemorrhages in adults (Fukui, 1997). This moyamoya angiographic pattern appears to be a nonspecific response to various underlying conditions, including SCD (Chaudari & Edwards, 1993; Fryer et al., 2003).

Psychological Complications

While advances in medical treatments have greatly improved the longevity of patients, the identification and management of the clinical psychological implications remains unsatisfactory. Individuals with SCD experience different levels of health, which can lead to differing levels of psychosocial functioning. Some cope relatively well and are able to attend school or work and are socially and physically active, while others cope inadequately and lead more restricted lives (Anie, 2005). Psychological complications have been identified in both children and adults, and include inappropriate pain coping strategies, reduced quality of life owing to restrictions in daily functioning, and anxiety and depression (Anie, 2005).

Psychological Coping

Coping strategies in both children and adults were found to fall into two groups. *Coping attempts* include using distraction and increased activity to manage the perception of pain. Conversely, *negative thoughts and feelings* coupled with *passive* psychological coping methods, like rest and increasing fluids has been shown to be positively associated with pain severity and health service utilization (emergency room visits, hospitalizations, etc.) in both children and adults (Gil et al., 1989). Another study found negative thinking and passive coping to be associated with more frequent pain episodes and hospitalizations in adult patients (McCrae & Lumley, 1998). The relationship between medication use and pain in the SCD population remains complex, especially with regards to opioid analgesia. Opioid abuse is approximately ten

percent in the SCD population, which is no higher than in other populations prescribed opioids for pain. Nevertheless, studies have shown that increased dosages of opioids are used as pain intensity increases, and concerns regarding overtreatment and subsequent dependency with opioids have been documented (Anie & Steptoe, 2003; Dampier et al., 2002; Konotey-Ahulu, 1998; Maxwell et al., 1999; Porter et al., 1998). While SCD patients often do not become addicted to opioids, a growing number of physicians withhold these drugs from their SCD patients. Reduced access to medications that help pain crises lead to more hospitalizations, and this population is often stigmatized for engaging in drug-seeking behaviors (National Heart, Lung, and Blood Institute [NHLBI], n.d.c). However, the NHLBI-funded Pain in Sickle Cell Epidemiology Study (PiSCES), a longitudinal study of pain in SCD, found significant positive relationships between chronic opioid use and negative coping, somatic symptom burden, and negative relationships with physical and mental quality of life (Smith et al., 2015).

Quality of Life

Health-related quality of life has been shown to be significantly reduced in adults with SCD when compared to the general population (Jenkinson et al., 1993). Impairments in quality of life may not be specific to SCD and are common to chronic painful conditions. However, children and adolescents with SCD tend to have a more disrupted quality of life than the general population, which is unlikely to improve as these individuals approach adulthood (Anie, 2005).

Anxiety and Depression

The biopsychosocial model of pain suggests that there are reciprocal relationships between biological, psychological, and social factors that impact the experience of pain (Pillai et al., 2013; Reader et al., 2020). Reader and colleagues conducted a systematic review including 29 studies of pain and emotional functioning in the pediatric SCD population and found a strong evidence of a relationship between increased pain and higher depressive and anxiety symptoms.

They also found that those who coped with their pain by using maladaptive cognitive strategies tended to experience poorer emotional functioning (Reader et al., 2020). Researchers on the PiSCES project examined depression and anxiety rates in adults with SCD and found that depression and anxiety predicted more daily pain and poorer physical and mental quality of life (Levenson, et al., 2008). While some studies have reported high rates of depression (Belgrave & Molock, 1991; Hasan et al., 2003; Schaeffer et al., 1999), a consistent pattern has failed to be established (Alao & Cooley, 2001; Molock & Belgrave, 1994). Nevertheless, patients with SCD commonly report low self-esteem and feelings of hopelessness as a result of frequent pain, increased hospitalizations, and loss of employment, which could all be indicators of increased depressive symptomology. It is important to consider whether anxiety and depression result from living with SCD which leads to a worse pain experience, or if frequent pain and hospitalizations result in depression. Regardless, individuals with SCD are experiencing increased levels of mood disturbances that should be addressed in conjunction with medical treatment.

Effects on Sleep Quality

Sleep plays a vital role in good health and well-being throughout life. Getting enough quality sleep at the right times can help protect mental health, physical health, and overall quality of life. To that effect, sleep deficiency can cause problems with learning, focusing, and reacting. Individuals who have poor sleep quality may have trouble making decisions, solving problems, controlling emotions and behavior, and coping with change (NHLBI, 2020). Tasks may take longer to finish, and a slower reaction time has been observed (NHLBI, 2020).

Sleep-Disordered Breathing

Disruptions to sleep quality can range from inadequate amount of time asleep, strenuous activity, bright artificial light, or large meals to use of nicotine, alcohol or caffeine too close to bedtime (NHLBI, 2020). However, some disruptions are less easily controlled. Sleep-disordered

breathing is an umbrella term for several chronic conditions in which partial or complete cessation of breathing occurs several times throughout the night, resulting in daytime sleepiness or fatigue that can interfere with a person's daily functioning and reduces quality of life (Heulitt & Ranallo, 2011). Several factors increase the risk for SDB, including smoking, family history, obesity, age, males, alcohol use, and large neck size (Ho, Moul, & Krishna, 2016; Peppard, Austin, & Brown, 2007; Peppard et al., 2013; Redline et al., 1994; 1999; Wetter et al., 1994). Polysomnograms, or sleep tests, measure several physiologic parameters during sleep, one of the most important measurements being breathing and its cessation during sleep. A breathing pause of 10 seconds or more is termed an *apnea*. Apneas are thought to be associated with oxygen desaturation (a decrease in blood oxygen) and other bodily responses as a person struggles to breathe (Heulitt & Ranallo, 2011). Desaturations also occur with hypopnea (partial decrease in air flow). The apnea-hypopnea index is the number of apneas and hypopneas that occur per hour of sleep and is an important measure of the severity of sleep apnea (Heulitt & Ranallo, 2011). An apnea-hypopnea index of more than 5 is generally warrants treatment (Sharma et al., 2015). Sleep-disordered breathing adversely affects daytime alertness and cognition and increases the risk of having a stroke (Yaggi et al., 2005).

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is the most common form of sleep-disordered breathing (SDB) and is associated with many adverse health outcomes (al Lawati et al., 2009; Caples et al., 2007; Young et al., 2008). It is characterized by repeated episodes of complete or partial obstructions of the upper airway during sleep and is associated with a reduction in blood oxygen saturation (Berry et al., 2012). A less common form, central sleep apnea, is when the brain does not send the proper breathing signals. Both result in repetitive events of insufficient air flow, oxygen absorption, and carbon dioxide exhalation (Heulitt & Ranallo, 2011). OSA has been

studied extensively in children with SCD (Mullin et al., 2012; Needleman et al., 1999; Rogers et al., 2010; Salles et al., 2009; Spivey et al., 2008). Children with SCD referred to sleep laboratories have been shown to have a 69% prevalence of OSA (Sharma et al., 2015). Increased prevalence of OSA in children with SCD is thought to be due to excessive adenoid and tonsillar growth (Maddern et al., 1989; Rogers et al., 2010). Therefore, treatment often includes tonsillectomy and adenoidectomy (Rogers et al., 2010). This is not the case for adults with SCD, as studies have shown a high burden of SDB in the absence of obvious tonsillar enlargement or oropharyngeal abnormalities (Sharma et al., 2015). As a result, management of adult sleep-disordered breathing is quite different from pediatric patients, and now that an increasing percentage of individuals with SCD are living into adulthood, more research on the breathing patterns of adults with SCD is necessary. One study revealed that up to 70% of adults with sickle cell disease have sleep disturbances, while another found a prevalence of 44% in an adult population, showing symptoms of disturbed sleep or excessive daytime sleepiness (Sharma et al., 2015; Wallen et al., 2014). The intermittent episodes of apnea in some patients with SDB may lead to hypoxemia that could trigger red blood cell sickling and result in the development of vaso-occlusive and hemolytic episodes (Raghunathan et al., 2018). Individuals with SCD and SDB reported more frequent hospitalizations related to pain crises than SCD individuals with no evidence of SDB (Sharma et al., 2015).

Treatments for OSA work by physically increasing the size of the upper airway. Continuous positive airway pressure (CPAP) is the standard of care for patients with OSA, which delivers pressurized air to the upper airway via a mask that pushes the airway open (Heulitt & Ranallo, 2011; Raghunathan et al., 2018). For children, tonsillectomies and adenoidectomies are considered the first choice in treatment. Nocturnal oxygen supplementation has also been proposed as a treatment for SDB in SCD. One study showed that patients with

SCD treated with nocturnal oxygen demonstrated an increase in hemoglobin (Ip et al., 2013). However, studies evaluating clinical benefit are lacking, CPAP adherence remains an issue, and there is not yet an effective and safe drug treatment for sleep apnea (Heulitt & Ranallo, 2011).

Medical Treatments

Anemia treatment depends largely on the cause (American Society of Hematology, n.d.). Iron deficiency anemia treatment usually involves taking iron supplements and changing diet, while treatment for vitamin deficiency anemias includes dietary supplements. For aplastic anemia, treatment can include blood transfusions or bone marrow transplants. For hemolytic anemias, like sickle cell disease, treating infections and taking drugs that suppress the immune system are common. Though similar to SCD, most forms of thalassemia are mild and require no treatment. More severe forms of thalassemia generally require blood transfusions, folic acid supplements, medication, splenectomy, or blood and bone marrow stem cell transplant (American Society of Hematology, n.d.).

The number of individuals with sickle cell disease is expected to increase, largely as a result of interventions such as newborn screening (i.e., state-mandated targeted genetic testing for all newborns), penicillin prophylaxis, primary stroke prevention, hydroxycarbamide treatment, and education about disease complications (Piel et al., 2017; Quinn et al., 2010; Ware et al., 2017). In high-income countries, childhood mortality is now close to that in the general population with an observed median survival of more than 60 years (Gardner et al., 2016; Le et al., 2015; Piel et al., 2017). A report published by the Journal of the American Society of Hematology in 2016 documented that some people with mildly symptomatic SCD may live as long as 86 years with proper management of the disease, including not smoking or consuming alcohol, maintaining a normal body mass index, along with strong family support (American Society of Hematology, 2016; Ballas et al., 2016). However, the four cases in this study were all

women, and had mild disease states that did not qualify them for treatment with hydroxyurea. Even with the best medical care, life expectancy for patients with SCD is reduced overall and quality of life is often compromised.

Pain Management

Treatment of pain episodes includes hydration, anti-inflammatory agents, and pain medication (Bender, 2017). Opiate analgesia is the most frequently used treatment in the management of severe pain, however careful monitoring is imperative as opiate-related over sedation has been identified as a cause of death in this population (National Confidential Enquiry into Patient Outcome and Death, 2008; Rees et al., 2010).

Transfusions

More than 90% of adults receive red blood cell transfusions, which involves either additive transfusions or by exchange, in which blood is also removed (Chou, 2013; Rees et al., 2010). Transfusions are given acutely for immediate benefits, including increased oxygen-carrying capacity and improved blood flow (Ware et al., 2017). It also helps prevent long-term complications by replacing rigid sickled cells with normal cells. Indications for chronic transfusions are most frequently related to stroke prevention, given that children and adults with a history of ischemic strokes are at a high risk for recurrence (Powars et al., 1978). Patients with SCD are at risk of alloimmunization because of differences between the ethnic origin of blood donors and patients (Vichinsky et al., 1990). It is important to note that chronic blood transfusion is inevitably associated with iron overload, which is often corrected with iron chelation, the removal of excess iron from the body with medications (Poggiali, et al., 2012; Rees et al., 2010).

Hydroxyurea

Hydroxycarbamide, also known as hydroxyurea, is a pharmacologic therapy for sickle cell disease and is increasingly used in both children and adults (Bender, 2017). It increases the

fetal hemoglobin (HbF) concentrations in individuals with SCD. HbF interrupts polymerization of deoxygenated HbS, since HbF is excluded from this polymer. HbF generally peaks in mid-gestation and represents less than 1% of total hemoglobin by the time a healthy, unaffected infant reaches 6 months of age (Piel et al., 2017). HbF also explains why infants do not show signs of SCD until about 5 or 6 months of age (Bender, 2017). Hydroxyurea increases HbF levels in SCD patients, but its distribution is heterogeneous. Cells with lower HbF levels are afforded less protection from polymerization-induced damage. As a result, hemolytic anemia persists, and individuals remain symptomatic. However, hydroxyurea has shown to provide a reduced rate of complications and possibly improved survival (Piel et al., 2017).

Additionally, and arguably most importantly, guidelines from the National Heart, Lung, and Blood Institute recommend hydroxyurea be used in all infants with HbSS beginning at 9 months of age regardless of clinical severity (American Academy of Pediatrics, 2014; Wang et al., 2011; Yawn et al., 2014). Hydroxyurea therapy has also been shown to decrease pain episodes by up to 50% and has also been shown to prevent recurrent stroke (Agrawal et al., 2014; Ware et al., 2004).

Endari

L-glutamine, commercially known as Endari, garnered considerable excitement in 2017 and was touted as the first new drug approved by the FDA for treatment of SCD in 30 years (Gardner, 2018; Ortiz, 2018; U.S. Food & Drug Administration, 2017). Sickled blood cells are more susceptible to oxidative stress or damage than normal blood cells. Sickled red cells absorb and utilize L-glutamine to a greater extent than normal cells, leading to a rise in the levels of cellular defenses against oxidative stress (Gardner, 2018). Niihara and colleagues demonstrated in clinical trials that all patients experienced a decrease in clinical symptoms when given L-glutamine (Niihara et al., 1998, 2014). Studies have demonstrated that use of this agent lowered

hospitalizations by 41%, the frequency of vaso-occlusive episodes were decreased by 25%, and the incident of acute chest syndrome was decreased by more than 50% (Niihara et al., 2014). However, due to high attrition rates of these clinical trials (nearly 33%), there exists a potential lack in quality of the research (Karon, 2017). Other criticisms include the drug's involved administration (mixing and drinking it down several times per day) which may lead to medication non-compliance, and its cost, with a 5g packet of L-glutamine costing around $600 (Gardner, 2018).

Stem Cell Transplant

Stem cell transplantation remains the only cure for patients with sickle cell disease (Bernaudin et al., 2007; Gluckman et al., 2017; Walters et al., 2016). The goal is to successfully replace the SCD individual's bone marrow (where red blood cells are created) with normal genotype cells before the development of organ dysfunction (Stuart & Nagel, 2004). Sibling matched transplantation procedures using bone marrow or cord blood stem cells can expect a 92% chance of cure with an overall survival of 95%, while peripheral blood stem cells are associated with increased mortality due to a high rate of graft failure (Bender, 2017; Gluckman et al., 2017). Despite its success, only 10%-20% of patients have unaffected matched sibling donors, restricting its application (Lê et al., 2015).

Gene Therapy

Gene therapy approaches to cure SCD are in a rapid state of clinical investigation (Hoban et al., 2016). Bone marrow is used to isolate stem cells, followed by ex vivo incubation with viruses containing an additional gene. After treatment with chemotherapy, the SCD individual receives re-infusion of the modified stem cells, which then repopulate the marrow and express the new gene (Ware et al., 2017). Gene therapy has been found to be successful in the sickle transgenic mouse, as mouse models have shown inhibition of red blood cell dehydration and

sickling (Pawliuk et al., 2001). Clinical trials with humans had encouraging preliminary results and could allow straightforward genetic correction in the future (Cavazzana et al., 2015; Ware et al., 2017). Clinical trials were briefly halted in early 2021 after two patients developed cancer (Kaiser, 2021) but the Food and Drug Administration permitted their resumption in June 2021 (Pagliarulo, 2021).

Psychological Treatments

Quality of life is dependent on the symptoms and the impact that an illness has on an individual. As such, early intervention is crucial for this population. Medical treatment, along with adequate psychological support, could improve quality of life. Psychological interventions should be offered as standard care in the management of SCD (Anie, 2005).

Psychoeducation

Psychoeducational interventions provide psychological support, while also focusing on improving the knowledge and understanding of patients regarding their illness (Anie, 2005). Information can lead to improved knowledge and better coping, as well as provide support and motivation of others through shared experience. Developmentally appropriate psychoeducation can be offered to children and their families, and studies have shown that group interventions help identify issues and concerns while providing a supportive environment (Anie et al., 2000).

Cognitive Behavioral Therapy

Cognitive behavioral therapy (CBT) posits that difficulties in living, relationships, general health, and other important areas of one's life have their origins in and are maintained by thoughts, emotions, and behaviors (Beck & Beck, 1995). Cognitive interventions challenge and change self-defeating thoughts to enable the patient to lead a more productive and satisfying life, while behavioral methods arise from the premise that inappropriate behaviors are learned and therefore can be unlearned. CBT can be offered to patients with SCD individually or in groups

and has been shown to reduce pain in adults (Thomas et al., 1999), while also improving mood and psychological coping ability (Anie et al., 2002).

Neuropsychological Effects

Neuropsychology is the study of brain-behavior relationships, often focusing on the behavioral effects of central nervous system damage due to injury or disease processes. Neuropsychological evaluations typically include an assessment of general intellectual functioning, including processing speed and working memory, verbal and nonverbal learning and memory, attention, executive functioning, primary sensory and motor functioning, language, visual-spatial skills, and social, emotional, and behavioral functioning. Sickle cell disease can lead to profound cerebral damage, which is associated with neuropsychological deficits (Hijmans et al., 2011). Neuropsychological deficits among children with SCD have been reported in a variety of domains. Several studies have reported pediatric SCD patients with deficits in general intellectual functioning, language and verbal abilities, visual-motor and visual-spatial processing, memory, and academic achievement (Edwards et al., 2007; Kral et al., 2001; Treadwell et al., 2005).

SCD has been associated with impairments in general intellectual functioning as measured by Intelligence Quotient (IQ). Children with SCD who have experienced overt strokes seem to be the most impaired, with a decrease of about 14 standard score points on the Verbal Comprehension Index of the Wechsler Intelligence Scale for Children, 3rd Edition (WISC-III; Bernaudin et al., 2000). Armstrong et al. (1996) found that children with silent cerebral infarcts scored approximately 7 standard score points lower on the Wechsler Scale (Wechsler Intelligence Scale for Children-Revised) Full-Scale IQ (FSIQ) and 9 standard score points lower on the Verbal IQ when compared to children with normal MRI (Schatz & Puffer, 2006).

Another study found that children with SCD who experienced silent cerebral infarcts had lower IQ than age-matched controls (85.6 vs. 91.2; Schatz et al., 2001).

While studies have reported overt stroke and its subsequent neuropsychological deficits to be more severe than the deficits associated with silent cerebral infarcts, up to 17% of SCD patients who are otherwise asymptomatic experience silent cerebral infarcts in the absence of any motor deficits but present with gross cognitive deficits (Brown et al., 2000; DeBaun et al., 2012; Glauser et al., 1995; Moser et al., 1996). Specifically, silent cerebral infarcts in children with SCD have been shown to produce subtle deficits in attention and concentration, executive function, and visual-motor speed and coordination (Kral et al., 2001). Another study found that children with SCD had poorer performance on measures of intellectual, academic, and general neuropsychiatric functioning when compared with siblings with sickle cell trait or normal hemoglobin. Hogan and colleagues (2006) demonstrated that SCD children with evidence of silent cerebral infarcts, overt, and covert strokes had a lower FSIQ than children with SCD and no evidence of silent infarcts. Further, ethnically matched control children without SCD showed an FSIQ greater than both of the aforementioned groups (DeBaun et al., 2012; Hogan et al., 2006). Additional studies have demonstrated that cognitive deficits in children with SCD exist in the absence of relevant MRI findings, and that deficits are multifactorial, complex, and arise from multiple etiological factors (Bernaudin et al., 2000; Steen et al., 2005).

Impairments in executive functioning have also been well-documented in children with SCD (Berkelhammer et al., 2007; Brandling-Bennett et al., 2003; Brown et al., 2000; Craft et al., 1993; DeBaun et al., 1998; Hijmans et al., 2011; Noll et al., 2001; Schatz et al., 1999). Deficits in these areas are expected, given that silent cerebral infarcts commonly occur in the frontal lobe white matter. The frontal lobes play a major role in executive functions, which are defined as higher order cognitive functions including abilities such as response inhibition, planning,

working memory, and attention (Anderson, 2001). These areas greatly affect other areas of neuropsychological functioning and are strongly related to academic and behavioral problems (Hijmans et al., 2011). For example, studies have found that children with SCD experienced significantly lower reading and spelling achievement scores and had overall academic achievement and goal attainment difficulties when compared to healthy controls (Fowler et al., 1988; Schatz, 2004). One study comparing 41 children with HbSS or HbS/B0-thalassemia and 38 controlled found children with SCD showed deficits in visuo-motor functioning as well as visuo-spatial working memory. Subtle deficits were also found for sustained attention and planning. However, researchers found no significant differences in terms of response inhibition and verbal working memory (Hijmans et al., 2011).

Cognitive dysfunction appears to worsen with age. While individuals with SCD are now living longer, with a median life expectancy of 42-47 years in the United States, there is limited data on neuropsychological functioning in the adult SCD population. Global cognitive impairment has been observed in patients with overt strokes, but children with no evidence of infarcts were found to have impaired cognitive functioning that increased with age (Vichinsky et al., 2010). Consequently, silent cerebral infarctions may produce neurocognitive deficits that persist throughout the lifespan (Edwards et al., 2007). Researchers examined neuropsychological functioning in adult SCD patients with no history of stroke and found that the SCD patients demonstrated poorer performance on timed tests of attention and concentration. They also reported that individuals without MRI or cerebral blood flow abnormalities had cognitive deficits, suggesting that subtle neuropsychological deficits can be associated with SCD in the absence of stroke (Sano et al., 1996). A similar study investigated neurocognitive dysfunction in neurologically asymptomatic adults with SCD and reported mean nonverbal function to be significantly lower in SCD patients than controls. They also reported significant differences in

global intellectual functioning, working memory, processing speed, and executive function (Vichinsky et al., 2010). A group of researchers in London examined the neuropsychological sequelae in an adult SCD population and found that while cognitive impairments were more prevalent in those who showed severe infarcts on MRI, there was also evidence of significant cognitive impairment on measures of executive functioning and processing speed in some patients with normal MRI. Their results suggest that MRI is not an adequate screening tool to identify SCD patients with cognitive impairment (Rawle et al., 2010). Of note, Cahill and colleagues demonstrated that individuals with sickle cell trait[6] do not appear to be at increased risk for cognitive decline in test scores of learning, memory, and executive function (Cahill et al., 2019).

Mechanisms of Neuropsychological Impairment in SCD

Sickled cells cause arterial blockage which leads to oxygen deprivation of organs and tissue. Arterial blockage generally occurs in the anterior and middle cerebral arteries and may result in infarct, predominantly in anterior brain regions (Pavlakis et al., 1989). This, coupled with decreased hemoglobin due to anemia, is likely a marker for reduced oxygen delivery to the brain. Hypoxia is a condition where a region of the body is deprived of adequate oxygen supply at the tissue level. It contributes to polymerization of HbS, which leads to vaso-occlusion and other complications (Eltzschig & Carmeliet, 2011).

Sleep-Disordered Breathing. In healthy individuals, disrupted sleep contributes to significant declines in cognitive functioning. Researchers have found that sleep loss reliably produces reductions in processing speed and attention, and deficits worsen with increasing time awake. Fortunately, these deficits may resolve after normal sleep is resumed (Waters & Bucks,

[6] Individuals who inherit one HbS gene and one normal hemoglobin gene and usually do not have any signs of sickle cell disease

2011). Coupled with the neurocognitive deficits associated with SCD, sleep disorders in this population may compound undesired neuropsychological effects.

One mechanism which may contribute to neuropsychological deficits is low hemoglobin oxygen saturation associated with sleep-disordered breathing. Sleep-disordered breathing (SDB) is associated with transient hypoxemia (abnormally low level of oxygen in the blood) and hypercapnia (abnormally high level of carbon dioxide in the blood), and has been reported in up to 41% of children with SCD (Epstein et al., 1989; Needleman et al., 1999; Pollak et al., 2010; Rogers et al., 2010; Rosen et al., 2014). Studies in adults and children with SCD have demonstrated associations between nocturnal desaturations and severity of anemia, frequency of vaso-occlusive crises and acute chest syndrome, cardiac abnormalities and diastolic dysfunction, priapism, and nocturnal enuresis (Gileles-Hillel et al., 2015; Halphen et al., 2014; Hargrave et al., 2003; Johnson et al., 2010). One group of researchers found an association between nocturnal hypoxemia (documented by overnight pulse oximetry) and central nervous system events in children with SCD (Kirkham et al., 2001). They postulated that the mechanisms underlying stroke and transient ischemic attacks could involve either the generation of cerebrovascular disease or the reduction of the threshold for infarction at arterial watershed zones and that chronic underventilation could allow continuing vascular and neuronal damage.

Neuropsychological Implications of Oxygen Desaturations in SCD

Hollocks and colleagues (2012) investigated the association of nocturnal oxygen saturation and sleep quality with neuropsychological measures of executive functioning in neurologically normal children with SCD.[7] They used the Behavior Rating Inventory of Executive functions (BRIEF) – Parent Form, which is a parental rating questionnaire of

[7] Researchers used two subtests of the WASI (Vocabulary and Matrix Reasoning) which provided an estimate for full-scale IQ (FSIQ; Hollocks et al., 2012).

executive functions, the Delis-Kaplan Executive Function Systems (D-KEFS) Tower test, which measures spatial planning, rule learning, and inhibition of impulsive responding, and the Wechsler Abbreviated Scale of Intelligence (WASI), which is a brief measure of intelligence. To measure overnight sleep data, they used cardiorespiratory sensors, airflow by nasal pressure cannula, and hemoglobin oxygen saturation by pulse oximetry (SpO_2). They found that the average nocturnal SpO_2 (M = 96.6%) fell within the normal range typically observed in a pediatric population although the minimum SpO2 (M = 88.9%) was considerably lower than the minimum SpO_2 value of 94.6% reported in the normal population (Uliel et al., 2004). Mean IQ was almost 15 points (1 *SD*) below the population average, placing participants in the low average range, which is similar to findings in a previous study of individuals without cerebral infarction (Schatz et al., 2002). Results also suggested an association between measures of nocturnal oxygen saturation and the Tower task, with mean and minimum overnight SpO_2 being significantly correlated with performance on this task. Hollocks et al. (2012) postulated that these findings provide evidence that desaturation is linked to poorer executive function, and that prefrontal cortical areas that are vital for executive functioning may be particularly vulnerable to disruptions in sleep. Nocturnal hemoglobin oxygen desaturation and sleep fragmentation may be a contributing factor to executive dysfunction in those with sickle cell anemia However, Bills et al. (2019) examined the cognitive functioning of 26 children with comorbid SCD and obstructive sleep apnea (OSA), 39 matched comparisons with SCD only, and 59 matched comparisons in children without a chronic health condition. They found no significant differences between children with comorbid OSA and SCD and children with SCD alone with regards to cognitive functioning. However, they did find significant differences on measures of processing speed and reading decoding, with healthy children scoring better than both chronic health condition groups.

Research on neuropsychological outcomes in older populations of SCD individuals who experience oxygen desaturations is limited. Whitesell et al. (2016) reported up to 50% of young adults with SCD in their study experienced sleep apnea, defined as an apnea-hypopnea index (AHI) of > 5 events/hour (Whitesell et al., 2016). Of note, three of their 20 subjects with more severe anemia were found to have nocturnal hypoxemia in the absence of sleep apnea. They suggested that prolonged and frequent hypoxemic episodes likely increase the risk for vaso-occlusive, cardiovascular, and neurologic complications of SCD, and further investigations could identify opportunities to prevent or reduce nocturnal hypoxia to improve outcomes for this population . Another group of researchers in the UK randomized children with SCD without a prior diagnosis of sleep-disordered breathing to receive nocturnal continuous positive airway pressure (CPAP) with supplemental oxygen as needed to maintain SpO_2 of 94% or higher. Compared to controls, the patients on CPAP showed reduced vaso-occlusive pain crises. Also observed was an improvement in certain cognitive domains, including processing speed and attention[8] (Marshall et al., 2009).

Need for Further Study

Compared to the number of studies conducted in the pediatric population, research on the adult sickle cell population remains minimal. Sleep-disordered breathing and sickle cell disease share many pathophysiological pathways, with the most common factor of hypoxemia, leading to complications associated with both diseases (Raghunathan et al., 2018). Consequently, there is sound scientific rationale to assume that individuals with sickle cell disease who also experience sleep-disordered breathing will have more severe complications, since sleep-disordered breathing will contribute to the already compromised pathologic states induced by the hypoxia due to

[8] Marshall and colleagues (2009) utilized five subtests from the WISC-IV UK. Coding and Symbol Search were used together to yield the Processing Speed Index (PSI). The researchers combined PSI with Cancellation subtest as a measure of visual attention skills under time pressure.

microvascular occlusion from vaso-occlusive events as a consequence of the disease. Largely unexplored is the potential effect of sleep-disordered breathing on neuropsychological functioning in this vulnerable population. No studies to date have examined the neuropsychological effects of nocturnal oxygen desaturation in individuals with SCD compared to individuals with non-sickle anemias and healthy controls.

This study aims to distinguish the neuropsychological effects of SDB in individuals with sickle cell disease above and beyond anemia in general, which may suggest more specific mechanisms of neuropsychological impairment, including vaso-occlusive events in conjunction with hypoxemia. While research in the adult population of SCD continues to expand, the neuropsychological functioning of these individuals is an area that warrants further study. As a result of negative neuropsychological effects of SCD, these individuals may face daily life challenges in areas of employment, financial management, medication adherence, utilization of community resources, and social functioning (Schatz & McClellan, 2006; Vichinsky et al., 2010). While medical advancements have increased longevity in individuals with SCD, quality of life remains compromised. Sleep-disordered breathing may be an important contributing factor in the neuropsychological functioning of individuals with SCD and further understanding of this relationship is warranted.

Research Questions and Hypotheses

Research Question

Are there differences in neuropsychological functioning due to the presence of nocturnal oxygen desaturations when comparing individuals with sickle cell disease to those with non-sickle anemias and healthy controls?

1. Hypothesis 1a: Individuals with sickle cell disease will demonstrate significantly lower general intelligence, processing speed, inhibition, and cognitive flexibility when compared to those with non-sickle anemia and healthy controls.
2. Hypothesis 1b: Individuals with an increased number of nocturnal oxygen desaturations will demonstrate significantly lower general intelligence, processing speed, inhibition, and cognitive flexibility.
3. Hypothesis 1c: Individuals with sickle cell disease and greater nocturnal oxygen desaturation events will demonstrate significantly lower general intelligence, processing speed, inhibition, and cognitive flexibility when compared to those with non-sickle anemia and healthy controls.

Chapter 3: Methodology

Study Aim

The purpose of this study is to expand the literature examining the neuropsychological implications of disordered sleep in the sickle cell population across the lifespan. More specifically, this study aims to examine the neuropsychological correlates of individuals with sickle cell disease who are experiencing nocturnal oxygen desaturations and compare them to individuals with non-sickle anemias and healthy controls. Further examination of neuropsychological functioning in this population could lead to early interventions to increase quality of life.

Research Design

This quantitative study is part of a larger IRB-approved project that was conducted at Children's Hospital Los Angeles (CHLA) on cerebral blood flow response to perturbations in oxygen tension in individuals with and without SCD. 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). All data was collected as part of this larger study and completed at CHLA.

In addition to a medical workup including MRI and blood draw, the participants were asked to wear a Wrist PAT device and an Actiheart device for 24 hours. Participants also underwent neuropsychological evaluation, which was comprised of a standardized battery (see Table 2) administered in an outpatient setting by a neuropsychologist or doctoral trainees 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 2

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	
Wechsler Intelligence Scale for Children – Fourth Edition	Coding, Symbol Search	WISC-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	
PROMIS Fatigue Scale			Fatigue

Participants

The sample for the current study was obtained from data collected as part of the aforementioned larger study. A subset of the larger study's SCD patients were identified for inclusion based on availability of all variables of interest. Participants who had missing demographic, neuropsychological, or oxygen desaturation data were not included in the analyses. Therefore, 50 participants with missing data were excluded. A subset of 9 to 42-year-old patients with sickle cell disease remained, along with a subset of 15 to 45-year-old patients with non-

sickle anemia. A subset of healthy controls were also included. The final sample consisted of 81 individuals (34 SCD, 18 non-sickle anemia, and 29 control).

Data Collection

Neuropsychological Protocol

As mentioned, participants completed a battery of assessments in the areas of general intellectual functioning, attention, language, verbal and non-verbal learning and memory, processing speed, visuomotor construction, and social-emotional functioning. Scores from measures assessing general intellectual functioning, processing speed, inhibition, and cognitive flexibility were analyzed (see Table 3).

Table 3

Neuropsychological measures selected for current study

Measure	***Subtest***	***Domain Measured***
WASI-II		General Cognition
WAIS-IV or WISC-IV	Coding	Processing Speed
D-KEFS	Color-Word Interference, Trial 3 (Trial 3 – Inhibition)	Inhibition
D-KEFS	Color-Word Interference, Trial 4 (Trial 3 – Inhibition/Switching)	Inhibition & Cognitive Flexibility

Wechsler Abbreviated Scale of Intelligence – Second Edition (WASI-II). The WASI-II is a brief screening measure of general intelligence (Wechsler, 2011). It has four subtests – Vocabulary, Similarities, Block Design, and Matrix Reasoning, which comprise the Verbal Comprehension Index and the Perceptual Reasoning Index. These indices are then combined to determine general intellectual functioning, or the Full Scale Intelligence Quotient (FSIQ). 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. Unlike the WAIS-IV and WISC-IV, the WASI-II FSIQ-4 does not

integrate processing speed as a component of intellectual functioning. Working memory is also not assessed with the WASI-II.

Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV) and Wechsler Adult Intelligence Scale – Fourth Edition (WAIS-IV). The WISC-IV and WAIS-IV as a whole are designed to measure intellectual ability in children and adults, respectively. The WISC-IV can be used for children between the ages of 6 and 16 (Wechsler, 2003). It was normed on a sample of 2,200 children between the ages of 6 years and 16 years 11 months and were stratified to closely match census data based on demographic variables of race and ethnicity, parent education level, and geographic region (Na & Burns, 2016). The WAIS-IV 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 (Wechsler, 2008). Both the WAIS-IV and WISC-IV are comprised of several primary index scores measuring various areas of cognition. As such, both measures contain the Coding subtest under the Processing Speed Index.

Coding. Coding is commonly used in research to assess processing speed and is included in both the WISC-IV and WAIS-IV. This subtest requires participants to transcribe a digit-symbol code using a key within a specific time limit. This subtest was selected as a measures of the participants' processing speed.

Delis-Kaplan Executive Function System (D-KEFS). The D-KEFS was created as a measure of various areas of executive functioning and contains nine subtests that can be used individually to examine these areas (Delis et al., 2001). This measure 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

executive functions of response inhibition and cognitive flexibility, and the Color-Word Interference Test (CW) was selected for this purpose.

Color-Word Interference Test. This subtest includes of four trials, which are modeled after the classic Stroop test (Golden, 1978). The first trial asks the examinee to identify the color of an organized array of squares quickly, which provides a measure of rapid naming. The second trial asks the examinee to quickly read the names of colors printed in black ink, measuring word reading speed. Performance on these first two trials provides an estimate of the validity of the last two trials. That is, if deficits are noted in Trial 1 and/or Trial 2, then Trials 3 (Inhibition) and 4 (Inhibition/Switching) are not considered valid measures of the executive functions. The third trial has 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 purple printed in pink ink). The examinee is asked to provide the name of the ink color rather than reading the word as quickly as possible, which provides a measure of response inhibition. In the fourth trial, examinees are required 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.

Oxygen Desaturations

Pulse oximetry has the ability to give continuous, non-invasive, and efficient monitoring of blood oxygenation without calibration, and is accurate for a wide range of clinical applications (Hay et al., 1989). It has been shown to be effective in estimating the arterial oxygen saturation in patients with sickle cell anemia (Fitzgerald & Johnson, 2001). Modern pulse oximeters can be placed on different body sites (e.g., fingertip, forehead, or earlobe). In this study, oxygen saturation and finger plethysmography[9] was recorded for 24 hours using a cuff placed on the

[9] Finger plethysmographs non-invasively measure changes in finger blood flow during wakefulness and sleep (Grote et al., 2003).

index finger and connected to a cell-phone sized device attached to the wrist. This device, called the WristPAT, was validated against in-lab polysomnography which has shown a documented correlation of 90% (Yalamanchali et al., 2013). Data collected overnight was analyzed and nocturnal oxygen desaturation events were recorded. Both an 88% drop in blood oxygen levels and a minimum event duration (10 seconds) needed to be met for an event to be recorded. A specific sleep study statistic was calculated as events per hour of analyzed data, where artifact data were not included. Obstructive sleep apnea is characterized by complete or partial cessations of breathing during sleep resulting in fragmented sleep and blood oxygen desaturations (Hoth et al., 2013). Previous studies have identified that significant nocturnal hypoxemia occurs in individuals with SCD, with only about half also demonstrating obstructive sleep apnea (Bills et al., 2019; Little et al., 2014; Whitesell et al., 2016). Thus, increased severity of apnea rather than a diagnosis in general may be associated with cognitive deficits (Bills et al., 2019). As a result, for the current study, the nocturnal oxygen desaturation metric was selected to represent hypoxemic events and will be treated as a continuous variable without specific cutoffs. This metric will be considered as a proxy of sleep-disordered breathing.

Data Analysis

SPSS Version 27 was utilized to analyze the data collected. Data analyses included examining the mean, standard deviation, frequency, cell counts and normality of the variables. Skewness, kurtosis, and patterns of residuals were also examined. Due to differences in sample size between the three groups (control, sickle cell disease, non-sickle anemia), unweighted effects codes were used to code disease status into two categories to be able to compare neuropsychological outcomes for participants with sickle cell disease to controls and those with sickle cell disease to those with non-sickle anemia, with sickle cell disease being the referent group. The nocturnal oxygen desaturation variable that represents a proxy of sleep-disordered

breathing is a continuous variable. This variable was re-centered around the mean of the overall sample ($\bar{x}$ = 3.411).

In order to determine potential significant differences in demographic factors between the three groups, the groups were compared using chi-square tests for categorical variables (i.e., gender, ethnicity, income). Given significant group differences related to current annual combined family income and ethnicity, these variables were incorporated as covariates during hypothesis testing.

Testing Assumptions

In order to test hypotheses, a multivariate categorical by continuous linear regression was performed with disease status (SCD, non-sickle anemia, and control group) and oxygen desaturations as independent variables, current annual combined family income and ethnicity as covariates, and performance on a measure of general intelligence (WASI-II FSIQ), processing speed (WISC-IV/WAIS-IV Coding), inhibition (D-KEFS Inhibition), and cognitive flexibility (D-KEFS Inhibition/Switching) as dependent variables. Linearity was established by visual inspection of a scatterplot and there was no evidence of multicollinearity, as evidenced by no tolerance values < 0.1 and no variance inflation factors (VIF) > 5. Although two unusual points were identified via examination of influence, none were deemed to need removal. There was homoscedasticity, as assessed by visual inspection of the studentized residuals plotted against the predicted values for the independent and dependent variables. The studentized residuals were normally distributed. Analysis of moderation was completed by creating a new high and low variable of the nocturnal oxygen desaturation variable one standard deviation above and below to determine the direction of the interaction.

Chapter 4: Results

Description of Participants

The 81 total participants included 46 females (57%) and 35 males (43%). Age ranged from 9 years to 63 years of age ($\bar{x}$ = 24.83). Participants were asked to identify their parents as either African American or Other, and 62% indicated that at least one of their parents identified as African American. Regarding socioeconomic status, current family income was considered. A majority of the sample reported a current family income of $20-39K (40%), while other portions of the sample indicated incomes of less than $20K (17%), $40-59K (16%), $60-79K (11%), $80-99K (9%), and $100K or above (7%; see Table 4).

Table 4

Demographic characteristics of the three groups combined

Demographic	**$\bar{x}$ (*SD*)**	
Age	24.83 (*10.75*)	
Demographic	***N***	**Frequency**
Gender		
Female	46	56.8%
Male	35	43.2%
Parent Race		
At least one parent identified as African American	50	61.7%
Neither parent identified as African American	31	38.3%
Current Combined Annual Family Income		
Less than $20,000	14	17.3%
$20-39,000	32	39.5%
$40-59,000	13	16%
$60-79,000	9	11.1%
$80-99,000	7	8.6%
$100,000 or above	6	7.4%

Demographic Differences and Relationships

Chi square tests were utilized to determine whether there were significant group differences in the categorical demographic variables (i.e., gender, ethnicity, current family income). While age varied across the three groups, the dependent variables (viz., neuropsychological outcomes) are normed based by age and therefore, analyzing group differences based on age was not necessary (see Table 5).

Gender

Binary gender was coded as either female or male. The control group was 62% female and 38% male. The sickle cell group was 53% female and 47% male, while the non-sickle anemia group was 56% female and 44% male. No significant differences in gender between groups were observed, x^2 (2, N = 81) = .55, p = .76.

Ethnicity

Ethnicity was collapsed into two options, either African American or Other given the prevalence of sickle cell disease in the African American population. Participants were categorized as African American if they reported having at least one parent who is African American and Other if they reported Other for both parents. The control group was 83% African American and 17% Other, while the sickle cell disease group was 76% African American and 24% Other. The non-sickle anemia group had no participants who reported having an African American parent (100% Other). As a result, there were significant differences in ethnicity between groups , x^2 (2, N = 65) = 37.59, p = < .001, and these differences were considered as covariates.

Current Combined Annual Family Income

While all three groups had a majority of participants endorsing a current combined family income of $20-39K (31% of controls, 47% of SCD, and 39% of non-sickle anemia), the variance

for the SCD group was lower than the other two groups, such that no participants endorsed an income of $80-99K or $100K or above, while 38% of controls and 11% of the non-sickle anemia group reported a family income above $80K. As a result, statistically significant differences between groups were observed, x^2 (10, N = 81) = 22.8, p = .01, and were considered in the analyses.

Table 5

Demographic characteristics of each group

	Control (*n* = 29)		**SCD (*n* = 34)**		**Non-sickle Anemia (*n* = 18)**		
Demographic	***N***	**Frequency**	***N***	**Frequency**	***N***	**Frequency**	***p***
Gender							.76
Female	18	62%	18	52.9%	10	55.6%	
Male	11	37.9%	16	47.1%	8	44.4%	
Race							<.001
At least one parent identified as African American	24	82.8%	26	76.4%	0	0%	
Neither parent identified as African American	5	17.2%	8	23.5%	18	100%	
Current Combined Annual Family Income							.01
$0-19,000	6	20.7%	7	20.6%	1	5.6%	
$20-39,000	9	31%	16	47.1%	7	38.9%	
$40-59,000	2	6.9%	6	17.6%	5	27.8%	
$60-79,000	1	3.4%	5	14.7%	3	16.7%	
$80-99,000	6	20.7%	0	0%	1	5.6%	
$100,000 or above	5	17.2%	0	0%	1	5.6%	

Dependent Variables

FSIQ

The WASI-II FSIQ has a mean of 100 (50th percentile) and a standard deviation of 15. Broadly average scores range from 85 to 115, with lower scores indicating poorer performance and higher scores indicating better performance. The control group performed in the average range with a mean of 100.14 (50th percentile) with a standard deviation of 13.18. The non-sickle anemia group also performed in the average range with a mean of 100.83 (50th percentile) and a standard deviation of 9.56. The sickle cell group also performed in the average range, though the mean was lower than the other two groups at 91.65 (30th percentile) with a standard deviation of 9.7. No outliers were identified. Overall, the combined groups performed in the average range with a mean score of 96.73, standard deviation of 11.75.

Processing Speed

The Coding subtest on both the WISC-IV and the WAIS-IV has a mean of 10 and a standard deviation of 3. The control group performed in the average range with a mean of 9.59 (37th percentile) and a standard deviation of 2.16. The non-sickle anemia group also performed in the average range with a mean of 10.17 (50th percentile) with a standard deviation of 3.22, while the sickle cell group performed in the low average range with a mean of 7.26 (16th percentile) with a standard deviation of 2.33. No outliers were identified and the combined groups performed in the average range with a mean of 8.74 (25th percentile) and a standard deviation of 2.77.

Inhibition

The Inhibition trial from the Color-Word Interference of the D-KEFS also has a mean of 10 and a standard deviation of 3. The control group performed in the average range with a mean of 10.24 (50th percentile) and a standard deviation of 2.49. The non-sickle anemia group also

performed in the average range with a mean of 9.89 (37th percentile) with a standard deviation of 2.76. The sickle cell group performed in the average range with a mean of 8.53 (25th percentile) and a standard deviation of 2.83. No outliers were identified and the combined groups performed in the average range with a mean of 9.44 and a standard deviation of 2.78.

Cognitive Flexibility

The Inhibition/Switching trial, from the Color-Word Interference of the D-KEFS, which measures cognitive flexibility, also has a mean of 10 and a standard deviation of 3. The control group performed in the average range with a mean of 9.45 (37th percentile) and a standard deviation of 2.48. The non-sickle anemia group also performed in the average range with a mean of 10 (50th percentile) with a standard deviation of 2.11. The sickle cell group performed in the average range with a mean of 8.26 (25th percentile) with a standard deviation of 3.13. No outliers were identified and the combined groups performed in the average range with a mean of 9.07 and a standard deviation of 2.77.

Hypothesis Testing

The aim of the current study was to distinguish the neuropsychological effects of nocturnal oxygen desaturations in individuals with sickle cell disease to those with non-sickle anemia and healthy controls. Hypotheses were tested using a multivariate linear regression to determine statistically significant differences between the three groups and their interaction with nocturnal oxygen desaturations on four outcome measures, while controlling for current family income and ethnicity.

Hypothesis 1a

The first hypothesis predicted that individuals with sickle cell disease would demonstrate significantly lower general intelligence, processing speed, inhibition, and cognitive flexibility when compared to those with non-sickle anemia and healthy controls.

FSIQ. Multivariate linear regression revealed no significant differences between the SCD group when compared to the other two groups with regard to FSIQ (WASI-II FSIQ, comparing SCD to controls, $b = 0.84$, $t(73) = 0.209$, $p = 0.84$; comparing SCD to non-sickle anemia, $b = 9.80$, $t(73) = 1.79$, $p = 0.08$).

Processing Speed. With regard to processing speed, no significant differences were found when comparing the SCD group with the control group (WISC-IV/WAIS-IV Coding, $b = 0.542$, $t(73) = 0.601$, $p = 0.55$). However, when comparing the SCD group with the non-sickle anemia group, processing speed was statistically significant, with the non-sickle anemia group performing better overall ($b = 5$, $t(73) = 4.05$, $p = <.001$).

Inhibition. Similar to processing speed, no significant differences were found when comparing the SCD group with the control group (D-KEFS CW Interference Inhibition, $b = 0.04$, $t(73) = 0.04$, $p = 0.97$). However, again, when comparing the SCD group with non-sickle anemia group, performance on a this measure of inhibition was significant, with the non-sickle anemia group performing better overall ($b = 2.7$, $t(73) = 2.07$, $p = 0.042$).

Cognitive Flexibility. Similar to processing speed and inhibition, no significant differences were found when comparing the SCD group with the control group (D-KEFS CW Interference Inhibition/Switching, $b = 0.922$, $t(73) = 0.93$, $p = 0.36$). A significant difference was revealed when comparing the SCD group to the non-sickle anemia group ($b = 4$, $t(73) = 2.94$, $p = 0.004$).

Hypothesis 1b

The second hypothesis predicted that individuals with an increased number of nocturnal oxygen desaturations, regardless of disease status, would demonstrate significantly lower general intelligence, processing speed, inhibition, and cognitive flexibility. No significant differences were revealed (FSIQ, $b = 0.036$, $t(73) = 0.07$, $p = 0.945$; Processing Speed, $b = 0.2$, $t(73) = 1.74$,

$p = 0.09$; Inhibition, $b = 0.135$, $t(73) = 1.07$, $p = 0.29$; Cognitive Flexibility, $b = 0.08$, $t(73) = 0.61$, $p = 0.541$).

Hypothesis 1c

The third hypothesis posited that individuals with sickle cell disease and greater nocturnal oxygen desaturation events will demonstrate significantly lower general intelligence, processing speed, inhibition, and cognitive flexibility when compared to those with non-sickle anemia and healthy controls.

FSIQ. Multivariate linear regression revealed no significant differences when examining the interaction of nocturnal oxygen desaturations between the SCD group when compared to the other two groups with regard to FSIQ (WASI-II FSIQ, comparing SCD to controls, $b = 0.25$, $t(73) = 0.87$, $p = 0.39$; comparing SCD to non-sickle anemia, $b = .0124$, $t(73) = 0.06$, $p = 0.95$).

Processing Speed. With regard to an interaction between oxygen desaturations and disease status impacting processing speed, significant differences were found when comparing the SCD group with the control group (WISC-IV/WAIS-IV Coding, $b = 0.55$, $t(73) = 2.08$, $p = 0.04$). Significant differences were also found when comparing the SCD group with the non-sickle anemia group ($b = 1.12$, $t(73) = 2.54$, $p = 0.013$). Simple slope analysis revealed that in both cases, higher values of nocturnal oxygen desaturations predicted lower processing speed scores for the SCD group when compared to both the non-sickle anemia group and the control group, suggesting a moderating effect of oxygen desaturations on processing speed (comparing SCD to controls, $b = 0.013$, $SE = 0.02$, $p = 0.05$; comparing SCD to non-sickle anemia, $b = 0.044$, $SE = 0.013$, $p = 0.013$).

Inhibition. When examining the interaction of nocturnal oxygen desaturations between the SCD group compared to the control group with regard to inhibition, no significant differences were found (D-KEFS CW Interference Inhibition, $b = 0.41$, $t(73) = 1.44$, $p = 0.15$).

Similarly, there was no significant interaction when comparing the SCD group with non-sickle anemia group ($b = 0.3$, $t(73) = 0.64$, $p = 0.53$).

Cognitive Flexibility. No significant differences were found when comparing the SCD group with the other two groups with regard to disease status interacting with oxygen desaturations and its impact on cognitive flexibility (D-KEFS CW Interference Inhibition/Switching, comparing SCD to controls, $b = 0.25$, $t(73) = 0.87$, $p = 0.39$; comparing SCD to non-sickle anemia, $b = 0.35$, $t(73) = 0.72$, $p = 0.48$).

Chapter 5: Discussion

The purpose of this study is to expand the literature examining the neuropsychological implications of disordered sleep in the sickle cell population across the lifespan. More specifically, this study aimed to explore the neuropsychological correlates of individuals with sickle cell disease who experience nocturnal oxygen desaturations and compare them to individuals with non-sickle anemias and healthy controls. Further examination of neuropsychological functioning in this population could lead to early interventions to increase quality of life.

Summary of Results

Disease status and its interaction with nocturnal oxygen desaturations, which was used as a proxy for disordered sleep, and their effect on various areas of neurocognitive functioning were examined. Interestingly, significant main effects were revealed in analyses comparing the SCD group with the non-sickle anemia group in processing speed, inhibition, and cognitive flexibility, while no differences were revealed when comparing SCD to the control group. While a main effect of nocturnal oxygen desaturations was not revealed, this variable did appear to act as a moderator in the interaction between disease status and processing speed, such that a greater number of oxygen desaturations in the SCD group when compared to the non-sickle anemia group resulted in lower processing speed scores for SCD individuals.

Interpretation of Findings

Main Effects

The SCD group, when compared to the non-sickle anemia group, appeared to perform more poorly in areas assessing processing speed, inhibition, and cognitive flexibility. As noted earlier, the D-KEFS CW Interference – Inhibition and D-KEFS CW Interference – Inhibition/Switching subtests are both timed tests. This means processing speed is a factor for

performance on these tasks. Theoretically, inhibition and cognitive flexibility are higher order executive functions while processing speed is a foundational ability that underlie higher order functions. Thus, individuals with slower speed of mental processing would inherently perform more poorly on both subtests. It is possible that a slower processing speed may have impacted inhibition and cognitive flexibility in the SCD population when compared to the non-sickle anemia population, which could account for these findings.

These findings are similar to previous research conducted in this population. Vinchinsky and colleagues also observed differences in processing speed and measures of executive functioning on the D-KEFS when comparing adults with sickle cell anemia to healthy controls and postulated that a possible cause of cognitive difficulties in this population is hypoxic dysfunction and subsequent reduced oxygen delivery to the brain (Vinchinsky et al., 2010). While the sample size was small, researchers in London also observed executive functioning and processing speed deficits in all 36 sickle cell participants, though severity of neurocognitive dysfunction was correlated with MRI findings, such that individuals with evidence of silent cerebral infarcts and severe infarcts on imaging performed worse on these measures (Rawle et al., 2010). Another group of researchers found similar results, with significant differences in processing speed in children with SCD when compared to healthy controls, citing insufficient oxygen delivery to the brain as a possible explanation (Bills et al., 2019).

Disease Status and Nocturnal Oxygen Desaturations

While an overall main effect of nocturnal oxygen desaturations on neuropsychological functioning was not revealed, it appears that when comparing the three groups, the SCD group performed more poorly on processing speed when oxygen desaturations were taken into account but only when compared to the non-sickle anemia group. Researchers from the University of South Carolina found that children with sleep apnea and sickle cell disease did not present with

greater cognitive deficits when compared to children with SCD only (Bills et al., 2019). However, another group of researchers found an association between nocturnal oxygen desaturation and executive functioning in children with SCA, and suggested that significant drops in nocturnal oxygen saturation may result in sleep fragmentation which may be related to neuropsychological problems (Hollocks et al., 2012). While Vinchinsky and colleagues demonstrated evidence of cognitive deficits in neurologically asymptomatic adults with SCD when compared to healthy controls, they cited not including a chronic anemia control group as a limitation of their study (Vinchinsky et al., 2010). The current study is one of the first to examine neurocognitive functioning in these three groups and these preliminary results have identified differences between individuals with sickle cell disease versus those with chronic anemia.

Treatment Implications

Researchers have demonstrated that CPAP therapy for SCD children significantly improved nocturnal oxygen saturations, performance on a processing speed task, and a self-reported reduction in pain during treatment (Marshall et al., 2009). They postulated that processing speed and attention showed greater sensitivity to the reversal of sleep-disordered breathing, possibly due to the impact of hypoxemia on frontal lobe functioning (Marshall et al., 2009). Poor adherence to using CPAP as prescribed has been well-documented in medical literature, with cognitive factors of the patient being cited as a potential barrier (Shapiro & Shapiro, 2010).

Findings from this study add to the growing literature of the potential cognitive impact of disordered sleep in the sickle cell population. These findings may be beneficial when treating these patients both medically and psychotherapeutically. Understanding the neurocognitive consequences of sickle cell disease may help medical providers present information to patients in ways that increase understanding. Considering potential processing speed deficits in this

vulnerable population, clear and paced dissemination of information is encouraged. Should CPAP therapy be recommended as part of treatment, these factors become especially important. Further, helping patients understand the downstream neuropsychological consequences of poor adherence may help increase compliance with treatment recommendations. This becomes important when treating these patients in a behavioral health setting. Cognitive behavioral therapy has been shown to be effective in reducing pain and psychological coping ability (Anie et al., 2002; Thomas et al., 1999). It is especially important for psychotherapists working with this vulnerable population understand the neuropsychological impact associated with both SCD and disordered-sleep to ensure adequate understanding and thus, improve adherence, reduce pain crises which may reduce hospitalizations, and improve medical decision making. While ensuring adequate sleep is important for all therapy patients due to its significant impact on mood, this becomes especially important when treating patients with SCD. Improved processing speed, as a result of improved sleep and oxygen delivery to the brain, may likely result in a better quality of life for these individuals.

Limitations and Future Directions

Several limitations should be considered in this study. The sample size is relatively small overall and the break down into groups further limits statistical power. A larger sample size would provide more power and generalizability to the population. In an effort to maintain power, children and adults were both included in this study. Differences in cognitive functioning and markers of disordered sleep between adults and children poses a potential limitation. A larger sample size examining adults and children separately would be beneficial. Further, there were demographic differences between groups, with no African American participants in the non-sickle anemia group. While the healthy control group was well-matched to the SCD group, better matched anemia controls would be ideal in future research. Due to limited available data, sleep-

disordered breathing was examined by using a proxy variable. Incorporating additional measures of disordered sleep (e.g., measures of respiration and airflow, measures of fragmented sleep, number of arousals, etc.) would provide more nuanced markers of disordered sleep. In addition to polysomnography, self-reported measures of sleep quality and daytime sleepiness would also provide a subjective measure of sleep. Similarly, measures of anxiety and depression would provide more information on the relationship between emotional functioning and sleep in this population. Inclusion of white matter hyperintensities from imaging would be an interesting next step, as silent cerebral infarcts along with normal MRIs have also been associated with impaired neuropsychological functioning in the SCD population.

In summary, this study adds to limited preexisting research on the relationship between disordered sleep and neurocognitive functioning in the sickle cell population by suggesting that higher rates of nocturnal oxygen desaturations may be associated with slower speed of mental processing when compared to those with non-sickle anemia. While further studies are needed to confirm and expand on these findings, these findings have the potential to aid in the identification of cognitive deficits and inform both medical and psychological treatment. Routine neuropsychological screening may contribute to early detection of cerebrovascular events in patients with SCD and potentially prevent adult neuropsychological dysfunction (Edwards et al., 2007). Given that brain injury secondary to cerebrovascular events may produce functional cognitive, social, and interpersonal impairments, it is imperative to screen for and manage neurocognitive deficits as part of routine and standard of care (Burlew et al., 2000; Edwards et al., 2007). Early and frequent neuroimaging and neuropsychological testing may identify those at risk and early rehabilitation efforts restoring oxygen may lead to a greater recovery of function and a higher quality of life for this vulnerable population.

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APPENDIX

Notice of Approval for Human Research

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

NOTICE OF APPROVAL FOR HUMAN RESEARCH

Date: September 28, 2021
Protocol Investigator Name: Sheena Ram
Protocol #: 21-01-1521
Project Title: Neuropsychological Implications of Nocturnal Hypoxemia in Sickle Cell Disease
School: Graduate School of Education and Psychology
Dear Sheena Ram:

Thank you for submitting your application for expedited 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. As the nature of the research met the requirements for expedited review under provision Title 45 CFR 46.110 of the federal Protection of Human Subjects Act, the IRB conducted a formal, but expedited, review of your application materials.

Based upon review, your IRB application has been approved. The IRB approval begins today September 28, 2021, and expires on September 27, 2022.

The consent form included in this protocol is considered final and has been approved by the IRB. You can only use copies of the consent that have been approved by the IRB to obtain consent from your participants.

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. Please be aware that changes to your protocol may prevent the research from qualifying for expedited review and will require a submission of a new IRB application or other materials to the IRB. If contact with subjects will extend beyond September 27, 2022, a continuing review must be submitted at least one month prior to the expiration date of study approval to avoid a lapse in approval.

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