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Working Memory in Children with Neurocognitive Effects from Sickle Cell Disease: Contributions of the Central Executive And Processing Efficiency

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ABSTRACT

Children with sickle cell disease (SCD) are at risk for neurocognitive impairment due to disease effects including stroke, sleep disordered breathing, anemia-induced hypoxia, and small vessel occlusion. In particular, problems in working memory are an area of concern due to the importance of this construct in determining intelligence and academic functioning. According to Baddely's model, working memory is composed of verbal and spatial working memory, but it is unclear whether one aspect of working memory is more impacted than another in children with SCD. In addition, little is known about the role of two key components in SCD-related working memory deficits: the central executive and processing/rehearsal speed. Consequently, the aims of this study were to examine potential differences in verbal versus spatial working memory and the role of the central executive and processing speed in working memory among children with SCD. In addition, MRI findings were examined to understand the relationship between working memory deficits and neurocognitive sequelae. The results indicated that children with SCD perform more poorly than healthy controls on measures of working memory, central executive, and processing speed, but that there is not a difference in magnitude of deficit between spatial and verbal working memory. The central executive was found to mediate the relationship between disease status and working memory, but this relationship was not found for processing speed. Finally, midsagittal corpus callosum size, a measure of the extent of normal appearing white matter, was a better indicator of cognitive deficits than visible cerebral infarction.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Chapter One: Background and Literature Review

It is well established that children with sickle cell disease (SCD) are at high risk for deficits in neurocognitive functioning (Berklehammer et al., 2007; Brown et al., 1993; Schatz et al., 1999; Schatz et al., 2002; Schatz & Roberts, 2007). Among these deficits, working memory is a prominent area of impairment that has important implications for competency in a range of other cognitive and academic skills. The specific cognitive skills affected and associated biological risk factors that lead to problems in working memory are not as well understood. In order to effectively remediate problems in neurocognitive functioning in this population, neuropsychological research needs to better identify these specific factors that can be targeted though techniques such as cognitive training (Klingberg et al., 2005; Holmes & Gathercole, 2014; Soderqvist et al., 2012). In the following sections, I will discuss SCD, the impact of the disease on the brain, and how the disease affects neurocognitive functioning. Then I will describe major conceptual models of working memory and the implications of these models for understanding working memory deficits in SCD. For the purposes of the present study I will focus on Baddeley's model of working memory to evaluate the role of the central executive and rehearsal efficiency as factors in SCD-related working memory deficits.

Overview of SCD and Impact on the Brain

SCD is a chronic, genetic health condition, which affects the blood by producing S-type hemoglobin instead of the typical A-type hemoglobin (Steinberg, 1984). S-type hemoglobin produces red blood cells that undergo structural changes causing a rigid cell

membrane and sickle-shaped cells with higher viscosity and lower oxygen-carrying capacity (Meier & Miller, 2012). The most common genotype is homozygous HbSS, or sickle cell anemia, which is associated with more frequent pain episodes and additional complications as compared to heterozygous genotypes such as HbSC and $Hb\beta^{+}$ thalassemia (Austin, Cohen, & Loseff, 2007). SCD affects 1 in 400 African American births and 1 in 1200 Hispanic-American births, but is also found in individuals from South or Central America, the Caribbean islands, Mediterranean countries, India and Saudi Arabia (Noll et al., 2001; Smith, 1999). Due to the rigidity and stickiness of the blood cells, blockage within the blood vessels can occur (Mousa & Qari, 2010; Yale, Nagib, & Guthrie, 2000), causing a vaso-occlusive pain episode, the hallmark symptom of SCD (Rees, Williams, & Gladwin, 2010). In addition to pain, children with SCD are also at risk for other complications including priapism, hip necrosis, anemia, jaundice, spleen damage, and eye problems (Rees et al., 2010; Wethers, 2000).

Prevalence. SCD can also affect the central nervous system. The associated effects of SCD on the brain cause significant disruption to quality of life including problems in academic achievement and social functioning (Brown et al., 1993, Noll, 1996). The most serious complication is stroke, which affects approximately 5% of children with SCD (Ohene-Frempong, 1998). The most common form of stroke in children is infarctive stroke while hemorrhagic stroke is more common in adults (Arkuszewski, 2010). The incidence of overt stroke is 1% of children with HbSC and $Hb\beta^{+}$ thalassemia and 5% of children with HbSS (Ohene-Frempong, 1998) with the highest rate occurring in the first decade of life (Adams, 1997; Arkuszewski, 2010).

Cerebral blood flow abnormalities may also appear without an overt stroke and are associated with cognitive deficits. The mostly widely understood source of neurologic deficits other than overt stroke is silent cerebral infarction (also referred to as silent stroke), a condition in which neuroimaging abnormalities consistent with cerebral infarction are detected in the absence of physical neurologic symptoms (Adams et al., 2001). Although silent stroke is considered to be less severe than overt stroke, both have been linked to neurocognitive complications (Schatz et al., 2001; Vichinsky et al., 2010). Silent stroke occurs in approximately 17 to 35% of children with SCD, 25% of which happen by adolescence (Pegelow et al., 2002; Moser et al., 1996; Steen, et al., 2003). Stroke has a high tendency of recurrence in children with SCD, with 67% of non-transfused patients having a subsequent stroke and 70% occurring in the first 3 years following initial stroke. A high risk of stroke recurrence can be reduced but not eliminated by chronic blood transfusion (Hulbert et al., 2006; Scothorn et al., 2002).

Neuroanatomical Effects of Stroke. Stroke in SCD is the result of vascular occlusion or hemorrhage in the brain (Adams et al., 1998); it is diagnosed by physical findings, supported by presence of vascular or parenchymal abnormalities on neuroimaging studies (Adams et al., 2001). Both overt and silent strokes occur with equal frequency in frontal, parietal and temporal lobes, although overt strokes more commonly affect the basal ganglia than silent strokes and involve both the cortex and deep white matter while silent strokes are confined to the deep white matter (Adams et al., 2001). The most common distribution for stroke in SCD is from brain regions relying on the middle cerebral artery followed by regions relying on the anterior cerebral artery. Thus, the dorsal regions of the frontal and parietal lobes are most often affected. Elevated transcranial doppler

ultrasound (TCD) velocities predict stroke risk in children with SCD by detecting elevated cerebral blood flow in the cerebral arteries. The elevated blood flow rate is typically caused by stenotic arteries that cause stroke either by restriction of blood flow or by causing artery-to-artery embolism (Adams, 1997).

In addition to visible cerebral infarction, children with SCD who have suffered an overt or silent stroke demonstrate decreased amounts of normal appearing white matter (Baldeweg et al., 2006), including smaller corpus callosum area on midsagittal section (Schatz and Buzan, 2006). Lesion volume and white matter deficits both appear to have an effect on cognitive ability including spatial abilities, language abilities, and information processing efficiency (Deary et al., 2006; Schatz et al., 1999).

Other Sources of Neurocognitive Deficit. Neurocognitive deficits also appear to occur without visible cerebral infarction, but the source of these deficits is not well understood (Schatz et al., 2002). Other possible sources of neurocognitive deficit include brain oxygenation and/or perfusion deficits in the absence of cerebral infarction. Sources of these functional brain effects may be sleep disordered breathing, anemia-induced hypoxia, or small vessel occlusion from sickling/sludging in the microvascular supply. For example, sleep disordered breathing has been associated with significantly raised middle cerebral artery blood flow velocities as well as significantly lower scores on measures of processing speed and visual attention (Hill et al., 2006). Subtle structural brain differences have been associated with chronic anemia as measured by low blood hematocrit level (Steen et al., 1999). Other forms of neurologic effects, such as inadequate brain perfusion, have been demonstrated in small case series but have not been studied in large or representative samples that allow for inferences about how

commonly these occur (Grueneich, et al., 2004). However, structural differences in the brain, such as cortical thinning and reduced volume of white matter tissue, can occur in children who have no visible cerebral infarction (Baldeweg et al., 2006; Daily, 2011). Anemia is present for children with more severe subtypes and is associated with lower blood oxygenation in the brain (Nahavandi et al., 2004) as well as age-related decline in cognitive performance (Vichinsky et al., 2010).

Neurocognitive Complications

The neurologic effects of SCD lead to decrements in cognitive skills that can be measured through intelligence tests designed to assess general cognitive ability (g) as well as more specific patterns of relative strengths and weaknesses. Studies that have examined differences among children with SCD find that group-level deficits are often due to a subset of children, suggesting selective neurologic effects in some children (Steen et al., 2005; Schatz et al., 2009). In a study of adults with SCD by Vichinsky and colleagues, the majority of participants were performing in the average range, but 33% of participants were performing in the below average range (2010). Armstrong and colleagues found that children who had experienced an overt stroke demonstrated the most significant deficits in IQ, with an average score of 70.8, children with silent stroke had an average IQ score of 82.8, and children with normal MRI's had an average IQ score of 90 (Armstrong et al., 1996). Even among children with no history of stroke, it appears that the group-level deficits in specific cognitive skills is due to approximately 25-30% of children who show poor performance, whereas the remaining children with SCD perform very similar to demographically-matched controls without SCD (Schatz et al., 2009).

Specific areas that are affected in children with SCD include attention, concentration, reading decoding (Brown, Buchanan et al., 1993) crystallized ability, processing speed, short-term memory (Schatz, Finke, & Roberts, 2004) and executive skills including working memory (Schatz & Roberts, 2007). Children with SCD also score lower than age-matched peers on measures of academic achievement and IQ, even in the absence of an overt or silent stroke (Schatz et al., 2002; Steen et al., 2005). However, other studies have found that children with SCD are performing overall in the average range in academic achievement (Smith, Patterson, Szabo, Tarazi, & Barakat, 2013). Symptoms of neurocognitive complications may appear in infancy and increase with age (Berklehammer, 2007). For example, studies have shown that deficits are already apparent even in young children. In a study of school readiness skills, kindergarteners with SCD, a sample that is not impacted by missed school days, scored significantly lower on a test of auditory discrimination, a skill necessary for learning to read (Steen et al., 2002).

Working Memory

Working memory involves the short-term maintenance and manipulation of information, which is important for tasks such as encoding information into long-term memory (learning), auditory comprehension, and reasoning (Baddeley, 2003). Working memory is also considered to be a critical function for most forms of higher-level cognition (McCabe, 2010). Due to the evidence that working memory is associated with academic ability (Alloway, 2004) and general intelligence (Conway, Kane, & Engle, 2003; Waiter, 2009) in children, understanding the prevalence and predictors of deficits

in working memory in children with SCD is important for providing academic and neurocognitive interventions for this population.

There are a variety of theoretical models that have been posited about the organization of working memory (Baddeley, 2012). These models vary in focus. For example, Cowen's embedded process theory involves a limited capacity attention focus that operates across areas of activated long term memory or Engle and colleagues' model which emphasizes inhibitory processes critical for shielding the memory content from potential disruption. Other models, like Jonides' model, are influenced by neuroimaging, and are based on the idea that short-term memory, long-term memory and perception are all located in the same anatomical regions. Computational models also contribute to the understanding of working memory, emphasizing computationally based interacting cognitive subsystems (Baddeley, 2012).

The multiple component model put forth by Baddeley is a leading model of working memory that has shown utility in understanding working memory development across the lifespan as well as working memory deficits in clinical populations (Baddeley, 2012). According to the multiple component model, working memory can be divided into modality specific rehearsal buffers including the phonological loop and visuospatial sketchpad, and a modality-independent central executive. The phonological loop is important for comprehension of speech under taxing situations while the visuospatial sketchpad measures the ability to hold and manipulate visuospatial representations and the central executive coordinates information from both of these systems (Baddeley 1992; Baddeley, 2003). Similar to the domain-general component of Baddeley's model, the executive attention model suggests that differences in working memory indicate

variations in attention control. For example, individuals with higher working memory capacity show better attentional control and are therefore better equipped to maintain and retrieve information when needed (Engle, 2002).

Adults and children with SCD show impairment on tasks of working memory in comparison to healthy controls (White, Salorio, Schatz & DeBaun, 2000; Vichinsky et al., 2010). Working memory is related to the ability to control attention, particularly under conditions that involve distraction or interference (Engle & Kane 2004 from McCabe 2010). Due to the evidence that children with SCD demonstrate problems with selective attention, children with SCD may also exhibit greater deficits in working memory (Craft et al., 1994; Schatz et al., 2001; Schatz, Craft, & Koby, 2000). Children with SCD who have experienced a stroke are at the greater risk for deficits in working memory (Brandling-Bennett, 2003; White, et al., 2000), with specific damage to key prefrontal regions (e.g., dorsolateral prefrontal cortex) associated with problems related to manipulating information in working memory (Brandling-Bennett, 2003).

It is unclear from prior research whether working memory deficits in SCD tend to be greater for specific types of information. In one study, researchers found that children with SCD show deficits in working memory, with more pronounced effects in the area of spatial working memory. However, the domain specific effects only showed a trend towards significance (Solorio, 2000). A second study indicated selective deficits for verbal working memory (Schatz & Roberts, 2005). The majority of studies examining working memory in children with SCD have yet to examine the individual contributions of verbal working memory and visuospatial working memory in children with SCD. For example, much of the existing literature focuses on verbal working memory with less

focus on visuospatial working memory tasks (White et al., 2000). Examining different domains of working memory is important to understand as it may provide guidance on rehabilitation strategies. For example, some researchers have suggested modality specific rehearsal systems, which suggests that children with SCD may have difficulties in working memory that reflect deficits in one area of working memory (i.e. the central executive) but not another area (i.e. the phonological loop) (Schatz & Roberts, 2005).

Working memory training leads to changes in brain structures and functions of the front parietal regions, which are critical for working memory (Takeuchi et al., 2011). Specific findings on the subsidiary or "slave systems" of working memory reveal that the tempoparietal region is indicated for the phonological loop, with Brodmann area 40 indicated as the location for the storage component and Broca's area indicated as the location for the rehearsal component. Although findings are less definitive for the underlying neural mechanisms of visuospatial working memory, research suggests that it is primarily localized in the right hemisphere (Baddeley, 2003). However, some studies suggest that a network of brain regions is associated with specific cognitive functions, including both the cortical structures and interconnecting white matter tracts. For example, the superior frontal and intraparietal cortex have been implicated as making up the visuo-spatial working memory network (Klingberg, 2006). Consequently more research is needed to understand how working memory is related to brain structures.

Central Executive

The four main functions of the central executive are focusing attention, dividing attention between two important targets or stimulus streams, switching between tasks, and the capacity to interface with long-term memory (Baddeley, 2012). Controlled by the

central executive, the episodic buffer is a limited capacity storage area that pieces together information to form integrated episodes (Baddeley, 2003). The dorsolateral prefrontal cortex is involved in the allocation and coordination of attentional resources, a unique process observed by the central executive component of working memory recruited during dual task performance. The anterior cingulate is also activated during dual task performance (D'Esposito, 1995; Collette & Van der Linden, 2002). Tasks assessing the central executive component of working memory most frequently show activation of the prefrontal dorsolateral cortex. However, it is likely that the central executive involves neural networks that include both prefrontal and posterior regions including posterior cortical areas and the posterior parietal cortex (Collette & Van der Linden, 2002).

Processing Speed

Processing speed refers to the speed that an individual completes basic cognitive processes with acceptable accuracy (Jacobson et al., 2011; Kail & Ferrer, 2007; Kaufman, DeYoung, Gray, Brown, & Mackintosh, 2009). Research shows that as children age, they are able to process information more rapidly in a variety of domains (Kail, 1991; Kail & Miller, 2006; Fry & Hale, 1996). According to Case, developmental increases in working memory performance are aided not only by increased speed of operations but also increased efficiency (1982). If information is not processed quickly and efficiently, it will be vulnerable to decay and interference from additional incoming information (Leonard et al., 2007). Better processing speed is associated with increased capacity of working memory, enhanced inductive reasoning, and greater accuracy in solving complex tasks such as arithmetic word problems (Kail & Ferrer, 2007).

Furthermore, age-related changes in speed of processing have both direct effects on cognitive performance and indirect effects by influencing the speed of more specific processes that, in turn, influence cognitive performance (Bayliss, 2005).

Processing speed, intelligence and working memory are correlated and develop in concert, influencing one another as they develop (Fry & Hale, 2000; Neisser et al., 1996). Processing speed and working memory are interrelated processes that occur such that faster processing speed leads to faster rehearsal, which should permit a greater amount of information to be held in working memory (Leonard et al., 2007). In addition, these two processes develop according to a developmental cascade where age related changes in processing speed lead to changes in working memory that lead to changes in performance on tests of fluid intelligence (Fry & Hale, 1996). For example, in a study by Fry and colleagues, researchers found that age related changes in processing speed mediated developmental increases in working memory capacity and that age related increases in processing speed and working memory accounted for half of total age-related effects on fluid intelligence (Fry & Hale, 1996). The greatest increase in processing speed occurs during early and middle childhood and continues to increase in late childhood and early adolescence, but reaches its limit in mid-to-late adolescence (Kail, 1991).

Research suggests that processing speed has a domain-general effect on working memory due to the effect that any task which requires attention prevents refreshment of information and a domain-specific effect on working memory through blocking of rehearsal or interference during verbal working memory tasks (Jarrold, Tam, Baddeley, & Harvey, 2011). Resource sharing models of working memory suggest that processing and storage functions of working memory compete for limited space and capacity. For

example in a study of reading span, poor readers used more working memory capacity to processing demands and less to storage demands, suggesting that the ability to process information with speed and efficiency may be better predictor of complex cognitive abilities than working memory (Daneman & Carpenter, 1980).

In addition to the impact on intelligence, processing speed affects specific aspects of cognitive functioning including language, making it an important target for intervention (Leonard et al., 2007). Children and adults with SCD score lower than controls on measures of processing speed (Schatz, Finke, & Roberts, 2004; Steen et al., 2005; Vickinsky et al., 2010). Children with SCD who have experienced a stroke spend significantly more time on processing speed tasks than a comparison group (children with SCD without stroke), but reaction time for both groups was slower on more difficult tasks (Salorio, 2000). Processing speed is also a significant predictor of working memory in healthy adults, even when IQ is controlled (Brown, Brockmole, Gow, & Deary, 2012). Therefore, processing speed could account for deficits in working memory in patients with SCD. However, some children with processing speed deficits may not have working memory deficits and vice versa, suggesting the importance of determining which mechanisms lead to the most functional impairment. For example, a study of young adults who received processing speed training showed significant improvement on measures of processing speed, but did not improve scores on measures of working memory, suggesting that these constructs may be separate (Takeuchi et al., 2011).

Imaging studies of processing speed show that training in this area leads to a reduction in the regional gray matter volume of the left superior temporal gyrus and the bilateral regions around the occipitotemporal junction (Takeuchi et al., 2011). However,

other studies suggest that efficient interregional communication between task relevant brain regions rather than functional differences in a specific brain region may be more salient in explaining processing speed differences, for example, through greater white matter tract integrity (Rypma et al., 2006; Penke et al., 2012).

Aims and Hypotheses

The purpose of this study is to gain a more comprehensive view of working memory in children with SCD by examining the contribution of the central executive and processing speed. In addition to this cognitive level of analysis, regional deficits in brain tissue will be examined to determine if region-specific relationships are observed for overall working memory, as well as the component elements of central executive and processing speed functions. Our working model is that the neurologic effects of SCD negatively impact processing speed, working memory, and central executive functioning, but that the degree of these effects varies across children with SCD. Therefore, we expect that at the group level children with SCD will show deficits across all three constructs (working memory, processing speed, central executive processes). Working memory deficits are also expected to occur to a similar degree across verbal and visual working memory, and both processing speed and central executive deficits can account for the working memory deficits. However, heterogeneity between children will occur with some children experiencing deficits in one area (i.e. processing speed) but not another (i.e. working memory) due to differential patterns of brain effects from SCD (e.g., decreased WM integrity, increased total lesion volume, lesions in specific prefrontal cortical regions). The specific hypotheses are:

(1) A demographically matched comparison group (healthy controls) will perform better on both measures of working memory (verbal and visuospatial), measures of processing speed, and measures of central executive processes than children with SCD.

(2) The magnitude of the deficit in verbal and spatial working memory in SCD will be similar, which we will define as an effect size difference for the two tasks of less than 5% explained variance.

(3) Including either processing speed or central executive measures into statistical models will significantly reduce the difference in working memory scores between children with SCD and controls. Thus, the pattern of associations will be consistent with processing speed and central executive deficits operating as mediators of the relationship between sickle cell disease status and working memory deficits.

(4) Within the SCD group, total volume of tissue effects (lesion volume, midsagittal CC area) will be associated with processing speed.

(5) Within the SCD group, the volume of tissue effects in prefrontal regions will be associated with overall working memory performance and central executive processes.

Chapter Two: Methods

Participants and Recruitment

Participants were recruited as part of a multi-site study to develop a new battery of executive function measures for use with children and adults experiencing neurologic disease. Children diagnosed with SCD genotypes at high risk for neurologic complications including HbSS and HbS-beta-thal^0 (n =34), and demographically-matched controls without neurologic disease (n = 85) were recruited from the South Carolina site of this study and used for these analyses of working memory. Exclusion criteria consisted of diagnosis of a co-morbid major medical, psychiatric, or developmental condition (e.g., autism, bipolar mood disorder, cancer, intellectual disability) or cognitive/motor limitations that would prohibit the child from participating in the cognitive testing.

Healthy controls were recruited from local after school care and summer care programs. These children were selected based on similar demographics as our SCD clinic population, who are primarily African-American and about half of whom are of lower socioeconomic status. Healthy controls were demographically similar to the SCD group with the exception of family income, which had a significantly higher representation of families earning more than $40,000 per year. In order to account for this difference, we controlled for family income in our analyses. Parents at these programs were sent a flyer with an accompanying letter, consent form, and demographic questionnaire for the study to return if interested. Children diagnosed with SCD were recruited at their clinic appointment at the Center for Children's Cancer and Blood Disorders at Palmetto Health

Richland. Children ranged in age from 8 to 18 with a mean age of 12.99 years. All children reported English as their primary language. Overall, children scored 13.18 on Dot Counting and 1.62 on the N-back task. Other descriptive statistics are presented in Table 2.1.

Procedures

Parents completed informed consent and children assented to participating in the study. Children participated in a single session of cognitive testing with a trained examiner. Two children with SCD and four healthy control children completed the testing in two sessions due to time constraints. Parents completed a demographic questionnaire and a behavioral report measure. If a family with a child with SCD wished to participate in the study, but the child was experiencing pain or other illness related complications, an assessment was scheduled for a later date. All children with SCD were offered the opportunity to complete an optional magnetic resonance (MR) imaging study. Eight participants completed the research MR exam. Those participants that did not wish to complete the research MR exam had a clinical MR/MRA exam within eighteen months of cognitive testing, however the majority of participants had MR exams within 3 months of testing (n = 27) and 3 participants had exams within 12 months of cognitive testing. Medical record reviews were conducted for the children with SCD to determine clinical history after cognitive testing and research MR exams had been completed. Reports from clinical exams were coded for study variables; a neuroradiologist reviewed the eight research scans to code the same variables.

Measures

EXAMINER Battery. The EXAMINER Battery provides factor scores that are created from 11 core variables used to compute a three-factor model (Fluency, Cognitive Control, Working Memory) and a Composite score based on a one-factor model. The factor scores are generated from several tasks including phonemic and category fluency tasks, a flanker task, a continuous performance test (CPT), a dot counting task, an n-back task, an anti-saccade task, a set-shifting task, and a behavioral rating form completed by the test administrator. Test–retest reliability for the battery was evaluated in 122 normal adult controls at an average interval of 25 days (Schatz, et al., 2014). The Executive Composite factor showed a test–retest reliability of $r = .93$. For the purposes of this study, we used the Working Memory factor and the Cognitive Control factor to represent central executive functions. In order to compute a processing speed variable, we computed the mean reaction speed from the flanker task and the set-shifting task. The dot counting task was used to represent verbal working memory and the n-back task was used for spatial working memory.

Working Memory Factor. The Working Memory factor is based on three variables derived from two tasks. The dot counting task and the n-back test. Test–retest reliability for the Working Memory factor was $r = .78$.

Cognitive Control Factor. The Cognitive Control factor is based on measures of inhibitory control, set shifting, and behaviors associated with the dysregulation of executive function. Within this factor are four variables including the total Flanker score, total Set Shifting score, anti-saccade total, and total dysexecutive errors. Higher scores

indicate poorer performance. The test–retest reliability for the Cognitive Control factor was r =.88.

Processing Speed Factor. The Processing Speed factor was computed as a mean of the reaction time scores from the Flanker task congruent trials and the Set Shifting non shift trials.

Dot Counting. The dot counting task measures verbal working memory. The participant counts the number of colored dots on the screen among distractors and then states the number of dots in each display. Higher scores indicate better performance on the task. This is considered a reliable measure of verbal working memory, α =.81.

N-Back Test. The n-back test measures spatial working memory. In this task children press a button whenever a square is presented in the same spatial location as the previous trial ("yes trials") and a different button if the square is presented in a different location as the previous trial ("no trials). Both total correct and d-prime are computed. Higher scores indicate better performance on the task. This is considered a reliable measure of nonverbal working memory, α =.64.

Set Shifting. The set shifting task measures accuracy and reaction time. In this task, participants match a stimulus on the top of the screen to one of two stimuli in the bottom corners of the screen. There are task-consistent blocks in which participants perform the task with only one element (either classifying shapes or classifying colors). In variant blocks participants switch back and forth between the two tasks pseudo-randomly with the target dimension expressed via the word ''shape'' or ''color'' presented at the bottom of the screen. Performance on the task-consistent and task-variant

blocks are compared to measure the performance differences between consistent and variant blocks (expressed in latency and accuracy) and the differences between switch and non-switch trials within the variant block (also expressed in latency and accuracy).

Flanker. In the Flanker Task, the participant focuses on a small cross in the center of the screen. After a short variable duration, a row of five arrows is presented in the center of the screen either above or below the fixation point. On half the trials, the flanking arrows are congruent with the direction of the center arrow and on half of the trials the flanking arrows are incongruent with the direction of the center arrow. The total Flanker score is derived from both error and response time data that is used to contrast performance on incongruent versus congruent trials.

Magnetic rResonance (MR) Exams and CC Measurement. All scans were collected without sedation. A total of twenty-eight children completed clinical MR, eight children completed research MR exams and four completed both scans. T1-weighted scans in the sagittal plane were used for CC measures. All of the clinical scans were collected on 1.5T scanners using a 2D T1-weighted spin echo sequence with a matrix size of 2563 192. A three-dimensional (3D) MP-RAGE sequence was used with a matrix of 2563 256 for research scans. All participants also had axial T2-weighted and T2-weighted FLAIR sequences that were used to identify regions with apparent cerebral infarction and a 3D time of flight MRA sequence to visualize the major cerebral arteries. Midsagittal CC measurements were completed as described previously (Schatz & Buzan, 2006). CC measurements were completed by two raters with high reliability (r = .98). Clinical and research scans showed comparable rank order and absolute size of the measurements for the participants completing both types of scans (e.g., total CC area was

M5 471.5mm2 for the clinical scans and M5 467.3mm2 for the research scans). Finally, the potential confound of normal demographic effects (e.g., age) impacting analyses of the CC variables was examined. Age and gender were determined to account for little variance in CC size. Therefore, observed CC area was used in all analyses without any age correction.

Statistical Methods

For hypothesis one, we used repeated measures and univariate ANOVA to determine whether normal controls will perform better on measures of working memory, processing speed, and central executive processes than children with SCD. Age was included as a covariate to reduce unexplained variance because EXAMINER variables were not age corrected. In addition, family income level was included as a covariate to eliminate variance that could be due to this potential confound. For hypothesis two, the similarity of the magnitude of the deficit in verbal and spatial working memory in SCD will be examined, which we will define as an effect size difference for the two tasks of less than 5% explained variance in the group by modality interaction term. For hypothesis three, we will use a regression approach to examine mediation effects to determine if including either processing speed or central executive measures into statistical models will significantly reduce the difference in working memory scores between children with SCD and controls. The Sobel test will be used to assess the extent of mediation. Finally, for hypotheses four and five, we will use a correlation to determine if within the SCD group, total volume of tissue effects (lesion volume, midsagittal CC area) is associated with processing speed and if the volume of tissue effects in prefrontal regions is associated with overall working memory performance and

central executive processes. The assumptions of normality, linearity, independence, and homoscedasticity were met for all analyses.

Table 2.1. *Descriptive Characteristics of the Sample*

Variable	**SCD**	**Normal Controls**
N (%)	34 (29.1)	83 (70.9)
Age (8 - 18yrs)	13.1 (2.54)	12.73 (3.16)
Family Income		
<$10K	7 (8.2)	8 (25.0)
$10K-19K	9 (10.6)	6 (18.8)
$20K-29K	16 (18.8)	9 (28.1)
$30K-39K	16 (18.8)	4 (12.5)
>$40K	37 (43.5)	5 (15.6)
Working Memory Factor	-.653	-.180
Dot Counting (Verbal Working Memory)	-.429	.161
N-back (Spatial Working Memory)	-.629	.182
Processing Speed	1040.80	836.80
Cognitive Control Factor (Central Executive)	.634	-.054

Chapter Three: Results

Hypothesis One: Healthy controls will perform better on both measures of working memory, measures of processing speed, and measures of central executive processes than children with SCD. Controlling for age and annual family income, normal controls performed significantly better than children with SCD on the dot counting test of verbal working memory, $F = 8.405$, $p = .005$, partial $\eta^2 = .073$, the N-back test of spatial working memory, $F = 14.532$, $p = .000$, partial $\eta^2 = .134$, working memory factor, $F = 15.167$, $p = .000$, partial $\eta^2 = .123$, processing speed, $F(1, 108) = 13.966$, $p = .000$, and central executive processes, $F(1, 111) = 23.785$, $p = .000$, partial $\eta^2 = .180$. Results of these analyses can be found in Tables 3.1 through 3.3.

Hypothesis Two: The magnitude of the deficit in verbal and spatial working memory in SCD will be less than 5% explained variance. There was not a significant difference in performance on verbal and spatial working memory in children with SCD, $F = 1.347$, $p = .249$. The modality factor accounted for less than 5% explained variance (partial $\eta^2 = .014$).

Hypothesis Three: Processing speed and central executive processes will operate as mediators of the relationship between sickle cell disease and working memory deficits. For the pattern of associations to be consistent with a mediation model, the independent variable (disease status) must be associated with both the mediator (processing speed, central executive) and the dependent variable (i.e., working memory).

These associations were established in testing Hypothesis 1 (see above). In addition, there should be a significant decrease in explained variance between the independent variable and dependent variable when adding the potential mediation.

In order to test for mediation, we followed Baron and Kenny's statistical guidelines (1986). First, we conducted a regression of the central executive on diagnosis. Then we conducted a regression of working memory on diagnosis. Finally, we conducted a regression of working memory on both central executive and diagnosis variables. Controlling for age and family income, diagnosis explains 34% of the variance in working memory [$R^2 = .34$, $F(3,108) = 18.85$, $p < .05$]. Including processing speed in the model does not account for significantly more variance in working memory [I$R^2 = -.002$, $F(4,103) = 13.95$, $p < .05$] ,and the Sobel test was not statistically significant ($z = -.60$, $p = .548$) (See Table 3.4). However, the parallel hierarchical regression model including the central executive as the mediator in the model was significant [I$R^2 = .058$, $F(4,106) = 17.87$, $p < .05$] and the Sobel test was statistically significant ($z = 2.88$, $p = .004$) (See Table 3.5).

Due to the apparent importance of the Cognitive Control factor in accounting for working memory deficits, we conducted follow-up tests of the individual variables that were used to compute this factor. ANCOVA models (controlling for age and family income) for each of these four variables are shown in Tables 3.6 through 3.9. We computed means for each of the subtests of the cognitive control factor to examine differences between children with SCD and normal controls. There were significant differences in scores between the two groups on the Set Shifting and Flanker score tasks. In order to determine whether scores on these specific subtests mediated the relationship

between diagnosis and working memory, we conducted regressions of diagnosis on Set Shifting and Flanker tasks and these tasks on working memory. The parallel hierarchical regression model including Set Shifting was significant [$IR^2 = .096$, $F(3,102) = 25.53$, $p < .05$] (See Table 3.10) and the Sobel test was statistically significant ($z = 2.17$, $p = .030$). The parallel hierarchical regression model including the Flanker score was also significant [$IR^2 = .074$, $F(3,98) = 25.64$, $p < .05$] (See Table 3.11). However, the Sobel test was not statistically significant at $p < .05$ ($z = 1.93$, $p = .054$). See figures 3.1 through 3.4 for graphical depictions of mediation models.

Hypothesis Four: Within the SCD group, total volume of tissue effects will be associated with processing speed. Using a Spearman correlation, we determined that processing speed is correlated with CC total area, CC anterior, and CC posterior at $p < .05$. See Table 3.12 and Table 3.13 for correlations.

Hypothesis Five: Within the SCD group, the volume of tissue effects in prefrontal regions will be associated with overall working memory performance and central executive processes. Using a Spearman correlation, we determined that working memory is correlated with CC anterior at $p < .01$, but is also correlated with CC posterior at $p < .01$. The same pattern occurs for verbal working memory at $p < .05$ for both CC anterior and CC posterior. However, spatial working memory showed only a trend toward significance with CC posterior and was not significantly correlated with CC anterior at $p < .10$. Central executive measures are correlated with CC anterior at $p < .05$ and CC posterior at $p < .10$.

Table 3.1. *Results of ANOVA of Verbal Working Memory*

Variable	**SS**	**df**	**MS**	***F***	***p***	***Partial η^2***
Intercept	15.91	1	15.91	19.88	.000	.158
Age	16.01	1	16.01	20.02	.000	.159
Family Income	.002	1	.002	.003	.960	.000
Diagnosis	6.73	1	6.73	8.41	.005	.073
Error	84.82	106	.800			
Total	109.00	110				

Table 3.2. *Results of ANOVA of Spatial Working Memory*

Variable	**SS**	**df**	**MS**	***F***	***p***	***Partial η^2***
Intercept	9166942.08	1	9166942.08	164.32	.000	.610
Age	1081837.28	1	1081837.28	19.39	.000	.156
Family Income	122342.59	1	122342.59	2.19	.142	.020
Diagnosis	779124.87	1	779124.87	13.97	.000	.117
Error	5857510.99	105	55785.82			
Total	9.45	109				

Table 3.3. *Results of ANOVA of Central Executive*

Variable	**SS**	**df**	**MS**	***F***	***p***	***Partial η^2***
Intercept	35.20	1	35.20	88.72	.000	.451
Age	27.63	1	27.63	69.63	.000	.392
Family Income	1.22	1	1.22	3.08	.082	.028
Diagnosis	6.73	1	6.73	8.41	.005	.073
Error	42.85	108	.397			
Total	89.48	112				

Table 3.4. *Processing Speed Regression*

Variable	**β**	**IR^2**	**Total R^2**
Step 1			
Age	.436	.252*	.252
Family Income	.065		
Step 2	-.308	.097*	.349
Diagnosis			
Step 3	-.057	.002	.351
Processing Speed			

Table 3.5. *Central Executive Regression*

Variable	**β**	**IR^2**	**Total R^2**
Step 1	.		
Age	.268	.251*	.251
Family Income	.021		
Step 2			
Diagnosis	.011	.093*	.345
Step 3			
Central Executive	-.344	.058*	.403

Table 3.6. *Results of ANOVA of Flanker Score*

Variable	**SS**	**df**	**MS**	***F***	***p***	***Partial η^2***
Intercept	54.37	1	54.37	45.13	.000	.315
Age	48.52	1	48.52	40.28	.000	.291
Family Income	11.09	1	11.09	9.20	.003	.086
Diagnosis	15.50	1	15.50	12.86	.001	.116
Error	118.07	98	1.21			
Total	6635.87	102				

Table 3.7. *Results of ANOVA of Set Shifting Score*

Variable	**SS**	**df**	**MS**	***F***	***p***	***Partial η^2***
Intercept	28.34	1	28.34	88.72	.000	.218
Age	50.04	1	50.04	69.63	.000	.330
Family Income	.97	1	.97	3.08	.326	.009
Diagnosis	17.10	1	17.10	8.41	.000	.144
Error	101.56	102	1.00			
Total	4623.83	106				

Table 3.8. *Results of ANOVA of Dysexecutive Errors*

Variable	**SS**	**df**	**MS**	***F***	***p***	***Partial η^2***
Intercept	2223.99	1	2223.99	47.08	.000	.343
Age	660.90	1	660.90	13.99	.000	.135
Family Income	86.62	1	86.62	1.83	.179	.020
Diagnosis	41.86	1	41.86	.89	.349	.010
Error	4251.59	90	47.24			
Total	15359.00	94				

Table 3.9. *Results of ANOVA of Antisaccade Score*

Variable	**SS**	**df**	**MS**	***F***	***p***	***Partial η^2***
Intercept	111.21	1	111.21	1.57	.217	.034
Age	756.73	1	756.73	10.67	.002	.192
Family Income	151.33	1	151.33	2.13	.151	.045
Diagnosis	102.49	1	102.49	1.45	.236	.031
Error	3192.80	45	70.95			
Total	38527.00	49				

Table 3.10. *Set Shifting Regression*

Variable	**β**	**IR^2**	**Total R^2**
Step 1			
Age	.368		
Family Income	.055	.260*	.260
Step 2			
Diagnosis	-.255	.099*	.359
Step 3			
Set Shifting	.263	.031*	.389

Table 3.11. *Flanker Score Regression*

Variable	**β**	**IR^2**	**Total R^2**
Step 1			
Age	.333		
Family Income	.040	.248*	.248
Step 2			
Diagnosis	-.221	.079*	.327
Step 3			
Flanker Score	.247	.034*	.361

Table 3.12. *Correlations*

	Working Memory	Proc. Speed	Central Exec	Lesion Volume	Total CC	CC Anterior	CC Posterior
Working Memory	_	-.362**	-.595**	-.192	.501**	.492**	.489**
Proc. Speed	-.362**	_	.781**	.291	-.409*	-.397*	-.406*
Central Exec	-.595**	.781**	_	.181	-.394*	-.373*	-.323
Lesion Volume	-.192	.291	.181	_	-.264	-.491**	-.020
Total CC	.501**	-.409*	-.394*	-.264	_	.882**	.913**
CC Anterior	.492**	-.397*	-.373*	-.491**	.882**	_	.663**
CC Posterior	.489**	-.406*	-.323	-.020	.913**	.663**	_

Table 3.13. *Correlations Controlling for Age*

	Working Memory	Proc. Speed	Central Exec	Lesion Volume	Total CC	CC Anterior	CC Posterior
Working Memory	_	-.215**	-.455**	-.439**	.359	.479**	.165
Proc. Speed	-.215**	_	.677**	.315	-.319	-.363*	-.202
Central Exec	-.455**	.677**	_	.422**		-.431**	.000
Lesion Volume	-.439**	.315	.422**	_	-.462**	-.565**	-.257
Total CC	.359	-.319	-.246	-.462**	_	.906**	.893**
CC Anterior	.479**	-.363*	-.431**	-.565**	.906**	_	.620**
CC Posterior	.165	-.202	.000	-.257	.893**	.620**	_

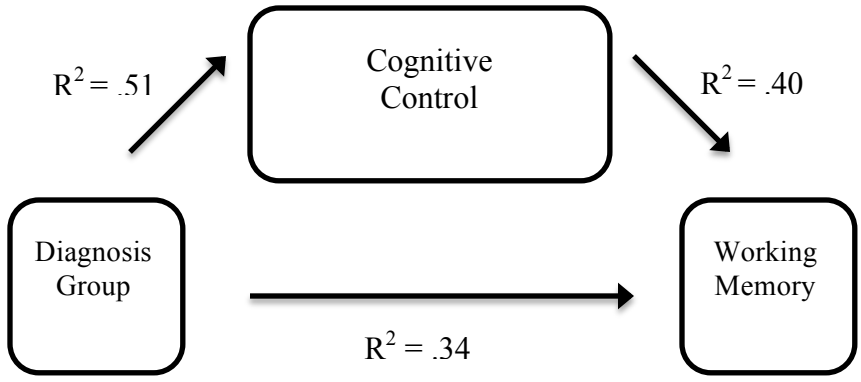

Figure 3.1. *Cognitive Control Mediation*

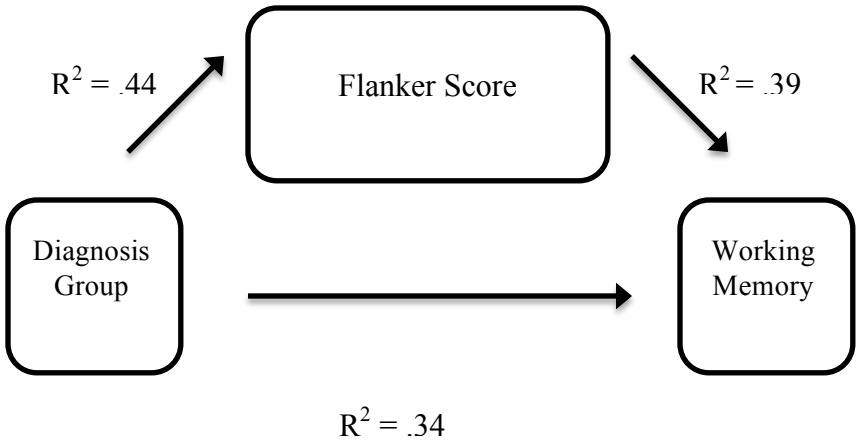

Figure 3.2. *Flanker Score Mediation*

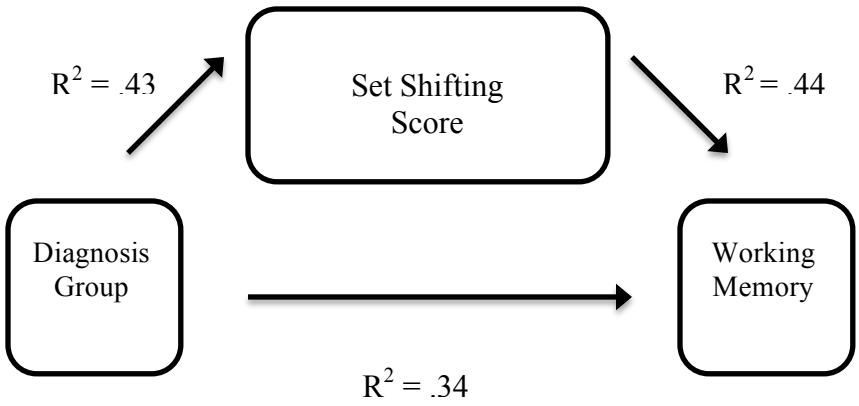

Figure 3.3. *Set Shifting Mediation*

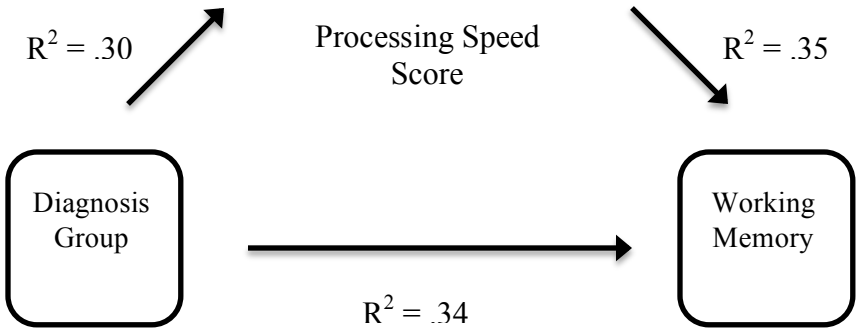

Figure 3.4. *Processing Speed Mediation*

Chapter 4: Discussion

The present study examined working memory in children with SCD as well as the contribution of specific central executive processes and processing speed to working memory functioning in this population. As expected, healthy controls performed better than children with SCD on measures of working memory, processing speed, and central executive functioning. This is not surprising considering evidence from previous studies that demonstrate that individuals with SCD show deficits in working memory compared to healthy individuals (White, Salorio, Schatz & DeBaun, 2000; Vichinsky et al., 2010). However, fewer studies have examined processing speed or the specific central executive processes of working memory. To better understand deficits in working memory among children with SCD, we analyzed whether there are differences between verbal and spatial working memory. Performance on these two modalities of working memory was not significantly different. Our findings suggest that assessment to detect problems and remediation to improve working memory may not need to be specific to verbal or spatial working memory, a finding that has been confirmed in other populations with working memory problems. For example, in a study of adolescents with ADHD, training either verbal or spatial working memory was equally as effective in improving working memory functioning (Gibson et al., 2011).

Central executive processes, but not processing speed, emerged as a mediator between diagnosis and working memory deficits associated with SCD. These findings

suggest that the deficits in the central executive are a more critical factor in determining overall working memory functioning in SCD rather than deficits in processing/rehearsal speed. Consequently, disease effects from SCD have differential effects on specific cognitive abilities rather than an overall effect on cognition. Other studies have demonstrated the importance of the central executive in cognitive functioning. For example, Geary and colleagues found that first grade children with higher central executive capacity used more strategies needed to correctly solve addition problems in comparison to children with lower central executive capacity (Geary, Hoard, & Nugent, 2012). Furthermore, research suggests that working memory is dependent on central executive functioning in typically developing children (Ang & Lee, 2008). However, caution should be taken when interpreting findings related to the role of processing speed in working memory. The cognitive control factor, which is created from four measures of inhibitory control, set shifting, and dysregulation of executive function, was used to measure central executive functions. In contrast, processing speed was derived from only two measures, suggesting there may be differences in the reliability and content coverage for how the two constructs were measured. In addition, some SCD patients were unable to complete either the flanker or set shifting tasks, which were used to calculate processing speed, due to difficulty with completing the task. Consequently, these patients most likely would have had the lowest processing speed scores but were not included in the analysis, possibly impacting the results due to restriction of range. However, other studies of children with SCD have found similar results suggesting that processing speed may not be as critical of a factor in determining working memory capability (Salorio, 2000).

Total lesion volume was not related to working memory, processing speed, or central executive processes. This variable does not take into account specific lesion location, which may have impacted findings. Due to the variability in the location of lesions in SCD, more detailed analyses of the extent of lesions in specific locations are difficult to conduct as one would need a very large sample of children with visible cerebral infarction. Also, only 18 participants demonstrated lesions on MRI scans, decreasing the sample size with variance on this measure. However, after controlling for age, total lesion volume was correlated with measures of working memory and the central executive, suggesting that lesion volume is an adequate indicator of brain effects for working memory processes.

Measures of processing speed, working memory, and central executive processes were correlated with both anterior and posterior corpus callosum measurements. This suggests that the corpus callosum measure, which correlates highly with overall white matter volume, may be a better indicator of brain effects from SCD than total lesion volume. Even when controlling for age, the corpus callosum anterior region was correlated with measures of processing speed, central executive and working memory, suggesting that this region in particular may be most critical to measure. Accurate measurements of brain damage may be more difficult to ascertain in children with SCD who have multiple sources of neurologic impairment. Thus, measures that are sensitive to the effects of multiple neurologic processes may be preferable for understanding total neurologic burden of the disease. In addition, due to the location and tissue composition of the corpus callosum, this structure is relatively easy to measure compared with other structures and may yield more consistent measurement across scanners than more subtle

brain structures. Thus, the midsagittal corpus callosum measure may lend itself well to use in large scale, multi-site studies.

Implications for future research and practice

This study further highlights the importance of working memory in children with SCD. Routine screening of children with SCD who are more likely to exhibit problems in working memory (i.e. more severe genotypes) will allow neuropsychologists to efficiently identify problems earlier in development and establish a remediation plan. In addition to working memory measures, this study demonstrates the need to include measures of central executive processes. Children low in this domain are likely to be more susceptible to problems in working memory and therefore associated problems in intelligence and academic functioning. Additionally, including corpus callosum measurements as a part of MRI scans might be useful for physicians to detect subtle changes in neurologic status, particularly if within patient data could be examined over time. The expected quantitative development of the corpus callosum with age has been well documented (Giedd et al., 1999; McLaughlin et al., 2007). Accurate assessment and more precise MRI scans have the potential to significantly improve the quality of life in children with SCD. Future research should explore whether adding additional methods of assessment (central executive measures and MRI screening) can detect more children with neurocognitive issues. In addition, future research studies using working memory training in children with SCD may consider adding strategies that address issues with specific central executive processes.

References

Adams, R.J., McKie, V.C., Brambilla, D., Carl, E., Gallagher, D., Nichols, F.T., et al. (1998). Stroke prevention trial in sickle cell anemia. *Controlled Clinical Trials*, *19*(1), 110-129.

Adams, R.J., McKie, V.C., Carl, E.M., Nichols, F.T., Perry, R., Brock, K., et al. (1997). Long-term stroke risk in children with sickle cell disease screened with transcranial doppler. *Annals of Neurology*, *42*(5), 699-704.

Adams, R.J., Ohene-Frempong, K., & Wang, W. (2001). Sickle cell and the brain. *Hematology*, *2001*(1), 31-46.

Ang, S.Y. & Lee, K. Central executive involvement in children's spatial memory (2008). *Memory*, 16(8), 918-933.

Armstrong, D., Thompson, R.J., Wang, W., Zimmerman, R., Pegelow, C.H.,…, Vass, K.(1996). Cognitive functioning and brain magnetic resonance imaging in children with sickle cell disease. *Pediatrics*, *97*(6), 864-970.

Arkuszewski, M., Melham, E.R., & Krejza, J. (2010). Neuroimaging in assessment of risk of stroke in children with sickle cell disease. *Advances in Medical Sciences*, *55(*2), 115-129.

Austin, S., Cohen, H., & Loseff, N. (2007). Haematology and neurology. *Journal of Neurosurgery and Psychiatry*, *78*(4), 334–341.

Baddeley, A. (1996). Exploring the central executive. *The Quarterly Journal of Experimental Psychology*, *49A*(1), 5-28.

Baddeley, A. (1992). Working memory. *Science*, 255(5044), 556-559.

Baddeley, A. (2003). Working memory: Looking back and looking forward. *Nature Reviews: Neuroscience*, *4*, 829-839.

Baldeweg, T., Hogan, A.M., Saunders, D.E., Telfer, P., Gadian, D.G., …, Kirkham, F.J. (2006). Detecting white matter injury in sickle cell disease using voxel-based morphometry. *Annuals of Neurology*, *59*(4), 662-672.

Berklehammer, L.D., Williamson, A.L., Sanford, S.D., Dirksen, C.L., Sharp, W.G., Marguiles, A.S. (2007). Neurcognitive sequelae of pediatric sickle cell disease: A review of the literature. *Child Neuropsychology, 13*, 120-131.

Brown, L.A., Brockmole, J.R., Gow, A.J., & Deary, I.J. (2012). Processing speed and visuospatial executive function predict visual working memory ability in older adults. *Experimental Aging Research*, *38*, 1-19.

Brown, R. T., Buchanan, I., Doepke, K., Eckman, J. R., Baldwin, K., Goonan, B., & Schoenherr, S. (1993). Cognitive and academic functioning in children with sickle-cell disease. *Journal of Clinical Child Psychology, 22*(2), 207-218.

Collette, F. & Van der Linden, M. (2002). Brain imaging of the central executive component of working memory. *Neuroscience and Behavioral Review*, *26*, 105-125.

Craft, S., Schatz, J., Glauser, T. A., Lee, B., & DeBaun, M. R. (1994). The effects of bifrontal stroke during childhood on visual attention: Evidence from children with sickle cell anemia. *Developmental Neuropsychology*, *10*, 285–297.

Deary, I.J., Bastin, M.E., Pattie, A., Clayden, J.D., Whalley, L.J.,…, Wardlaw, J.M. (2006). White matter integrity and cognition in childhood and old age. *Neurology*,

66, 505-512.

Giedd, J.N., Blumenthal, J., Jeffries, N.O., Rajapakse, J.C., Vaituzis, C,…, Castellanos, X. (1999). Development of the human corpus callosum during childhood and adolescence: A longitudinal study. *Neuropsychopharmacology and Biological Psychiatry*, *23*(4), 571-588.

Gibson, B.S., Gondoli, D.M., Johnson, A.C., Steeger, C.M., Dobrzenski, B.A. & Morrissey, R.A. (2011). Component analysis of verbal versus spatial working memory in adolescents with ADHD: A randomized, controlled trial. *Child Neurospychology*, *17*(6), 546-563.

Grueneich, R., Ris, M.D., Ball, W., Kalinyak, K.A., Noll, R., Vannatta, K., & Wells, R. (2004). Relationship of structural magnetic resonance imaging, magnetic resonance perfusion, and other disease factors to neuropsychological outcome in sickle cell disease. *Journal of Pediatric Psychology*, *29*(2), 83-92.

Hill, C.M., Hogan, A.M., Onugha, N., Harrison, D., Cooper, S., McGrigor, V.J., …Kirkham, F.J. (2006). Increased cerebral blood flow velocity in children with mild sleep-disordered breathing: A possible association with abnormal neuropsychological function. *Pediatrics*, *118*(4), 1100-1108.

Holmes, J. & Gathercole, S.E. (2014). Taking working memory training from the laboratory into schools. *Educational Psychology*, *34*(4), 440-450.

Hulbert, M., Scothorn, D., Panepinto, J., Scott, J., Buchanan, G.,…, & DeBaun, M. (2006). Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: A retrospective cohort study of 137 children with sickle cell anemia. *Journal of Pediatrics*,

149(5), 710-712.

Jacobson, L.A., Ryan, M., Martin, R.B., Ewen, J., Mostofsky, S.H., Denckla, M.B., & Mahone, E.M. (2011). Working memory influences processing speed and reading fluency in ADHD. *Child Neuropsychology*, *17*(3), 209-224.

Kail, R. (1991). Processing time declines exponentially during childhood and adolescence. *Developmental Psychology*, *27*(2), 259-266.

Kail, R.V & Ferrer, E. (2007). Processing speed in childhood and adolescence: Longitudinal methods for examining developmental change. *Child Development*, *78*(6), 1760-1770.

Kaufman, S.B., DeYoung, C.G., Gray, J.R., Brown, J., & Mackintosh, N. (2009). Associative learning predicts intelligence above and beyond working memory and processing speed. *Intelligence*, *37*, 374-382.

Klingberg, T. (2006). Development of a superior frontal-intraparietal network for visuo-spatial working memory. *Neuropsyhologia*, *44*(11), 2171-2177.

Klingberg, T., Fernell, E., Olesen, P.J., Johnson, M., Gustafsson, P.,…, & Westerberg, H. (2005). Computerized training of working memory in children with ADHD: A randomized, controlled trial. *Journal of the American Academy of Child & Adolescent Pyschiatry*, *44*(2), 177-186.

Leonard, L.B., Weismer, S.E., Miller, C.A., Francis, D.J., Tomblin, J.B., & Kail, R.V. (2007). Speed of processing, working memory, and language impairment in children. *Journal of Speech, Language, and Hearing Research*, *50*, 408-428.

McLaughlin, N.C.R., Paul, R.H., Grieve, S.M., Williams, L.M., Laidlaw, D.,…, Gordon, E. (2007). Diffusion tensor imaging of the corpus callosum: A cross-sectional

study across the lifespan. *International Journal of Developmental Neuroscience*, *25*(4), 215-221.

Meier, E.R. & Miller, J.L. (2012). Sickle cell disease in children. *Drugs*, *72*(7), 895-906.

Moser, F., Miller, S., Bello, J., Pegelow, C., Zimmerman, R., Wang, W., Ohene-Frempong, K., Schwartz, A., Vichinsky, E., Gallagher, D., Kinney, T. (1996). The spectrum of brain MR abnormalities in sickle-cell disease: A report from the Cooperative Study of Sickle Cell Disease. *American Journal of Neuroradiology*, *17*(5), 965-972.

Nahavandi, M., Tavakkoli, F., Hasan, M.Q., Wyche, M.Q., & Castro, O. (2004). Cerebral oximetry in patients with sickle cell disease. *European Journal of Clinical Investigation*, *34*(2), 143-148.

Neisser, U., Boodoo, G., Bouchard, T.J., Boykin, A.W., Brody, N.,…, Urbina, S. (1996). Intelligence: Knowns and unknowns. *American Psychologist*, *51*(2), 77-101.

Noll, R.B., Vannatta, K., Koontz, K., Kalinyak, K. (1996). Peer relationships and emotional well-being of youngsters with sickle cell disease. *Child Development*, *67*, 423-436.

Ohene-Frempong, K., Weiner, S.J., Sleeper, L.A., Miller, S.T., Embury, S., . . . , The Cooperative Study of Sickle Cell Disease (1998). Cerebrovascular accidents in sickle cell disease: Rates and risk factors. *Blood*, *91*(1), 288–294.

Pegelow, C., Macklin, E., Moser, F., Wang, W., Bello, J., Miller, S., Vichinsky, E., DeBaun, M., Guarini, L., Zimmerman, R., Younkin, D., Gallagher, D., Kinney, T. (2002). Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. *Blood*, *99*(8, 3014-3018.

Penke, L., Munoz Maniega, S., Bastin, M.E., Valez Hernandez, M.C., Murray, C…,

Deary, I.J. (2012). Brain white matter tract integrity as a neural foundation for general intelligence. *Molecular Psychiatry*, *17*, 1026-1030.

Rees, D.C., Williams, T.N., & Gladwin, M.T. (2010). Sickle cell disease. *The Lancet*, *376*, 2018-2031.

Rypma, B., Berger, J.S., Prabhakaran, V., Bly, B.M., Kimberg, D.Y…, D'Esposito, M. (2006). Neural correlates of cognitive efficiency. *Neuroimage*, *33*, 969-979.

Schatz, J. (2004). Brief report: Academic attainment in children with sickle cell disease, *Journal of Pediatric Psychology*, *29*(8), 627-633.

Schatz, J., Brown, R.T., Pascual, J.M., Hsu, L., & DeBaun, M.R. (2001). Poor school and cognitive functioning with silent cerebral infarcts and sickle cell disease. *Neurology*, *56*, 1109-1111.

Schatz, J. & Buzan, R. (2006). Decreased corpus callosum size in sickle cell disease: Relationship with cerebral infarcts and cognitive functioning. *Journal of the International Neuropsychological Society*, *12*, 24-33.

Schatz, J., Craft, S., & Koby, M. (2000). A lesion analysis of visual orienting performance in children with cerebral vascular injury. *Developmental Neuropsychology*, *17*(1), 49-61.

Schatz, J., Craft, S., Koby, M., Siegel, M.J., Resar, L.,…, DeBaun, M.R. (1999). Neuropsychologic deficits in children with sickle cell disease and cerebral infarction: Role of lestion site and volume. *Child Neuropsychology*, *5*(2), 92-103.

Schatz, J., Finke, R., Kellett, J.M., & Kramer, J.H. (2002). Cognitive functioning in children with sickle cell disease: A meta-analysis. *Journal of Pediatric Psychology*, *27*(8), 739-748.

Schatz, J., Finke, R., & Roberts, C. W. (2004). Interactions of biomedical and environmental risk factors for cognitive development: A preliminary study of sickle cell disease. *Journal of Developmental & Behavioral Pediatrics, 25*(5), 303-310.

Schatz, J. & Roberts, C. (2005). Short-term memory in children with sickle cell disease: Executive versus modality-specific processing deficits. *Archives of Clinical Neuropsychology*, *20*, 1073-1085.

Schatz, J. & Roberts, C. (2007). Neurobehavioral impact of sickle cell disease in early childhood. *Journal of the International Neuropsychological Society*, *13*, 933-943.

Schatz, J., Stancil, M., Katz, T., & Sanchez, C.E. (2014). EXAMINER executive function battery and neurologic morbidity in pediatric sickle cell disease. *Journal of the International Neuropsychological Society*, *20*, 29-40.

Scothorn, D., Price, C., Schwartz, D., Terrill, C., Buchanan, G.,…, & Debaun, M. (2002). Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke. *Journal of Pediatrics*, *140*(3), 348-354.

Smith, K.E., Patterson, C.A., Szabo, M.M., Tarazi, R.A., & Barakat, L.P. (2013). Predictors of academic achievement for school-age children with sickle cell disease. *Advances in School Mental Health Promotion*, *6*(1), 5-20.

Soderqvist, S., Nutley, S.B., Ottersen, J., Grill, K.M., & Klingberg, T. (2012). Computerized training of non-verbal reasoning and working memory in children with intellectual disability. Frontiers in Human Neuroscience, 6(271), 1-8.

Steen, R., Emudianughe, T., Hankins, G., Wynn, L., Wang, W., Xiong, X., Helton, K. (2003). Brain imaging findings in pediatric patients with sickle cell disease.

Radiology, *228*(1), 216-225.

Steen, R.G., Fineburg-Buchner, C., Hankins, G., Weiss, L., Prifitera, A., & Mulhern, R.K. (2005). Cognitive deficits in children with sickle cell disease. *Journal of Child Neurology*, *20*(2), 102-107.

Steen, R.G., Hu, J., Elliot, V.E., Miles, M.A., Jones, S., & Wang, W.C. (2002). Kindergarten readiness skills in children with sickle cell disease: Evidence of early neurocognitive damage. *Journal of Child Neurology*, *17*(2), 111-116.

Steen, R.G., Xiong, X., Mulhern, R.K., Langston, J.W., & Wang, W.C. (1999). Subtle brain abnormalities in children with sickle cell disease: Relationship to blood hematocrit. *Annuls of Neurology*, *45*(3), 279-286.

Steinberg, M.H. (1984). The sickle hemoglobinopathies: Genetic analysis of common phenocopies and new molecular approaches to treatment. *American Journal of Medical Sciences, 288*, 169-174.

Takeuchi, H., Taki, Y., Hashizume, H., Sassa, Y., Nagase, T., …., Kawashima, R. (2011). Effects of training of processing speed on neural systems. *The Journal of Neuroscience*, *31*(34), 12138-12148.

Tarazi, R.A., Grant, M.L., Ely, E., & Barakat, L.P. (2007). Neuropsychological functioning in preschool-age children with sickle cell disease: The role of illness-related and psychosocial factors. *Child Neuropsychology*, *13*, 155-172.

Vichinsky, E.P., Neumayr, L.D., Gold, J.I., Weiner, M.W., Rule, R.R.,…, Armstrong, F.D. (2010). Neuropsychological dysfuction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. *Journal of the American Medical Association*, *303*(18), 1823-1831.