Quality of Life and Neurocognitive Functioning in Children with Sickle Cell Disease:

Investigating the Feasibility of a Computerized Cognitive Training Program

by

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Department of Psychology and Neuroscience
Duke University

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David Rabiner

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Jennifer Rothman

Dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in the Department of Psychology and Neuroscience in the Graduate School of Duke University

2014
ABSTRACT

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Abstract

Children with sickle cell disease (SCD) have a high risk of neurocognitive impairment. No known research, however, has examined the impact of neurocognitive functioning on quality of life in this pediatric population. In addition, limited research has examined neurocognitive interventions for these children. In light of these gaps, two studies were undertaken to (a) examine the relationship between cognitive functioning and quality of life in a sample of children with SCD and (b) investigate the feasibility and preliminary efficacy of a computerized working memory training program in this population. Forty-five youth (ages 8-16) with SCD and a caregiver were recruited for the first study. Participants completed measures of cognitive ability, quality of life, and psychosocial functioning. Results indicated that cognitive ability significantly predicted child- and parent-reported quality of life among youth with SCD. In turn, a randomized-controlled trial of a computerized working memory program was undertaken. Eighteen youth with SCD and a caregiver enrolled in this study, and were randomized to a waitlist control or the working memory training condition. Data pertaining to cognitive functioning, psychosocial functioning, and disease characteristics were obtained from participants. The results of this study indicated a high degree of acceptance for this intervention but poor feasibility in practice. Factors related to feasibility were identified. Implications and future directions are discussed.
Dedication

This work is dedicated to my family for all their love and support. I am especially thankful to my parents for the encouragement and opportunity to pursue my interests, and for helping me keep it all in perspective. And to Ben and Sam, for all the everyday everything that fills my life with such joy.
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Finally, I would like to thank all the children and families who are affected by sickle cell disease who participated in this project. I appreciate their time, enthusiasm, and input, without which this type of research would not be possible. They have been wonderful collaborators, and I will take their stories with me as I carry on research in this field.

This research was supported by the Elizabeth Munsterberg Koppitz Fellowship from the American Psychological Foundation.
1. Introduction

Sickle cell disease (SCD) is a group of autosomal recessive hemoglobinopathies characterized by the presence of abnormal hemoglobin (HbS). During conditions of low oxygen, HbS molecules clump together forming sticky, stiff, and fragile crescent or sickle-shaped red blood cells. The sickle-shaped cells can clog small blood vessels and easily break into pieces, thereby obstructing blood flow to the body’s tissues and organs. The obstructed blood flow leads, in turn, to vasoocclusive pain crises. Indeed, severe, debilitating pain—experienced in the bones, joints, abdomen, and soft tissues—is the most common and distinguishing clinical symptom associated with SCD. In addition to the experience of pain, vasoocclusion and chronic deoxygenation can lead to a number of serious medical complications, including asplenia, acute chest syndrome, stroke, avascular necrosis, priapism, dactilytis, and organ failure.

There are several forms of SCD, with varying degrees of clinical severity. Sickle cell anemia (HbSS) is the most prevalent form of the disease and also is considered the most severe. Persons with HbSS generally endure an earlier disease onset, greater frequency of symptoms and earlier mortality (Charache, Lubin, & Reid, 1989). Other common forms of SCD include HbSC and HbS beta-Thalassemia. Throughout the lifespan, patients living with SCD will experience tremendous variability in the
frequency and severity of symptoms. This is true both for patients with different sickle cell genotypes and for patients with the same genotype.

Worldwide, an estimated 300,000 newborns are diagnosed with SCD each year, and approximately 5% of the world’s population is believed to carry the disease (WHO, 2005). The prevalence of SCD varies significantly across ethnic groups and geographic regions. The presence of the sickle cell mutation was thought to arise as an evolutionarily adaptive trait because of its observed protection against the malaria virus.

As a result, there is a dense distribution of the sickle cell gene found among persons whose ancestors are from regions with endemic malaria, most prevalently, sub-Saharan Africa. Initially, it was believed that the HbS gene migrated from a single mutation (Gelpi, 1973). Later research, however, suggested that the mutation arose independently at least three separate times, resulting in distinct haplotypes: (a) the Benin, Senegal, or Cameroon haplotypes from West Africa; (b) the Central African Republic haplotype (i.e., the Bantu haplotype); and (c) the Arab-Indian haplotype from the Middle East and Asia (Lapoumeroulie et al., 1992; Pagnier et al., 1984).

The most recent epidemiologic data indicate that approximately one in every 400 African-Americans and one in every 1000 to 1400 Hispanic-Americans born in the United States are born with SCD. These data are relatively consistent with the prevalence rates across Europe (Weatherall, 2008). In developed countries, on average,
Individuals with HbSS live well into their forties, while persons with HbSC and HbS-beta thalassemia live into their sixties (Platt et al., 1994). Childhood mortality is increasingly rare due to universal newborn screening and medical advancements in the field. Access to hydroxyurea, an oral medication that increases the levels of fetal hemoglobin and transcranial doppler screenings to identify patients at risk for stroke also have helped reduce clinical morbidity in many patients with SCD. Further, recent research has suggested the possibility of a cure for persons with SCD through bone marrow transplantation (Krishnamurti et al., 2008). Unfortunately, however, even if a cure is found, children with SCD are likely to experience late effects from years spent living with the disease that will impact overall quality of life. Thus, even as the prospect of cure becomes more promising, the need to address issues of quality of life will persist and in many ways has never been more important.

In 2009, the American Society of Pediatric Hematology/Oncology (ASPHO) publicly recognized the need to address quality of life issues at their Sickle Cell Summit. In the context of a broad agenda to improve care and research for patients with this illness, the Summit included a direct and explicit aim to evaluate and improve quality of life standards. The ASPHO’s inclusion of quality of life aims was notable because non-imminent concerns, such as quality of life issues, had not been clearly included in the agendas of prior sickle cell initiatives. In fact, a long history of clinical and research
disparities for patients with SCD has, by and large, precluded the availability of time and money to address issues beyond those of physical health. Thus, in the context of an already-marginalized research agenda, quality of life aims have not been prioritized.

Unfortunately, this has led to ongoing disparities in research and interventions directed at assessing and improving well-being in patients with SCD. Smith and colleagues (1999) conducted a structured search of the literature from Medline and PsycINFO that revealed 17 articles on quality of life in pediatric SCD compared to 81 articles on quality of life in survivors of pediatric acute lymphoblastic leukemia (ALL). Relative to the incidence rates of SCD and pediatric ALL—2000 and 2400, respectively (National Newborn Screening and Genetics Resource Center & Association of Public Health Laboratories, 2003; Smith, Ries, Gurney, & Ross, 1999)—there are disproportionately few articles on quality of life in SCD (Figure 1). Similar findings were evident in a cursory review of NIH-funded trials, per the RePORT database, in which there were only three projects on SCD that ostensibly included quality of life evaluations as their primary aim. Further, among most of the recent major research networks in SCD (e.g., SWiTCH, TWiTCH, Baby Hug), quality of life aims have often been secondary to medical outcomes. This is not to undermine the importance of these trials and the medical data obtained through this research, but rather to highlight the lack of focused attention to quality of life issues in SCD.
1.1 Quality of Life Research

The small body of literature on quality of life in SCD overwhelmingly has focused on the assessment of social, emotional, and physical functioning, which is now formally recognized as “health-related quality of life” (HRQL). The HRQL construct emerged in the medical psychology literature as an answer to the breadth-of-coverage problems inherent to the concept of quality of life. The focus is narrowed to variables relevant to health, and thus cultural, political, and societal factors are generally excluded (Ferrans, Zerwic, Wilbur, & Larson, 2005).

Research specifically examining HRQL in children with SCD was initiated in the late 1990s and has grown slowly since. Indeed, a more recent review of the literature available on Medline indicated that there have been only approximately 30 studies published regarding HRQL in pediatric SCD (Bonner, 2010). Although studies of HRQL in SCD are in their infancy, this construct has enormous potential to help us understand the gravity of this illness on the physical and mental well-being of children and their families. This construct provides clinicians with another clinically-relevant outcome variable by which they can assess a child’s health status and functional impairment. Thus, integrating HRQL provides a more comprehensive assessment of a child’s or family’s needs, which can then be addressed by their provider.
Early research assessing HRQL in children with SCD has examined the influence of the illness on well-being. For example, research has shown that chronic medical complications in SCD—such as pain crises, stroke, and avascular necrosis—can affect functional (i.e., social, emotional, cognitive, and physical) well-being. Under these circumstances, the disease is understood to be the cause of measured impairment in HRQL. While it is undeniably important to understand the impact of SCD on HRQL, it is not an all-encompassing conceptualization. Indeed, findings from recent research suggests that demographic and psychosocial factors such as socioeconomic status (SES), neighborhood characteristics, and family functioning, for example, are significant predictors of HRQL (Tarazi, Grant, Ely, & Barakat, 2007). Similarly, poor family functioning significantly predicts social behavioral problems—a component of HRQL—in children with SCD, above and beyond disease factors (Barbarin, Whitten, Bond, & Conner-Warren, 1999; Brandow, Brousseau, Pajewski, & Panepinto, 2010; Kell, Kliwerer, Erickson, & Ohene-Frempong, 1998). Thus, in order to better understand HRQL in patients with SCD, it will be important to continue addressing the relative impact of primary disease traits (e.g., pain, disease severity), psychosocial factors (e.g., SES, family functioning), and secondary disease factors (e.g., cognitive impairment, fatigue). There is great potential to better understand a child’s overall functioning by including these
variables within the quality of life framework, and may assist in dismantling certain barriers to improving well-being in patients with SCD.

1.2 Cognitive Functioning and Quality of Life

Children with SCD are at a high risk for neurocognitive impairment, which has potential implications for overall HRQL. A meta-analysis conducted by Schatz et al. (2002) indicated that children with SCD often scored lower on general IQ measures than healthy children, with 51% of studies reporting significant differences. When examining specific cognitive abilities, more robust and consistent differences were found, with 71% of studies reporting significant deficits in at least one cognitive domain (Schatz et al., 2002). Deficits have been found most often in attention, processing speed, and working memory, as well as verbal and language domains (Bernaudin et al., 2000; Brown, 1993; Knight, Singhal, Thomas, & Serjeant, 1995; Noll et al., 2001; Schatz, Finke, & Roberts, 2004; R. G. Steen et al., 2005; Wang et al., 2001; Wasserman, Wilimas, Fairclough, Mulhern, & Wang, 1991).

Cerebrovascular accidents (CVAs), including silent and overt infarcts, are well-recognized as a major cause of neurocognitive impairment (Buchanan, DeBausn, Quinn, & Steinberg, 2004). Indeed, Schatz and colleagues (Schatz, Brown, Pascual, Hsu, & DeBaun, 2001) found that 79% of children with a silent cerebral infarct exhibited deficits. Importantly however, they also found that 36% of children without infarct had
significant cognitive deficits in at least one domain, compared with 11% of sibling controls. It has been suggested that a chronic anemic state and reduced oxygenation to the brain are associated with these decrements in neurocognitive functioning (Steen et al., 2003). Further, psychosocial variables, (e.g., caregiver stress, poor nutrition), also have been identified as risk factors for poor neurocognitive functioning in pediatric patients with SCD (Tarazi et al., 2007). Collectively, children with SCD face multiple risk factors for neurocognitive impairment, which can have a lifelong impact and are theoretically relevant to overall HRQL.

Cognitive decrements in children with SCD are significant and progressive (Schatz & Roberts, 2007; Thompson Jr, Gustafson, Bonner, & Ware, 2002; Wang et al., 2001). Studies have documented an initial decrease in cognitive functioning between 12 and 24 months of age (2002) with evidence of deficits in attention and executive functioning in pre-school-aged children (Schatz & Roberts, 2007). Declines in cognitive scores suggest that children with SCD are falling behind their peers in abilities that are central to learning and academic progress. A longitudinal study of school-aged children documented progressive declines in cognitive ability from early childhood throughout middle and late childhood (Wang et al., 2001). Further, the impact of cognitive impairment is evident in studies documenting that children with SCD have high rates of
enrollment in special education services relative to peers and are likely to struggle with academic achievement throughout school (Schatz, 2004).

Children who struggle in school are more likely to have poor social and emotional functioning (Chen, Chang, & He, 2003; Dobbs, Doctoroff, Fisher, & Arnold, 2006), which puts them at risk for lower levels of overall well-being compared to unaffected peers. Thus, in light of data documenting cognitive impairment and resultant academic challenges in children with SCD—which increases the risk for poor social and emotional functioning—it stands to reason that there is a meaningful relationship between neurocognitive functioning and HRQL in this population. Despite this, no known research has explored this relationship empirically. In light of this gap, the first aim of the current study is to examine the relationship between quality of life and cognitive functioning in a sample of children with SCD. It is hypothesized that cognitive functioning will significantly predict quality of life in this sample of pediatric patients. It is also hypothesized that psychosocial and family/caregiver resources will moderate the relationship between cognitive functioning and HRQL in these children.
2. Methods

2.1 Participants

Children with sickle cell disease (any genotype) aged 8-16 were recruited from the Pediatric Sickle Cell Clinic at the Duke Children’s Health Center. The most recent demographic data indicate that there are 420 patients followed in the Duke Pediatric Comprehensive Sickle Cell Center (218 females and 212 males). Of the 420 patients, there are 36 sibling groups including 5 sets of twins. The mean age is 8.9 years (range 0-19). The majority of patients are Black or African American. Of the 412 patients in this racial category at least 41 have parents who were born outside of the United States (Nigeria [6], Ghana [5], Jamaica [2], Congo [2], Sudan [1], Haiti [1], Liberia [1], Dominican Republic [1], Togo [1], and Senegal [1]. Three patients are White (Hispanic ethnicity). Three patients are Native American. Two patients are of mixed racial categories [Black or African American/White (Hispanic ethnicity) and Black or African American/Native Hawaiian or Other Pacific Islander]. Further, one hundred thirteen (27%) are taking hydroxyurea. Twelve (2.9%) receive chronic blood transfusion for primary or secondary stroke prevention. Two have successfully undergone hematopoietic stem cell transplantation. Thus, the children followed in this clinic represent a range in disease severity. Exclusion criteria, outlined below, were utilized to ensure the data would not
inadvertently be biased by serious medical or psychological conditions that are known to affect both cognitive functioning and quality of life.

**Exclusion criteria:** 1) estimated IQ ≤ 70; 2) evidence of clinical stroke (via physician report or medical record); 3) a history of pervasive developmental disorder (by history); 4) insufficient fluency in English.

### 2.2. Procedure

In an effort to coordinate research sessions with the child’s regularly scheduled clinic visits, eligible children were approached by the treating hematologist to determine interest in the study. After obtaining written informed consent and assent (when appropriate), child participants and a caregiver completed several questionnaires assessing the child’s quality of life and cognitive ability. Additional measures were collected pertaining to demographics and the parent’s experience of having a child with a chronic illness. Both children and their caregiver received a $10 gift card to a local store to compensate them for their time. Finally, data to assess disease severity were obtained from the child’s medical records.

### 2.3. Measures

*The Pediatric Quality of Life Inventory* (PedsQL; Varni et al., 1999) is a widely used 23-item measure of quality of life during the past month. Using this measure, various pediatric chronic health conditions evidence lower quality of life reports when
compared to non-medical control peers (Varni, Limbers, & Burwinkle, 2007). Both the parent and child rate the child’s functioning on the following dimensions of quality of life: physical functioning, social functioning, emotional functioning, and school functioning. Moreover, this inventory utilizes age-based versions in order to ensure appropriateness for the child’s age. The PedsQL has been validated in a sample of children with SCD and the parent form has been validated as a proxy for child functioning (McClellan, Schatz, Sanchez, & Roberts, 2008). Higher scores on this measure suggest better quality of life. Average scores for children without any known acute or chronic medical condition range from 78.63 to 87.42 (Varni, Seid, and Kurtin, 2001).

*The Behavior Rating Inventory of Executive Functioning* (BRIEF; Gioia, Isquith, Guy, & Kenworthy, 2000)) is an 86-item, parent-rated measure that assesses a wide range of executive abilities. Items collapse into three indices: Behavioral Inhibition, Metacognition, and Global Executive Control. In this study, the Metacognition Index was identified as a primary predictor of cognitive ability. The items comprising the Behavioral Regulation Index are highly correlated with measures of emotional distress (e.g., internalizing symptoms from the Child Behavior Checklist), and therefore were excluded from this study due to our primary interest in neurocognitively-mediated skills. The Metacognition Index reflects children’s ability to cognitively manage
activities, and monitor and adapt their performance accordingly. In other words, it relates to a child’s ability to problem-solve across contexts. This index is comprised of the Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor subscales. T-scores are calculated on a normative sample of same-age and same-gender peers; higher scores indicate greater impairment.

*Wechsler Abbreviated Scale of Intelligence* (WASI; Wechsler, 1999) is a brief measure of intelligence usable with people aged 6 to 89 years. For this project, the Vocabulary and Matrix Reasoning were used at baseline to estimate IQ to verify that children have adequate intellectual functioning (e.g., IQ ≥ 70) to participate in the study.

*Parent Experience of Child Illness* (PECI; Bonner et al., 2006)) is a 25-item measure of a primary caregiver’s experience caring and coping with a chronically-ill child. Items collapse into four subscales including Guilt and Worry, Unresolved Sorrow and Anger, Long-Term Uncertainty, and Emotional Resources. In this study, the Long-Term Uncertainty scale provided a measure of parental stress and burden, and was identified a priori as a potential moderator in the models of quality of life.

*The Visual Analog Pain Scale* (Wong & Baker, 1988) is a rating of current pain experienced by the child. The child is asked to rate his/her pain on a scale from 0-10. The scale utilizes faces that progress from smiling to frowning to help the child match their experience of pain.
The Hollingshead Two-Factor Index of Socioeconomic Status (Hollingshead, 1957) provides an estimate of a family’s overall SES. It takes into consideration the occupation of the parent(s) and their level of education.

Disease severity. There is no standard measure of disease severity that is widely used in SCD. Thus, number of hospitalizations in the past year was used as a proxy of disease severity, which was gathered from the child’s medical record.

2.4 Statistical Methods

Descriptive statistics were calculated to summarize the demographic and medical variables and measures of quality of life and cognitive functioning.

Correlational analyses were used for two purposes. First, correlational analyses were conducted to examine how the predictor variables (i.e., indices of cognitive functioning per the BRIEF) related to the outcome variables (i.e., parent-rated and self-rated HRQL). Second, correlational analyses were used to examine how the demographic variables (i.e., age, SES) and medical variables (i.e., pain, disease severity) were related to the outcome variables.

Hierarchical linear regression (HLR) was used to assess the contribution of executive functioning to quality of life outcomes. In each HLR, age, SES, and pain were entered in Step 1. The demographic and pain were chosen a priori for use in Step 1 because previous literature has demonstrated an important relationship between these
factors and overall well-being or quality of life in this patient group (Palermo, Riley, & Mitchell, 2008; J. A. Panepinto, O'Mahar, DeBaun, Loberiza, & Scott, 2005; J. Panepinto, Pajewski, Foerster, Sabnis, & Hoffmann, 2009). An index of cognitive ability, per the Metacognition Index of the BRIEF, was included in Step 2 in order to determine the role this plays in quality of life after controlling for the effect of disease and demographic characteristics. To provide an estimate of the unique proportion of the variance accounted for by cognitive ability in the HLR models, individual semipartial $r^2$ (spr$^2$) values were reported. Finally, proximal measures of a family’s psychosocial resources and stress (i.e., SES, Long-Term Uncertainty from the PECI) were identified a priori as theoretically-relevant moderators and were included in Step 3 of these exploratory analyses. This enabled us to examine the interactive effect beyond that of the individual variables.
3. Results

3.1 Participants

Participants included 45 children (24 males) with SCD and a parent or caregiver. Children ranged in age from 8 to 16 years \((M = 12.3\) years). Forty-four of the 45 children were African American (97.7%) without evidence of an overt stroke (confirmed by medical records). Children had a mean IQ of 97.3 \((SD=12.5)\). Mean level of pain was 0.70 \((SD=1.66)\) and mean level of disease severity was 1.14 \((SD=1.21)\). Demographic variables are summarized in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Study 1 Participant Demographics and Medical Characteristics</th>
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<tbody>
<tr>
<td><strong>Demographic Variables</strong></td>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>African American</td>
</tr>
<tr>
<td>Native American</td>
</tr>
<tr>
<td><strong>Medical Variables</strong></td>
</tr>
<tr>
<td>Genotype</td>
</tr>
<tr>
<td>SS</td>
</tr>
<tr>
<td>SC</td>
</tr>
<tr>
<td>Beta-Thalassemia</td>
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<tr>
<td>Disease Severity</td>
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</tbody>
</table>
3.2 Descriptive Statistics

3.2.1 Quality of Life

Preliminary screening of skewness and kurtosis indicated normally distributed data. Levels of quality of life were measured by child self-report and also via parent proxy-report using the Pediatric Quality of Life Inventory (PedsQL). Descriptive statistics were utilized to examine mean levels of quality of life in the current sample. Mean levels of Health were 75.4 (child; $SD=17.0$) and 69.6 (parent; $SD=24.3$); Social 79.40 (child; $SD=22.7$) and 76.2 (parent; $SD=23.2$); Emotional 71.2 (child; $SD=22.3$) and 71.4 (parent; $SD=20.2$); School 63.2 (child; $SD=22.3$) and 56.9 (parent; $SD=23.5$); and overall QOL 72.3 (child; $SD=17.3$) and 68.0 (parent; $SD=20.5$). No significant differences between parent and child reports emerged for any of the domains. Mean levels are summarized in Table 2.

<table>
<thead>
<tr>
<th></th>
<th>Parent Rating M ± SD</th>
<th>Youth Rating M ± SD</th>
<th>Test Statistic*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Health</td>
<td>69.6 ± 24.25</td>
<td>75.4 ± 17.04</td>
<td>-1.13</td>
</tr>
<tr>
<td>Social</td>
<td>76.2 ± 23.19</td>
<td>79.4 ± 22.06</td>
<td>-0.65</td>
</tr>
<tr>
<td>Emotional</td>
<td>71.4 ± 20.19</td>
<td>71.2 ± 22.34</td>
<td>0.06</td>
</tr>
<tr>
<td>School</td>
<td>56.9 ± 23.48</td>
<td>63.2 ± 22.30</td>
<td>-1.25</td>
</tr>
<tr>
<td>Total HRQL</td>
<td>68.0 ± 20.45</td>
<td>72.3 ± 17.28</td>
<td>-1.03</td>
</tr>
</tbody>
</table>

*Test statistic is a Student’s t-test; no significant differences were observed
3.2.2 Executive Functioning

Executive skills were assessed by parent-report on the Behavior Rating Index of Executive Function (BRIEF). Mean scores were calculated for each subscale of the Metacognition Index and are summarized in Table 3. Scores fell in the Average range on the Initiate ($M = 53.5$), Working Memory ($M = 54.8$) Plan/Organize ($M = 53.8$), Organization of Materials ($M = 50.6$), and Monitor ($M = 50.2$) subscales. The mean for the Metacognition Index was $T = 55.7$.

<table>
<thead>
<tr>
<th>Scale</th>
<th>$M \pm SD$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metacognition</td>
<td>55.7 ± 14.53</td>
</tr>
<tr>
<td>Initiate</td>
<td>53.5 ± 11.17</td>
</tr>
<tr>
<td>Plan/Organize</td>
<td>53.8 ± 12.25</td>
</tr>
<tr>
<td>Organization of Material</td>
<td>50.6 ± 11.92</td>
</tr>
<tr>
<td>Monitoring</td>
<td>50.2 ± 12.07</td>
</tr>
<tr>
<td>Working memory</td>
<td>54.8 ± 11.33</td>
</tr>
</tbody>
</table>

3.3 Correlational Analyses

Correlational analyses are summarized in Table 4. Correlations were run in order to examine the association between outcome variables (i.e., child-rated HRQL and parent-rated HRQL) with indices of executive functioning, demographic characteristics, and disease variables. Child-rated HRQL was significantly associated with pain ($r = -0.40$, $p<.05$) and BRIEF Metacognition ($r = -.35$, $p<.05$). It was not significantly associated with disease severity, family socioeconomic status (SES), BRIEF Behavioral Regulation,
BRIEF Global Executive Composite, intelligence, or age. Parent-rated HRQL was significantly associated with the child’s age ($r = .37, p<.05$), the Metacognition Index ($r = -.45, p<.01$), Behavioral Regulation ($r = -.50, p<.01$), and the Global Executive Composite ($r = -.56, p<.001$). Parent-rated HRQL was not significantly associated with disease severity, pain, SES, or intelligence.
Table 4: Correlations Between Study Predictors and Outcome Variables of Interest

<table>
<thead>
<tr>
<th></th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
<th>6.</th>
<th>7.</th>
<th>8.</th>
<th>9.</th>
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</thead>
<tbody>
<tr>
<td>1. Child-rated HRQL</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Parent-rated HRQL</td>
<td>.38</td>
<td>--</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Age</td>
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<td>.37</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. SES</td>
<td>.08</td>
<td>.23</td>
<td>.31</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Disease severity</td>
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<td>.05</td>
<td>-.14</td>
<td>.27</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Pain</td>
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<td>-.12</td>
<td>.10</td>
<td>.17</td>
<td>.24</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. FSIQ</td>
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<td>.30</td>
<td>.05</td>
<td>.43</td>
<td>.09</td>
<td>.17</td>
<td>--</td>
<td></td>
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<tr>
<td>8. BRIEF Behavioral Regulation</td>
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<td>-.03</td>
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<td>-.10</td>
<td>.11</td>
<td>-.32</td>
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<td></td>
</tr>
<tr>
<td>9. BRIEF Metacognition Index</td>
<td>-.35</td>
<td>-.45</td>
<td>-.08</td>
<td>-.22</td>
<td>-.12</td>
<td>.09</td>
<td>-.36</td>
<td>.72</td>
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</tr>
<tr>
<td>10. BRIEF Global Exec. Fx.</td>
<td>-.27</td>
<td>-.56</td>
<td>-.06</td>
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<td>-.08</td>
<td>.04</td>
<td>-.44</td>
<td>.84</td>
<td>.84</td>
</tr>
</tbody>
</table>
3.4 Models of quality of life

In order to examine the impact of neurocognitive functioning on quality of life, two hierarchical regression analyses were conducted with child-rated quality of life and parent-rated quality of life as the outcome variable (see Statistical Methods above). The results of each model are presented below.

3.4.1 Child model

The proposed child model explained approximately 25% of the variance in quality of life (Adj. $R^2 = 0.25$, $F(8, 36) = 2.53, p<.05$; Table 5). Pain was a significant predictor of overall quality of life ($\beta = -.43, t = -2.81, p<.05$), in which lower levels of pain were associated with higher ratings of quality of life. Age was also a significant predictor in the final model ($\beta = .36, t = 2.15, p<.05$), in which a younger age was associated with lower levels of quality of life. Above and beyond the effect of demographic characteristics and pain, executive skills (per the BRIEF) and were a significant predictor of overall HRQL. Specifically, greater executive impairment predicts lower levels of HRQL ($\beta = -0.39, t = -2.55, p<.05$). Although the final step of the model was significant, neither the interaction of SES and cognitive functioning nor the interaction between parental experience of their child’s illness and cognitive functioning uniquely contributed to the prediction of child-rated quality of life.
3.4.2 Parent model

The proposed parent model explained approximately 26% of the variance in quality of life (Adj. $R^2 = 0.26$, $F(8, 36) = 2.55$, $p<.05$; Table 6). The child’s age was a significant predictor of overall quality of life ($\beta = 0.37$, $t = 2.08$, $p<.05$), in which a younger age was associated with lower levels of HRQL. Other demographic (i.e., SES, child’s sex) and disease characteristics were otherwise not significant predictors in this model. Above and beyond the contribution of disease and demographic variables, cognitive skills significantly predicted parent-rated HRQL. Specifically, greater executive impairment predicts lower levels of HRQL ($\beta = -0.33$, $t = -2.13$, $p<.05$). Finally, although the final step of the model was significant, neither the interaction of SES and cognitive functioning nor the interaction between parental experience of their child’s illness and cognitive functioning uniquely contributed to the prediction of parent-rated quality of life (Table 6).
<table>
<thead>
<tr>
<th>Steps</th>
<th>Outcome</th>
<th>Variables</th>
<th>Statistics by Step</th>
<th>Statistics by Variable</th>
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<td></td>
<td></td>
<td>Total R²</td>
<td>R² Change</td>
</tr>
<tr>
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<td>Age</td>
<td></td>
<td>.42</td>
<td>.45</td>
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<tr>
<td></td>
<td>Pain</td>
<td></td>
<td>-.42</td>
<td>-.37</td>
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<tr>
<td></td>
<td>SES</td>
<td></td>
<td>-.11</td>
<td>-.11</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td></td>
<td>.28</td>
<td></td>
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<tr>
<td>2</td>
<td>Exec Fx</td>
<td>Parental Stress</td>
<td>.42</td>
<td>.14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exec Fx *Parental Stress</td>
<td>.03</td>
<td>.02</td>
</tr>
<tr>
<td>3</td>
<td>SES*Exec. Fx</td>
<td></td>
<td>.42</td>
<td>.00</td>
</tr>
</tbody>
</table>
Table 6: Hierarchical Linear Model Examining Outcomes of Parent-Rated Quality of Life

<table>
<thead>
<tr>
<th>Steps</th>
<th>Variables</th>
<th>Total R²</th>
<th>R² Change</th>
<th>Partial R²</th>
<th>Beta</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
<td>Parent Rated HRQL</td>
<td>Parent Rated HRQL</td>
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<td>.34</td>
<td>1.83</td>
<td>.08</td>
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<td>1</td>
<td>Age</td>
<td>.20</td>
<td>.20</td>
<td>-.28</td>
<td>-.27</td>
<td>-1.54</td>
<td>.14</td>
</tr>
<tr>
<td></td>
<td>Sex</td>
<td>-.22</td>
<td>-.18</td>
<td>-1.19</td>
<td>.24</td>
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<tr>
<td></td>
<td>Pain</td>
<td>-.09</td>
<td>-.09</td>
<td>-0.49</td>
<td>.63</td>
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<tr>
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<td>-.27</td>
<td>-1.54</td>
<td>.14</td>
</tr>
<tr>
<td></td>
<td>Executive Functioning</td>
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<td>-.38</td>
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<td>.03</td>
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<tr>
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<td>Parental Stress</td>
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<td>-1.92</td>
<td>.07</td>
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<td></td>
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<tr>
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<td>Executive Functioning</td>
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<td>-.13</td>
<td>-0.73</td>
<td>.47</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>SES*Exec. Fx</td>
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<td>.18</td>
<td>-.98</td>
<td>.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. Discussion

The current study examined the impact of cognitive functioning on quality of life. The sample of children with SCD and their parents reported relatively high levels of overall quality of life. Intellectual functioning fell in the average range and levels of executive functioning were also average. Consistent with hypothesized outcomes, the current results suggest that cognitive functioning has a significant impact on subjective reports of overall well-being in children with SCD. More specifically, executive impairments contribute to lower levels of child- and parent-rated HRQL.

Executive functioning, as captured by the Metacognition Index of the BRIEF, is a higher-order cognitive ability that enables children to appropriately plan, organize, and initiate action in order to solve problems across contexts. It spans verbal and nonverbal processes, and relies on specific cognitive abilities including fluid reasoning, working memory, and attention, which are often affected in pediatric SCD (Schatz et al., 2002). These types of skills are crucial for adaptive social interactions (e.g., the ability to attend to social cues and respond appropriately), school functioning (e.g., the ability to attend to in-class lectures and organize and complete homework), and emotional functioning (e.g., the ability to recognize emotions and soothe or cope in the face of emotionally-challenging situations). Thus, children who have deficits in these cognitive domains are at a higher risk for poor social, emotional, and school functioning, each of which are
central aspects of HRQL. Indeed, this theoretical account is consistent with the current findings, in which both parents and children reported poorer quality of life in the context of weaker executive skills.

The impact of neurocognitive impairments on HRQL in children with SCD likely persists into adulthood. Evidence suggests that adults suffering from SCD have significant difficulty pursuing and maintaining occupational goals (Baskin et al., 1998; Baskin et al., 1998; Utsey, 1991). One study of adult adjustment in SCD reported that less than 50% of patients were employed full- or part-time (Edwards, Telfair, Cecil, & Lenoci, 2001). This finding may be partially attributable to neurocognitive deficits and associated difficulties with academic achievement, which collectively prevent individuals from acquiring the skills needed for vocational success. The long-term impact of cognitive impairment in patients with SCD is important to recognize, especially when considering the value of early interventions that remediate cognitive deficits. By addressing underlying neurocognitive impairments early in the disease trajectory, there is the potential to facilitate educational and occupational pursuits, and ultimately to improve the quality of life.

4.1 Moderating Factors

In an effort to better understand the relationship between neurocognitive functioning and HRQL, exploratory analyses examined families’ psychosocial resources
as potential moderators. Among pediatric patients with SCD, research indicates that emotional well-being and level of stress carried by caregivers is a significant predictor of a child’s executive skills and educational attainment (Armstrong, Birnie-Lefcovitch, & Ungar, 2005; Crowley & Kazdin, 1998). Further, socioeconomic status (SES) is a well-established predictor of quality of life across populations, including patients with SCD (Palermo et al., 2008; J. A. Panepinto et al., 2005). In light of this, emotional and socioeconomic resources were theoretically important variables to explore in the context of cognitive functioning and HRQL. Contrary to hypotheses, however, the psychosocial resources of the primary caregiver or family did not moderate the relationship between cognitive functioning and quality of life in the current sample of children with SCD.

While parents and families play an influential role in children’s lives, and likely buffer against other risk factors for poor quality of life, they may not be as impactful when it comes to moderating the effect of weak cognitive skills. In the context of a child’s cognitive functioning, it is possible that the academic environment may be a more important influence. Data regarding the academic environment, including access to academic supports (e.g., 504 plans, Individualized Education Plans), grades, type of school (e.g., Montessori, magnet, charter schools), and academic achievement or grade point average, were not assessed as part of this study. Thus, it is possible that a supportive school environment or adequate achievement in the face of cognitive
Impairments may moderate the impact between cognitive functioning and quality of life in school-aged children with SCD. This is particularly important to consider given that academic success is significantly impacted by weak cognitive skills (Schatz et al., 2002; Schatz, 2004), and that there is a long-term negative impact of poor academic functioning on HRQL (Baskin et al., 2000).

Unfortunately, however, many children with SCD do not have access to adequate school-based supports (Herron, Bacak, King, & DeBaun, 2003). This may relate to lack of awareness by the school or parents regarding the risk of neurocognitive impairment and resultant academic difficulties in children with SCD. Alternatively, for families who face multiple stressors, including caring for a child with a chronic illness, financial stress, and caregiver burden in single-parent homes—all of which can affect families managing SCD—there may not be available time and/or access to services to facilitate school-based supports. Collectively, these issues may make it difficult for parents to identify cognitive challenges in their children and advocate for educational services. In addition, schools may not be equipped with the knowledge or resources to identify and support children at-risk for, or struggling with, cognitive impairments secondary to an illness (Shaw & McCabe, 2007; Thies, 1999). This may be especially true for children in low-income school districts, which often have even less access to resources.
4.2 Current Intervention Efforts

Even when school-based supports are accessed, however, it may not be adequate to promote achievement in children with SCD. For example, King and colleagues (2007) aimed to increase the use of educational resources by children with SCD and stroke using a multidisciplinary healthcare approach. Their results indicated that this program helped all students in need obtain special education services, which was a significant improvement from baseline, when less than two-thirds were receiving services. The program, however, was unsuccessful at decreasing the number of school absences or grade retention, as only 20% of students eligible for graduation received their diplomas. Thus, providing access to general academic resources may be necessary but not sufficient to improve educational outcomes in children with SCD. It is also unlikely that this approach would be enough to improve deficits in HRQL associated with underlying cognitive impairment.

While there has been recognition of the need for neurocognitive interventions for children with SCD, there is only one known study that has adapted a remediation program for this population. Yerys and colleagues (2003) assessed the feasibility and efficacy of academic tutoring plus school-based memory training in children with SCD. The program demonstrated good feasibility (82% completion rate) and efficacy, which was manifested in gains in memory and reading in the intervention group compared
with controls. However, this intervention was limited by the fact that it is a school-based program that requires resources that may not be available to all students in all districts. It is a limited model that may prove challenging to implement in practice.

Other intervention efforts have focused on the potential benefits of medical treatments on neurocognitive abilities (Adams et al., 1998; King, Noetzel, White, McKinstry, & DeBaun, 2008; Puffer, Schatz, & Roberts, 2007; Scothorn et al., 2002). A study by Puffer et al. (Puffer et al., 2007) assessed cognitive functioning of children with silent cerebral infarct being treated with hydroxyurea (HU) as compared to those on standard therapy. Results indicated significantly higher scores on verbal comprehension, fluid reasoning, and global cognitive ability in the HU group.

Finally, while pharmacological interventions for cognitive impairment have been efficacious in other pediatric groups (e.g., methylphenidate for survivors of childhood cancer (Mulhern et al., 2004), their effectiveness in children with SCD is less certain. In part, this may relate to racial disparities in psychostimulant prescription prevalence, with research indicating that African Americans are significantly less likely to be prescribed psychostimulants than their Caucasian counterparts (Zito, Safer, Dosreis, & Riddle, 1998). Moreover, the safety of these medications in children with SCD has yet to be examined. This is an important consideration given the cardiovascular warnings associated with psychostimulant therapy and a disease-related risk for cardiovascular
dysfunction in patients with SCD (Haywood, 2009). Thus, there is a clear need for research on neurocognitive treatments that are feasible and efficacious in pediatric SCD.

4.3 Limitations and Future Directions

There were several limitations to the current study that are important to note before considering the implications of this research and future directions. First, this study was limited by the lack of objective cognitive data from neuropsychological tests. There has been significant discussion in the pediatric literature regarding the ideal informant, due to recognized discrepancies between parents, teachers, children, and healthcare provider reports (Sawyer, Antoniou, Toogood, & Rice, 1999; Wake, Hesketh, & Cameron, 2000). Thus, having more objective measures and/or additional informants (e.g., teachers) could have strengthened the findings.

In addition, the current study was limited by a relatively small sample size. With only 45 children, analytical approaches were limited and additional models of mediation or moderation could not be examined. Including additional models would be particularly interesting because it could help identify specific targets for intervention. Despite these limitations, however, it is important to note that the current findings provide empirical evidence that neurocognitive functioning has a significant impact on overall HRQL. In light of this and the high risk of cognitive impairment in children with SCD, interventions that target the neurocognitive impairments underlying the
documented functional deficits are sorely needed. This will be examined in the following study.
5. Study 2: A Novel Cognitive Intervention for Children with SCD

5.1 Cognitive Training programs

Cognitive Training (CT) programs have been used for decades to reduce or stabilize neurocognitive deficits in populations of individuals with accidental or disease-related brain injury. CT activities can include paper-and-pencil tasks, memory games, and one-on-one instruction with a cognitive “coach,” usually a neuropsychologist, occupational therapist, educator, or similar professional. Most CT programs emphasize activities designed to improve specific cognitive deficits through repetitive practice of related skills. For example, individuals with memory problems might practice remembering lists of words or numbers of increasing length or complexity in order to improve their skill. In this way, although many CT programs also include compensatory elements (e.g., making lists, using electronic planners), the primary aim of CT is to restore or improve cognitive functioning.

Research on the efficacy of CT is difficult to summarize given the variety of clinical populations with which it has been employed, and the variability in format (e.g., individual vs. group), setting (e.g., home vs. clinic), length of intervention, and outcomes measured (e.g., quality of life, neurocognitive functioning). However, CT has been associated with improved functioning in several child and adult populations, including
those with traumatic brain-injury (Cicerone, 2002; Tiersky et al., 2005), dementia (Cahn-Weiner, Malloy, Rebok, & Ott, 2003; Cipriani, Bianchetti, & Trabucchi, 2006; Hofmann et al., 2003; Moore, 2001), schizophrenia (Bell, Fiszdon, Bryson, & Wexler, 2004; Fiszdon, Bryson, Wexler, & Bell, 2004), mild cognitive impairment (Cipriani et al., 2006), and ADHD (Klingberg et al., 2005; Klingberg, Forssberg, & Westerberg, 2002). A recent meta-analysis of over 85 CT studies concluded that individuals receiving such treatment receive significantly more benefit than those in control/placebo conditions (Cicerone et al., 2005).

In the past several years, many computerized CT programs have been developed specifically to target attention and working memory problems, primarily in children and adolescents diagnosed with Attention-Deficit Hyperactivity Disorder (ADHD). Most consist of a series of attention/short-term memory tasks of increasing complexity, and there is emerging support for their efficacy with the ADHD population (Kerns, Eso, & Thomson, 1999; Klingberg et al., 2005; Klingberg et al., 2002; Slate, Meyer, Burns, & Montgomery, 1998).

Computerized CT programs provide several practical and therapeutic benefits over traditional paper-and-pencil or therapist-directed activities. Specifically, they can be administered at home, allowing children to receive more frequent CT sessions with little inconvenience. This is particularly advantageous for patients with SCD, many of
whom live a considerable distance from the nearest treatment center. In addition, computerized CT programs automatically adjust the level of difficulty according to the progressing skill of the patient. This allows for maximal gains, as well as maintained interest in, and motivation for, program activities. The latter benefit is particularly salient for children, who often find computer-based learning activities of inherent interest. Moreover, research also has indicated that computerized CT programs are feasible and efficacious in children with a range of intellectual ability, including persons with mild impairment (IQ < 80) (Van der Molen, Van Luit, Van der Molen, Klugkist, & Jongmans, 2010). This is an important consideration given that children with SCD may have intellectual disabilities (Schatz et al., 2002).

5.1.1 Cogmed RM

Recently, Klingberg and colleagues developed a computerized CT program that aims to attenuate deficits in working memory (Klingberg et al., 2005; Klingberg et al., 2002). The program, called Cogmed RM (RoboMemo), consists of game-like exercises including two visuo-spatial working memory tasks and a spatial-verbal working memory task (Figure 2). Feedback about participants’ performance is given visually and verbally to increase interest and compliance. Difficulty of the training tasks increases with the skill of the participant on a trial-by-trial basis. In addition, the program is adaptable for home use, with minimal training and support.
The efficacy of Cogmed RM has been assessed in samples of children with ADHD in two randomized, double-blind, placebo-controlled trials (Klingberg et al., 2005; Klingberg et al., 2002). Children completed CT from a home-based computer, training in 40-minute sessions, multiple times a week, for 5 weeks. Results were robust and indicated that children who completed the intervention improved significantly on numerous working memory tasks, as well on parent-rated reports of ADHD symptoms (Klingberg et al., 2005; Klingberg et al., 2002). Importantly, the authors reported that these gains remained significant at a 3-month follow-up assessment. Effect sizes for most outcome measures were large, and were broadly consistent with those obtained from many medication trials using psychostimulants with ADHD samples. Furthermore, 88% of the participants who successfully completed the treatment met compliance criteria, defined as successfully completing at least 25 days of treatment over a 5-week period (average = 25.2 days).

More recently, Cogmed RM was tested in a sample of pediatric cancer survivors (Hardy, Willard, Allen, & Bonner, 2013). This randomized trial included both an intervention group that completed an adaptive version of the program and an active control group. Compliance rates for the trial (n = 20) were high (Mean = 98.1% of sessions completed, SD = 6.02%). Feasibility and acceptability indicate high levels of participant and parental satisfaction with the intervention. Indeed, 94.4% of parents
reported that they were somewhat or very satisfied with their child’s participation in the intervention, and 68.7% of children indicated that they often or always enjoyed their training sessions. Further, data from the Cogmed Training Index, a program-specific score that is used to gauge children’s progress with working memory skills targeted by the Cogmed tasks, indicated that participants achieved a mean training index improvement of 31 (SD = 11, range = 15 – 54), very similar to that of a sample of 550 children with ADHD who completed the program with a mean index improvement of 26.2. Finally, survivors who completed the adaptive version evidenced increases in attention (d = .56) and working memory (d = .53; as measured by the Wide Range Assessment of Memory and Learning – Second Edition) and decreases in parent-rated attention problems (d = .50; as measured by the Conners-3 Parent Rating Scale) as compared to survivors completing the non-adaptive version.

5.1.2 Summary and Rationale

Research clearly indicates that children with SCD have multiple risk factors for functional impairment. Compounding their vulnerabilities is the fact that SCD almost exclusively affects the African-American population, which has been largely underrepresented in clinical research. Disparate attention has been given to psychological interventions in this group of children, which has made it difficult to form a consensus regarding treatment for their cognitive impairment. In fact, the few
interventions that have been tested have had only mild success and have little empirical basis for their methods. Consequently, there is a significant need for novel interventions aimed generally at attenuating risk factors for poor quality of life, specifically neurocognitive deficits, in this historically-underserved group. The current proposal highlights the merits of a home-based, cognitive training program that targets areas of known impairment in children with SCD.

While the neurocognitive interventions have been proven feasible and efficacious in other pediatric populations (e.g., ADHD, cancer survivors) – suggesting promise here – children with SCD and their families face unique psychosocial and medical stressors which override the assumption of identical outcomes in this population. For example, psychosocial and sociodemographic factors (e.g., parental stress, coping strategies, limited access to resources, lack of knowledge regarding illness-related factors) as well as individual medical factors, notably the child’s level of pain, have been recurrently cited in the sickle cell literature as barriers to successful medical and psychological interventions (Bakarat, Smith-Whitley, & Ohene-Frempong, 2002; Day, Brunson, & Wang, 1992; Reese & Smith, 1997). In light of these considerations, it remains critical to assess feasibility and acceptability of the computerized CT program in pediatric sickle cell patients.
5.2 Study Aims

5.2.1 Primary Aims

Specific Aim 1: To assess the acceptance of the computerized cognitive training program for patients with SCD as measured by success with recruitment efforts and enrollment goals.

Hypothesis: Children with SCD will be successfully recruited and enrolled as measured by an interest rate of 50% of those approached about participation and an enrollment rate of 75% of those eligible.

Specific Aim 2: To assess compliance with the computerized cognitive training program in pediatric participants with SCD.

Hypothesis: Children with SCD will be compliant with the home-based computerized cognitive training as defined by 75% of enrolled participants meeting an 80% compliance rate for the intervention program (i.e., completion of at least 20 sessions).

Specific Aim 3: To assess qualitative aspects of feasibility including technical feasibility, ease of use, and satisfaction.

Hypothesis: The majority of children will report adequate technical feasibility, find the Cogmed program easy to use, and find the games enjoyable.
5.2.2 Exploratory Aims

Exploratory Aim 1: To determine preliminary efficacy of the cognitive training program for criterion outcomes (i.e., attention, executive functioning and working memory measures).

Hypothesis: Participants who complete the intervention protocol will evidence significant increases in working memory, attention, and executive functioning compared to baseline performance.
6. Methods

The goal of the current proposal is to establish feasibility of, and compliance with, the Cogmed CT intervention in a small sample of participants, ages 8-16 years old, with SCD. This age range was selected because it includes children who are old enough to complete this program, and still young enough to reliably be treated in the pediatric system.

Given that the primary aim of this study is acceptance and feasibility, there are minimal exclusion criteria. Children were excluded from the study if they had evidence of an intellectual disability (IQ<75), had a motor, visual, or auditory handicap that prevented computer use, had been diagnosed with an autism spectrum disorder (by history), had evidence of an overt stroke (via medical record review), or were not fluent in English.

Participants were initially approached about this study during their regularly scheduled hematology visits, and were introduced to the study team by their treating provider. Prospective study participants were provided with additional information about the study and, if interested and available, were scheduled for their baseline screening visit. Eligible and consenting participants completed a brief battery of measures and questionnaires (see Measures below) assessing cognitive functioning, quality of life, and psychosocial (e.g., SES, family functioning) variables. Subsequently,
individuals were randomized to the intervention arm or a waitlist control group (Figure 2). Given that efficacy is a secondary study aim, a two-to-one randomization schedule was implemented. As such two-thirds of participants were immediately enrolled in the intervention condition (Cogmed RM), and the other one-third were assigned to an 8-week waitlist. Participants in the waitlist condition were subsequently offered the opportunity to participate in the intervention.

![Study Design Diagram]

**Figure 1: Study Design**

Participants who were randomized to the intervention condition were trained on the Cogmed program by the clinic staff immediately following their baseline assessment. Cogmed is a computer program that can be accessed via a secure website on
the Internet, however families without easy and reliable access to the Internet were provided the option of accessing the program on a CD Rom (n=2). Further, children without dedicated access to a computer were provided with a laptop to complete the intervention (n=13).

The Cogmed program consists of twelve visually engaging exercises that target working memory and executive functioning skills. Difficulty of the tasks is automatically adjusted on a trial-by-trial basis throughout each training session to match a child’s current memory span; as the child becomes more proficient, the exercises become more difficult. Children were asked to complete between 3 and 5 sessions per week, for a total of 25 sessions. Sessions typically last between 30 and 45 minutes, depending on the child’s working memory span.

A treatment “coach” (trained by Cogmed) was made available to parents and children by phone throughout the intervention period. Weekly phone contact with the coaches was also scheduled to collect compliance and feasibility data. Any problems that arose (e.g., training issues, adverse events, technical problems) were addressed during these phone calls. Technical assistance was also provided by Cogmed at no additional cost, though this was rarely needed.

Throughout training, the intervention coach had instant access to detailed information about children’s training sessions including length and frequency of
training as well as outcomes (pass or fail) of each trial. Using this information, the training coach modified the training sequence or made suggestions to the child and/or parent about how progress can be maximized (e.g., by taking a short break after three failed trials to prevent frustration). Strategies to promote treatment success and compliance were based on cognitive-behavioral principles (e.g., positive reinforcement, self-encouragement, problem-solving). Scheduled phone meetings were set up at least once per week with an intervention coach to encourage compliance, track progress, provide feedback, and answer any questions during the treatment period. Consistent with how Cogmed is delivered clinically, reinforcers ($5 or less) were offered every 8 sessions for participants.

Participants initially assigned to the adaptive intervention arm were asked to return to the clinic within two weeks of completing the intervention program for brief follow-up testing. This included an assessment of working memory function and executive functioning on a computerized testing battery (Cogstate; see measures) and a brief test of academic skills. Additional information was collected from parents pertaining to their child’s cognitive functioning and quality of life. Children also completed quality of life outcome measures. Finally, parents and children completed a feasibility and acceptance questionnaire pertaining to their experience participating in the Cogmed intervention.
Participants who were initially randomized to the waitlist control were also asked to participate in an identical assessment, excluding the feasibility measure, approximately 8-weeks after their baseline assessment. Subsequently, the waitlist group was enrolled in the Cogmed intervention program, following the same protocol as described above. All participants enrolled in the waitlist condition opted to participate in the intervention. After completing the intervention, these participants were asked to return to clinic for a final evaluation to collect data regarding criterion efficacy and feasibility. Child participants and their parents received $50 for completing each study-related clinic visit.

6.1 Measures

**Demographic Questionnaire** was used to collect baseline data regarding age, sex and race of the child and socioeconomic status of the family (income, education levels). The two-factor Hollingshead Index was calculated from this information to provide an estimate of the family’s socioeconomic status (Hollingshead, 1957). The Hollingshead Index ranges from 8 to 66.

**Child Behavior Checklist** (CBCL; Achenbach, 1991) is a well-known parent-completed measure of children’s psychosocial functioning. The CBCL was administered at baseline and completed by parents.
**Pediatric Inventory for Parents** (PIP; Streisand, Braniecki, Tercyak, & Kazak, 2001) is a 42-item parent-rated questionnaire that assesses characteristics of families caring for a child with a chronic illness. The impact of a chronic illness is evaluated across four domains of functioning: Communication, Emotional Distance, Medical Care, and Role Function. Outcomes from the PIP were used to explore family-level variables associated with feasibility.

**Pediatric Quality of Life Inventory** (PedsQL; Varni, Seid, & Rode, 1999) is a 23-item questionnaire of children’s quality of life (i.e., physical, social, emotional, and school) over the past month completed by the child and caregiver. The PedsQL was used as an exploratory outcome measure of quality of life, and administered at baseline and post-intervention by both parent and child.

**Wechsler Abbreviated Scale of Intelligence** (WASI; Wechsler, 1999) is a brief measure of intelligence usable with people aged 6 to 89 years. A 2-subtest version was used at baseline only to estimate IQ of children (IQ ≥ 75 for inclusion in the study).

**CogState** (Maruff et al., 2009) is a computerized testing software package that offers a range of semi-automated assessment modules for individuals aged 6-90. The objective measures of executive function were assessed using the Groton Maze Learning; working memory was evaluated using the One-Back task and the Continuous Paired Association task. Finally attention was examined through the Identification task. This battery takes
about 20-minutes to administer. Reliability is .77 with no practice effects when testing intervals > 1-month (Falleti, Maruff, Collie, & Darby, 2006). It was administered at all time points.

**Woodcock-Johnson Tests of Achievement-Third Edition** (WJ-III; Woodcock, McGrew, & Mather, 2006) will be used for two purposes: a) The Understanding Directions provided an ecologically-valid measure of working memory and auditory attention. This subtest was administered at all time points to assess a child’s “real world” working memory functioning. In addition the Letter-Word Identification, Math Calculation, and Spelling subtests were administered to obtain a brief measure of academic functioning.

**Behavior Rating of Inventory of Executive Function** (BRIEF; Gioia et al., 2000) is a widely-used questionnaire measures of executive functioning. It was completed by parents in order to track the presence of cognitive difficulties over time and was administered at baseline and post-intervention.

**Feasibility Interview:** There is no standardized measure of feasibility/acceptability for this type of intervention. Therefore, in a previous trial with survivors of childhood cancer (Hardy et al., 2013), a 13-item survey was developed for parents and children assessing technical feasibility, adherence, satisfaction, and ease-of-use. The Feasibility Interview was completed by the parent and child at their post-intervention assessment.
**Treatment compliance:** Cogmed automatically tracks the number and length of children’s sessions, along with their progress through program levels. This is accomplished through a secure website over the Internet.

**Medical and disease variables.** Medical variables (e.g., genotype, medications, disease severity) were abstracted from medical records. These data were used to assess medically-relevant variables associated with feasibility in this study and to ensure eligibility criteria were met.
### Table 7: Study 2 Measures

<table>
<thead>
<tr>
<th>Measure</th>
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<td></td>
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<td>Demographic Questionnaire</td>
<td>Parent</td>
</tr>
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<td>Behavioral Func.</td>
<td>CBCL</td>
<td>Parent</td>
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<tr>
<td>Quality of life</td>
<td>PedsQL</td>
<td>Parent/Child</td>
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<td>Parent/Family Stress</td>
<td>PIP</td>
<td>Parent</td>
</tr>
<tr>
<td><strong>Medical Factors</strong></td>
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<td>Disease Severity</td>
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<td>Medical Events</td>
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</tr>
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<td>Technical Feasibility</td>
<td>Feasibility Questionnaire</td>
<td>Parent / Child</td>
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<tr>
<td>Ease of Use</td>
<td>Feasibility Questionnaire</td>
<td>Parent / Child</td>
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<tr>
<td>Satisfaction</td>
<td>Feasibility Questionnaire</td>
<td>Parent / Child</td>
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<td><strong>Cognitive and Academic</strong></td>
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<td>Intelligence</td>
<td>WASI</td>
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<td>Continuous Paired Association</td>
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</tr>
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<td>Working Memory</td>
<td>One-Back Task Cogstate</td>
<td>Child</td>
</tr>
<tr>
<td>Working Memory</td>
<td>Understanding Directions WJ-III</td>
<td>Child</td>
</tr>
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<td>Executive functioning</td>
<td>Groton Maze Cogstate</td>
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<td>Metacognition Index BRIEF</td>
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<tr>
<td>Academic Skills</td>
<td>WJ-III</td>
<td>Child</td>
</tr>
</tbody>
</table>

### 6.2 Statistical Methods

#### 6.2.1 Primary Aims

Feasibility was defined in terms of the *acceptance, compliance,* and outcomes from the *feasibility questionnaire* (i.e., average ease of use, technical feasibility, and satisfaction).

Each aspect of feasibility is described below.
Acceptance of the intervention was determined by patient/family interest in the intervention among prospective participants who were approached (target rate of 50% expressing interest in participating) and success with recruitment efforts and randomization goals (i.e., rate of enrollment among participants consented ≥75%). A Z-test for binomial proportion with continuity correction was used to examine whether the acceptance and enrollment rates are lower than the target. Reasons for non-participation were documented qualitatively.

Compliance was examined following completion of the intervention using a measure of compliance obtained from the Cogmed program data. This outcome was defined by 75% of participants achieving 80% compliance with the intervention A Z-test for binomial proportion with continuity correction was used to examine whether the compliance rate is lower than the target. A series of t-tests (for continuous variables) and Chi-square tests (for non-continuous variables) were conducted to examine potential differences between participants who were compliant (i.e., 80% completed) and noncompliant. Correlational analyses were also used to determine psychosocial, medical, and cognitive factors associated with the total number of sessions completed.

Technical feasibility, ease of use, and satisfaction were measured through youth and parent reports on the Feasibility Questionnaire. Given the exploratory nature of this study, descriptive and summary statistics were used to report parent and child ratings.
of intervention completion, as well as the intervention’s technical feasibility, ease-of-use, and satisfaction at end-point.

6.2.2 Exploratory Aim

Given that the primary aim of this study is feasibility, a plan to assess preliminary efficacy was put in place in the event the intervention is deemed feasible. It was proposed that descriptive statistics would be used to summarize the objective and criterion referenced measures at baseline and post-intervention. Medical, psychosocial, and environmental factors that are related to short-term efficacy of the intervention would be qualitatively assessed. A one-way analysis of covariance (ANCOVA) was planned, with the pre-test score on the outcome variable as covariate.

Preliminary efficacy of the intervention was to be evaluated through subjective and objective measures. Parent-rated executive function and working memory were assessed using the Metacognition subscales from the BRIEF. Objective measures of executive functioning would be assessed using the Groton Maze Learning and Set Shifting tasks of CogState, while working memory was assessed using the One-Back task from CogState and the Understanding Directions task from the WJ-III. For exploratory purposes, we also assessed other outcomes that reflect transfer of training (e.g., tasks from the WJ-III). Mixed models would be used to determine changes over time in
attention functioning and working memory at post-intervention and estimate effect sizes of each outcome.
7. Results

7.1. Acceptance

Acceptance was measured at two points: (i) the number of prospective participants approached who expressed interest in the study (the interested-acceptance rate) and (ii) the number of consented and screened individuals who subsequently enrolled (the enrollment-acceptance rate). The target interested-acceptance rate was 50%, while it was 75% for the enrollment acceptance rate.

Seventy-four prospective participants were approached (Figure 3). Of these 74 individuals, 64 youths and their respective caregiver (82%) expressed interest in participating in the study, resulting in an interested-acceptance rate significantly higher than the 50% target ($p<.01$).
Of the 64 the prospective participants who expressed interest, 26 indicated that they would not be able to commit the requisite time to the study and chose not to be contacted in the future. The remaining 38 individuals indicated that they would like to be contacted in the future regarding participation. Of this 38, 14 prospective participants were never reached despite repeated follow-up efforts. Of the 24 prospective participants who were reached, six were scheduled for a pre-study assessment but did not attend the scheduled appointment. Despite subsequent efforts to contact them, these
six participants were never subsequently reached. Finally, 18 of the 74 (24.3%) prospective participants who were approached consented and completed their pre-study screening.

While not included as a construct in the predetermined study aims, it is important to consider the gap between the number of individuals who expressed interest (i.e., n=64) and the number who ultimately enrolled (i.e., n=18). This reflects the degree of commitment by children and families to this intervention (i.e., commitment-acceptance). The rate of commitment-acceptance is well below 50% (p<.01), and should be considered as part of the broader construct of acceptance.

All 18 participants who were screened for the study were randomized to the active intervention group (n=12) or waitlist control group (n=6). All waitlist participants opted to enroll in the intervention after the waitlist period. Thus, 18 participants (100%) who were consented and screened enrolled in the intervention, resulting in an enrollment-acceptance rate that was also significantly greater than the 75% target (p<.05).

### 7.1.1 Descriptive Statistics for Participants

Participants included 18 children (12 males) with SCD and a parent or caregiver. Children ranged in age from 8 to 16 years (M = 12.2 years). All children were African American (100%) without evidence of an overt stroke (confirmed by medical records). Children had a mean IQ of 100.2 (SD=9.19); this is higher than the average range
reported in pediatric SCD, which is closer to a standard score of 90 (Schatz et al., 2002).

The mean number of hospitalizations per year was 2.0 (SD=2.22). The family SES

Demographic variables are summarized in Table 8.

<table>
<thead>
<tr>
<th>Table 8: Demographic Data Study 2</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Demographic Variables</strong></td>
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<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td><strong>Medical Variables</strong></td>
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<td>Genotype</td>
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<td>SS</td>
</tr>
<tr>
<td>SC</td>
</tr>
<tr>
<td>Beta-Thalasemia</td>
</tr>
<tr>
<td>Disease Severity</td>
</tr>
</tbody>
</table>

7.2 Compliance

Compliance has been defined previously as completion of more than 20 days of training (>80% of sessions) (Hardy et al., 2013). Our target compliance rate was 75% of the participants enrolled in the intervention.

Of the 18 participants enrolled in the intervention, one child has not had an opportunity to complete all training days and has been excluded from the analyses.

Among the remaining 17 participants, three children (16.6%) were deemed compliant (p<.01). All three compliant participants completed 100% of the training days (25
sessions). The remaining 14 participants (82.4%) were deemed non-compliant because they completed less than 20 days of training ($p<.01$). This is significantly lower than our target rate of 75% of participants reaching compliance. The 17 participants enrolled in the intervention completed an average number of nine training days ($SD=8.69$).

Of the 17 participants enrolled in the intervention, 14 completed the post-study assessment. Despite repeated efforts to contact the other three children, they were never reached and thus are deemed lost to follow-up.

**7.2.1 Descriptive Statistics**

Among those who completed the intervention, two were male and one was female. They had a mean age of 11.2 ($SD=3.19$). All had been randomized to the active intervention group at baseline. The three individuals had a mean IQ of 114 ($SD=4.35$) and a mean working memory score (per the Understanding Directions task of the WJ) of 102.7 ($SD=5.03$). Their mean score on the Metacognition Index of the BRIEF, a measure of executive ability, was 35 ($SD=4.58$). Finally, the mean number of serious medical events that were experienced among completers during their participation in the Cogmed CT intervention was 1.33 ($SD=1.15$). Descriptive characteristics for completers are provided in Table 9.

Among participants who did not complete the intervention (i.e., “non-completers”), the mean age was 12.3 ($SD=2.26$). They had a mean IQ of 98.7 ($SD=6.74$).
and a mean working memory score (per the Understanding Directions task of the WJ) of 92.9 (SD=12.62). Their mean score on the Metacognition Index of the BRIEF, a measure of executive ability, was 60.8 (SD=15.18). Finally, the mean number of serious medical events that were experienced among non-completers during their participation in the Cogmed CT intervention was 1.8 (SD=2.25). Basic demographic characteristics for non-completers are provided in Table 9.

Table 9: Demographic Comparison Between Completers and Non-Completers

<table>
<thead>
<tr>
<th></th>
<th>Completers $M \pm SD$</th>
<th>Non-completers $M \pm SD$</th>
<th>Test Statistic$^{*}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>11.2 ± 3.19</td>
<td>12.3 ± 2.26</td>
<td>0.78</td>
</tr>
<tr>
<td>Gender</td>
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<td>Male</td>
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</tr>
<tr>
<td>Female</td>
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<td>4</td>
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</table>

$^{*}$Test statistic is Student’s t-test for age and chi-square for gender

7.2.2 Factors Associated with Compliance and Non-Compliance

Exploratory analyses were conducted to examine factors associated with noncompliance. Given the small sample size and limited power to detect between-group significant findings, a series of t-tests was used to examine between-group differences across psychosocial (i.e. socioeconomic status, parental functioning, externalizing behavior), medical (i.e., number of medical events during the intervention phase, somatic complaints and disease severity) and cognitive variables (i.e., estimated IQ.
working memory per the Understanding Directions task of the WJ-III and executive functioning per the BRIEF). Findings are presented in Table 10.

The data revealed significant differences between completers and non-completers across domains of functioning (Table 10). Specifically, at baseline, completers had significantly lower levels of somatic problems, per the CBCL ($p=0.01$, $t=3.10$), and parents/caregivers reported significantly fewer medical care needs, per the Medical Care index of the PIP ($p<.01$, $t=3.70$). There was no difference between groups, however, in the number of serious medical events experienced while enrolled in the intervention ($t=0.03$, NS), or disease severity ($t=-0.33$, NS). Baseline cognitive skills differed significantly between completers and non-completers. Specifically, youth who completed the intervention had significantly higher IQs ($p<.01$; $t=-3.66$) and significantly stronger executive skills, per the Metacognition Index of the BRIEF, than those who did not ($p<.01$; $t=2.89$). In addition, completers had lower levels of externalizing behavior, as assessed by the CBCL (e.g., symptoms of inattention, rule-breaking behavior) than completers ($p<.01$; $t=3.70$) Socioeconomic status and parental role functioning was not significantly different between the groups (respectively, $t=-1.89$, NS; $t=1.70$, NS).

Due to the number of overall analyses, application of the Bonferroni correction did not allow for the retention of the significance of all findings. It is notable, however, that many of the comparisons yielded large effect sizes (Table 10) and thus it is likely
that a larger sample size would yield results that would survive correction for multiple comparisons.
### Table 10: Comparison Between Completers and Non-Completers

<table>
<thead>
<tr>
<th></th>
<th>Completers</th>
<th>Non-completers</th>
<th>Test Statistic</th>
<th>Effect size</th>
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<td>Genotype</td>
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<td>SS</td>
<td>3</td>
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<tr>
<td>SC</td>
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<td>3</td>
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<tr>
<td>Beta Thalassemia</td>
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<tr>
<td>Medical Events</td>
<td>1.33 ± 1.15</td>
<td>1.8 ± 2.25</td>
<td>1.33</td>
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<td>Disease Severity</td>
<td>2.33 ± 2.52</td>
<td>1.86 ± 2.25</td>
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<td>Somatic Complaints (CBCL)</td>
<td>50.0 ± 0.00</td>
<td>62.5 ± 13.33</td>
<td><strong>3.10</strong></td>
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<td><strong>Cognitive Variables</strong></td>
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<tr>
<td>IQ</td>
<td>114 ± 4.35</td>
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<td>Working Memory</td>
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<td>Executive Functioning</td>
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<tr>
<td>Externalizing Symptoms</td>
<td>35.7 ± 3.79</td>
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<td>Parental Role Function (PIP)</td>
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<td>Family SES</td>
<td>47.0 ± 3.46</td>
<td>37.1 ± 8.66</td>
<td><strong>-1.90</strong></td>
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*Student’s t-test for continuous variables and chi-square analysis for categorical variables

*Test Statistic: Student t-test; +Effect size is Cohen’s $d$ (0.50=large effect, 0.30=medium effect, 0.10=small effect)
In addition to exploring between-group differences, correlational analyses were used to explore factors associated with the number of training sessions completed. Psychosocial, medical and cognitive variables were included in the correlational analyses in order to capture additional variables that may be relevant to compliance. Results are presented in Table 11. Significant correlations were identified between baseline cognitive factors (i.e., IQ and executive functioning per the Metacognition Index of the BRIEF) and the total number of sessions completed ($p<.05$, $r=0.59$ for IQ; $p<.05$, $r=-.55$, Figure 4).

**Figure 3: Bland-Altman Plot Total Sessions by Executive Functioning**

In other words, each of higher IQ and less executive impairment was associated with a greater number of training sessions completed. No other correlations reached statistical significance. Of note, due to the large number of correlations, application of the Bonferroni correction did not allow for the retention of significant results. These correlations, however, yielded a large effect size (Table 11) and thus it is possible that a
larger sample size would allow for significant findings to persist in the context of multiple comparisons.
Table 11: Correlations Between Predictor Variables and Number of Sessions Completed

<table>
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<tr>
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<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
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<th>7.</th>
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<td>1. Number of sessions completed</td>
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<td>2. IQ</td>
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<tr>
<td>5. Parent-rated school functioning</td>
<td>.45</td>
<td>.78</td>
<td>.59</td>
<td>-.60</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Child-rated school functioning</td>
<td>-.01</td>
<td>.60</td>
<td>.39</td>
<td>.69</td>
<td>.61</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Externalizing behavior</td>
<td>-.25</td>
<td>-.80</td>
<td>-.28</td>
<td>.72</td>
<td>-.52</td>
<td>-.58</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Age</td>
<td>-.39</td>
<td>.13</td>
<td>.13</td>
<td>.23</td>
<td>.49</td>
<td>.32</td>
<td>-.03</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Somatic problems</td>
<td>.37</td>
<td>-.59</td>
<td>-.62</td>
<td>.55</td>
<td>-.64</td>
<td>-.52</td>
<td>.55</td>
<td>.72</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>10. Medical events during study</td>
<td>.11</td>
<td>-.35</td>
<td>.13</td>
<td>-.14</td>
<td>-.17</td>
<td>-.32</td>
<td>.01</td>
<td>-.27</td>
<td>.27</td>
<td>--</td>
</tr>
<tr>
<td>11. Disease severity</td>
<td>.23</td>
<td>-.24</td>
<td>.35</td>
<td>.01</td>
<td>-.28</td>
<td>-.31</td>
<td>.44</td>
<td>-.38</td>
<td>.03</td>
<td>.38</td>
</tr>
</tbody>
</table>
7.3 Results from the Feasibility Questionnaire

7.3.1 Technical Feasibility

Technical feasibility was assessed through parent/caregiver and youth responses on the Feasibility Questionnaire. In addition, data regarding technical feasibility were obtained during weekly coach calls with the children who participated, which are described herein.

The majority of parents/caregivers reported adequate technical feasibility, indicating that the Cogmed program worked every time they tried it (71.4%) and denied any problems with the computer (64.3%). Youth participants reported greater difficulties, with only 53.3% of children stating that the Cogmed program worked every time. However, children generally denied any difficulties with the computer itself (69.2% reported no problems). Of note, 13 out of 18 participants in this study did not have designated access to a computer to use for the intervention, and a computer was provided to them for the duration of the study.

Information pertaining to the specific nature of technical difficulties was also reported. Specifically, four parents/caregivers reported that the program would occasionally freeze, which was also reported by three children. Three children also reported difficulties with their Internet connection, which occasionally dropped and would therefore disrupt their participation in the program. In addition, it is also notable that three participants in the intervention did not have an Internet connection available
to them in their home and were provided with a wireless dongle by the study team in order to connect to program. The Cogmed program was also installed on the computers of these three participants in order to circumvent connectivity issues with a less reliable Internet source.

### 7.3.2 Ease of Use

Ease of use, a component of feasibility, was assessed via the Feasibility Questionnaire. Parents/caregivers reported that the program was easy to use, including very easy or somewhat easy to login (92.9%), start the games (85.7%), use the mouse (100%) and carry out the tasks procedurally (64.3%). Youth participants reported that it was either very easy or somewhat easy to login (85.7%), start the games (85.7%), and use the mouse (76.9%). Children reported somewhat greater difficulty carrying out the tasks procedurally, however, with 42.9% of participants reporting that this was either somewhat or very easy, 35.7% reporting it was neither easy nor difficult and 21.4% reporting that it was somewhat or very hard. Children also reported that they sometimes (35.7%) or often/always (35.7%) experienced frustration while carrying out the tasks.

Parents/caregivers observed less frequent frustration, reporting that their child was frustrated sometimes (42.9%) or never/rarely (14.2%). Notably, the majority of children were generally able to complete the Cogmed exercises without frequent assistance from their parent/caregiver. Indeed, 85.7% of parents/caregivers reported that their child never or rarely needed their help to complete the program and 85.7% of children reported that
their parents *never, rarely* or *sometimes* provided assistance. Data pertaining to the intervention’s ease of use are presented in Tables 12 and 13.

**Table 12: Parent/Caregiver Ease of Use Responses**

<table>
<thead>
<tr>
<th>Questions: “How often…”</th>
<th>Parent/Caregiver Responses (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did you help your child with the exercises?</td>
<td>Never/Rarely</td>
</tr>
<tr>
<td>Did your child experience frustration?</td>
<td>12 (85.7%)</td>
</tr>
<tr>
<td>Questions: “How easy or difficult was it for your child to…”</td>
<td>Very/Somewhat Easy</td>
</tr>
<tr>
<td>Log into the program</td>
<td>13 (92.9%)</td>
</tr>
<tr>
<td>Start the games</td>
<td>12 (85.7%)</td>
</tr>
<tr>
<td>Using the mouse</td>
<td>14 (100%)</td>
</tr>
<tr>
<td>Carry out the exercises</td>
<td>9 (64.3%)</td>
</tr>
</tbody>
</table>
Table 13: Child Ease of Use Responses

<table>
<thead>
<tr>
<th>Questions: “How often…”</th>
<th>Child Responses (N=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never/Rarely</td>
</tr>
<tr>
<td>Did your parents help you with the exercises?</td>
<td>7 (50%)</td>
</tr>
<tr>
<td>Did you experience frustration?</td>
<td>4 (28.6%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Questions: “How easy or difficult was it for you to…”</th>
<th>Very/Somewhat Easy</th>
<th>Neither Easy/Hard</th>
<th>Somewhat/Very Hard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logging into the program</td>
<td>12 (85.7%)</td>
<td>-</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>Starting the games</td>
<td>12 (85.7%)</td>
<td>-</td>
<td>2 (14.3%)</td>
</tr>
<tr>
<td>Using the mouse</td>
<td>10 (76.9%)</td>
<td>-</td>
<td>3 (23.1%)</td>
</tr>
<tr>
<td>Carrying out the exercises</td>
<td>6 (42.9%)</td>
<td>5 (35.7%)</td>
<td>3 (21.4%)</td>
</tr>
</tbody>
</table>

7.3.3 Satisfaction

Participant satisfaction with the Cogmed CT program was assessed via the Feasibility Questionnaire. There was some variability across items comprising “satisfaction” within and between parents/caregivers and youth participants. Specifically, 54.5% of parents/caregivers reported that their child never or rarely complained about the training exercises but only 21.4% of youth respondents agreed. Children were more likely to report that they sometimes (42.8%) or often/always (35.7%) complained while carrying out the intervention tasks. Half of the youth participants also reported that they either often or always felt bored during the exercises, which was consistent with approximately one third of parents/caregivers (35.7%). Finally, children
reported that they sometimes (42.8%) enjoyed completing the exercises, while the majority of parents/caregivers reported that their children often or always found the Cogmed tasks enjoyable (57.1%). These findings are presented in Tables 14 and 15.

<table>
<thead>
<tr>
<th>Table 14: Parent/Caregiver Satisfaction Ratings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parent/Caregiver Responses</strong> (N = 14)</td>
</tr>
<tr>
<td><strong>Questions: “How often...”</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Did your children complain about the exercises?</td>
</tr>
<tr>
<td>6 (54.5%) 3 (27.3%) 2 (18.2%)</td>
</tr>
<tr>
<td>Did your children feel bored during the computer exercises?</td>
</tr>
<tr>
<td>5 (35.7%) 4 (28.6%) 5 (35.7%)</td>
</tr>
<tr>
<td>Did your child enjoy completing the exercises?</td>
</tr>
<tr>
<td>2 (18.2%) 4 (28.6%) 8 (57.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 15: Child Satisfaction Ratings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child Responses</strong> (N = 14)</td>
</tr>
<tr>
<td><strong>Questions: “How often...”</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Did you complain about the exercises?</td>
</tr>
<tr>
<td>3 (21.4%) 6 (42.8%) 5 (35.7%)</td>
</tr>
<tr>
<td>Did you feel bored during the computer exercises?</td>
</tr>
<tr>
<td>4 (28.6%) 3 (21.4%) 7 (50.0%)</td>
</tr>
<tr>
<td>Did you enjoy completing the exercises?</td>
</tr>
<tr>
<td>3 (21.4%) 6 (42.8%) 5 (35.7%)</td>
</tr>
</tbody>
</table>

As part of the Feasibility Questionnaire, parents provided open-ended explanations to the question, “How did you typically respond when your child complained about doing the exercises?” Their responses offer qualitative data on the type of support offered to their child. The most common response from parents was to remind their child that they had made a commitment and needed to finish (n=8).
other instances, parents told the children not to complain (n=2), offered praise (n=1),
instructed the child call the treatment coach (n=1), and indicated it was okay to stop the
exercises (n=1).

During weekly coaching calls, the treatment coach attempted to support the
parents and children, utilizing Motivational Interviewing (MI) strategies to encourage
compliance with the training sessions. Among 369 attempts at connecting with families
over the course of this study, there were 202 instances of non-contact (e.g., leaving a
message, phone number disconnected, voicemail unavailable), despite having coaching
call times scheduled. Thus, the treatment coach had difficulty making contact with
children and their parents to offer support and troubleshoot throughout the
intervention.

7.3.4 Motivating factors

As part of the Feasibility Questionnaire, parents/caregivers and their children
were asked to consider factors that might increase compliance or motivation to complete
the exercises. Among parent/caregivers, 35.7% indicated that more money at the pre-
and post-study visits would motivate their child, while 28.6% suggested that more
frequent rewards during the intervention would increase their child’s motivation (small
rewards were provided every eight sessions). The majority of parents/caregivers
reported that fewer required sessions (57.1%) and shorter sessions (50%) would have
helped increase compliance. Notably, eight parents/caregivers (57.1%) reported that
their child would have participated regardless of whether a monetary incentive was offered.

Among the child respondents, 42.9% reported more money at the pre- and post-study visits and/or increased frequency of rewards throughout the intervention period would have been an incentive. The majority of children reported that fewer required training sessions would have increased their compliance (64.3%), as would have shorter sessions (71.4%).

7.4 Efficacy

Due to the poor compliance and weak feasibility overall, exploratory efficacy aims could not be examined. Descriptive statistics among compliant participants and factors associated with compliance are described above.
8. Discussion

The current study assessed the acceptance and feasibility of a computerized CT intervention, Cogmed, in children with SCD. The results of this study suggest that Cogmed was acceptable in our sample of pediatric patients with SCD. This is a particularly notable finding, as no broadly accessible interventions for cognitive impairment have been deemed acceptable in this illness group. However, it is also important to note that although families expressed a high level of interest and acceptance for the intervention, their level of commitment to participation was low. Indeed, about three quarters of families who expressed interest in participating declined screening and enrollment. There was also a low rate of compliance among individuals who ultimately enrolled. The target compliance rate was not achieved in the context of the current protocol, in which the Cogmed program was administered at home for a total of 25 sessions over an eight-week period (three to five sessions per week). The majority of children in this study were unable to complete the intervention, even when afforded additional time beyond the pre-designated eight-week period.

Issues related to treatment adherence in pediatric SCD extend well-beyond the findings of this study, and are an important concern facing the field. While there is no universal statistic, compliance with medical regimens in this population has been described as moderate to low (Barakat, Smith-Whitley, & Ohene-Frempong, 2002), and evidence of poor compliance is documented across treatment targets. For example,
compliance with prophylactic penicillin hovers around 50% (based on urinalysis; (Bitarães, Oliveira, & Viana, 2008; Teach, Lillis, & Grossi, 1998), while prescription refill rates for hydroxyurea—a daily oral medication used as a primary treatment for SCD—range from 49% (Thornburg, Calatroni, Telen, & Kemper, 2010) to 60.5% (Patel, Lindsey, Strunk, & DeBaun, 2010). Moreover, attendance at regularly scheduled clinic appointments has been documented around 50% to 60%, and more than one third of patients undergoing apheresis receive treatment outside of the prescribed timeframe (Aygun et al., 2009). Collectively, these data reflect a pervasive pattern of poor treatment adherence. Thus, the poor compliance in the current intervention may be a reflection of a larger problem that affects management of pediatric SCD.

8.1. Health Belief Model

Theoretical models of health behavior help provide a framework in which the poor compliance outcomes from this study can be better understood. The Health Belief Model (HBM; Rosenstock, 1974) is a particularly useful framework that has previously been applied in pediatric sickle cell research (Boateng, Puffer, Allen, Bonner, & Thornburg, 2013). It suggests that health behavior is influenced by an individual’s perception of risk, barriers toward action, and facilitators toward action. The perception of risk is also moderated by organismic factors (e.g., cognitive factors, behavioral traits), sociodemographic variables, or motivating cues (e.g., education about risk). In the
context of the current study, compliance with the Cogmed intervention is the health behavior of interest, and the risk factor of interest is cognitive impairment.

Using the HBM as a guide, the following section will examine factors related to compliance (Figure 5). This section will be grounded in the feasibility data presented in the results, and then expanded in consideration of theoretically relevant factors that were not assessed as part of the protocol. This will begin with a discussion of barriers. The identified barriers fall into one of three broad categories: technological barriers, programmatic barriers and medical barriers. Concerns within each of these domains impeded feasibility and are discussed in detail below.

8.1.1 Barriers

8.1.1.1 Technological Barriers

The majority of participants in the current study denied any problems using the computers, yet they reported some degree of difficulty using the Cogmed program, which was not expected. Specifically, participants reported that the program would freeze, either preventing them from opening it or forcing them to restart the computer. It is possible that reports of freezing are better accounted for by an older computer or a poor Internet connection than technical problems with the Cogmed site. While these types of issues are certainly frustrating and can be discouraging, they are ultimately less burdensome than having to travel to a rehabilitation center, which would be required for traditional cognitive remediation. Thus, while this may have affected feasibility to
some degree, it is important to recognize the reality of potential treatment options, which all have their benefits and drawbacks.

In addition to reports of freezing, three families did not have access to the Internet in their home. While they were able to play the Cogmed games with the use of a dongle or through the Cogmed CD, it was difficult to upload the training data to the website reliably due to the Internet speed and/or the need to take the computer to a WiFi hotspot. This often caused delays between training sessions for these individuals, as participants needed to upload their data every fourth session before the program would permit them to continue.

Further, the majority of families who participated in this study were unable to provide their child with designated access to a computer. While laptops were provided to many families in the study, this finding is important to consider in the context of translational research. It also speaks to the fact these families, as a whole, have relatively low financial and material resources (Farber, Koshy, Kinney, & Disease, 1985). While socioeconomic resources were not related to outcomes in the current study, it will be important to be mindful of these variables in future research as access to resources has been shown to affect treatment compliance in other contexts (Apter, Reisine, Affleck, Barrows, & ZuWallack, 1998; Chen, Cole, & Kato, 2003; Gallo & Matthews, 2003).
8.1.1.2 Programmatic Barriers

Results from the feasibility questionnaire raised several programmatic concerns that likely impacted the success of this intervention. The most common critiques of the program by both caregivers and children were the length of each session (typically lasting 45 minutes) and the number of required sessions. This is a notable finding given that this has not been a prominent concern in other populations (e.g., ADHD, pediatric cancer survivors; Hardy et al., 2013).

The time commitment required by this program—both in terms of the length of each session and the number of required sessions—was a barrier from the outset. While the proposed intervention was highly acceptable to families, a number of families ultimately declined participation due to schedule constraints. The most commonly reported barrier to participation was lack of time. Families often cited concerns about their child being able to complete the intervention in the face of existing school demands. Secondary concerns also were raised about balancing the time demands of the intervention with existing medical appointments and parental work schedules.

Data regarding competing demands or daily schedule constraints were not collected for participants who enrolled in this study. However, the fact that the duration of sessions was consistently reported to be problematic raises the question of whether these children have limited time and/or support to carry out the Cogmed intervention. This may be the case for any child who was enrolled in an afterschool program during
this study, thereby extending the time spent at school and away from home in the evening. Indeed, a recent report indicated that African-American children are far more likely than their peers to be enrolled in an afterschool program (i.e., 24% versus 15%) or be unsupervised after school (28%; Afterschool Alliance, 2009). If children do not get home until 5 p.m., there is limited time to carry out daily tasks (e.g., homework, chores, dinner) before bedtime, which may preclude their compliance with the Cogmed program. In addition, while the majority of children were able to carry out the Cogmed tasks without the help of a parent, previous research has suggested that supportive parent-child interactions can have a positive influence on the child’s participation in this type of cognitive training intervention (Chacko et al., 2013). Thus, for children whose parents were not available due to long work hours or other demands (e.g., parenting multiple children, household chores), there may have been fewer opportunities for support around their participation in the study, which ultimately could have reduced compliance.

The hypothesized time constraints and low levels of parental support are even more salient given that children in this study were disengaged from the Cogmed games. Although the Cogmed intervention is designed to be an engaging, game-like program, many of the children in the current study did not appear interested in the exercises. Indeed, the majority of children often felt bored and complained while completing the games. If this activity is not engaging, it may add to the general burden of
responsibilities experienced by patients with SCD. As a result, completing the intervention will be hard to prioritize in the context of multiple responsibilities, limited time and low levels of support from a caregiver.

8.1.1.3 Medical Barriers

The programmatic barriers of this intervention—namely the length and number of sessions—have relevance to the medical demands faced by many pediatric patients with SCD. Children with SCD often have multiple daily treatment targets (e.g., oral medication, daily hydration, pain management), in addition to routine clinic visits and/or monthly apheresis (plus pre-transfusion labs). Compounding these routine treatment demands is the fact that children are at risk for medical sequelae, which could result in hospitalization. Indeed, more than 75% of children who participated in this study had at least one hospitalization while enrolled, and more than one-third of participants had two or more hospital stays. This is an added layer of stress or burden that children with SCD and their families face.

It is possible that children with SCD and their families are relatively depleted by their disease management needs. In turn, it may be more challenging for these children to reach compliance with the computerized CT protocol, which includes three to five 45-minute sessions per week. This is consistent with theories of self-regulatory fatigue—grounded in Baumeister’s work on ego-depletion (Baumeister, Bratslavsky, Muraven, & Tice, 1998)—in which chronic disease management, or even the need for disease...
management, results in poorer medical compliance by patients (Nes, Ehlers, Whipple, & Vincent, 2013).

Consistent with the theory of self-regulatory fatigue, the results indicate that caregivers of non-compliant participants reported a higher frequency of medical care demands (e.g., bringing children to clinic, making medical decisions, facing/handling health- and medical-related changes). Interestingly, this finding was in the absence of differential disease severity, treatment type (i.e., hydroxyurea versus transfusion) or number of serious medical events between completers and non-completers. Thus, this finding may relate to the fact that the frequency of medical care demands was subjectively reported and, on average, parents/caregivers of non-completers may have the perception or felt-experience of greater demands. In the context of compliance, parents/caregivers who feel greater stress or burden may not be able to support their child’s participation in the program to the extent necessary.

8.1.2 Facilitators of Compliance

8.1.2.1 Individual Factors

The current results also revealed important data that suggest the child’s baseline cognitive skills are related to the number of sessions completed. Specifically, children with stronger intellectual and cognitive skills completed more sessions during this study. In this regard, strong cognitive skills may be conceptualized as a facilitator of completion within the framework of the HBM.
There are several reasons why stronger intellectual and executive skills may have facilitated participation in the Cogmed sessions. It is likely that children with stronger intellectual and executive skills may have stronger problem solving skills that enabled them to get through the games more quickly or with less frustration. In addition, and arguably more important, children with stronger intellectual and executive skills may be better able to plan, organize, and therefore find time in their week to complete the tasks. Given that there was not a significant association between objective measures of working memory and total number of sessions completed, it may have less to do with ease of the tasks and more to do with planning or the ability to follow through.

8.1.2.2 Programmatic Facilitators

In addition to reducing barriers, the HBM also indicates that health behavior can be improved in the presence of external facilitators. The results of the current study evidenced several facilitators of compliance. Specifically, enrolled participants universally reported that the Cogmed program was easy to use. It was procedurally simple and children were largely able to complete it without the assistance of a parent. This is a significant value of the computerized CT approach, as traditional cognitive remediation protocols require in-person visits with a remediation therapist. A clinic-based approach would likely be prohibitive for families given that attending medical clinic visits is already associated with low adherence (Crosby et al., 2009).
8.1.2.3 Behavioral Reinforcement

A subset of children and parents also reported that more frequent rewards or a larger monetary payment for participation may have increased the likelihood of completion. While the majority of participants and their parents reported that they would have participated without a monetary incentive, this external reward was a bonus and may have helped facilitate participation, at least on a limited basis.

Figure 4: Understanding Feasibility in the Context of the Health Belief Model

8.2 Improving Compliance and Overall Feasibility

Aligned with the HBM, future research in this area should strive to attenuate some of the barriers to compliance and increase cues to action and facilitators in order to
improve overall feasibility of this intervention. There are several modifications that could be considered in an effort to reduce these barriers, which are described below.

**8.2.1 Perception of Risk**

The perception of risk for negative health outcomes is central to the HBM; it is a motivating factor for patients and individuals to effect behavioral change (Boateng et al., 2013). There are no known data that report on parents’ perception of risk for neurocognitive deficits in pediatric SCD, and unfortunately these data were not collected during this study. However, research has cited that parents perceive varying degrees of risk for stroke in SCD (Fullerton, 2006), and stroke is one of the major risk factors for cognitive impairment (Schatz et al., 2002). If knowledge of stroke risk is not universal it seems likely that knowledge of cognitive impairment—a concern that is secondary to medical health events—is relatively low. This is problematic, as the HBM suggests that knowledge of risk is an important motivator of treatment. Indeed, the adherence literature in SCD suggests that caregivers the perception of risk is significantly associated with compliance to primary treatment targets such as hydroxyurea and blood transfusion, in addition to secondary stroke prevention interventions such as transcranial Doppler screenings (Eckrich et al., 2013).

In light of this, education about risk factors should be an integral part of this type of intervention, and has been shown to be an important *cue to action* for children with SCD (Boateng et al., 2013). The literature on pediatric cancer survivorship offers multiple
models of education and health promotion that may be particularly appropriate to adapt here to help improve compliance. Specifically, research has evidenced that education for parents early on can improve their ability to monitor and manage late effects of cancer and its treatment (Landier, Wallace, & Hudson, 2005; Mulhern et al., 1995). Guidelines have been disseminated by the Children’s Oncology Group, which identify specific areas of risk that can be communicated to parents and children by providers and electronically through a website (Oeffinger, Hudson, & Landier, 2009). A similar model could be implemented in SCD in order to help increase patient and caregiver awareness of the developmental health risks – including neurocognitive decrements – associated with this disease. Dissemination early on through multiple sources (e.g., health care provider, schools, Internet websites) might increase caregivers’ ability to identify neurocognitive deficits and seek services or treatments to remediate weaknesses.

In addition to early education, Donze and Tercyak (2006) developed a model of education and health promotion that targets youth cancer survivors directly, which could be adapted in pediatric SCD. This model, referred to as the Survivor Health and Resilience Education (SHARE) Program and is based in part on the HBM, and strives to increase awareness of late effects, reduce barriers to health promotion, increase perceived benefits, and improve self-efficacy. It entails a half-day workshop, which is supplemented with three follow-up telephone booster calls. The booster phone calls are intended to increase motivation, provide positive feedback, offer additional education
and support to promote behavior change. In addition, barriers to action can be addressed and problem-solved, while cues to action can be enhanced during these supplemental sessions. Several studies have shown this model to be efficacious in promoting health behaviors in adolescent and young adult survivors (Mays et al., 2011; Tercyak, Donze, Prahlad, Mosher, & Shad, 2005).

The SHARE Program was specifically developed and made relevant for adolescent survivors of pediatric cancer, however, it could be easily adapted to suit the needs of children with SCD and their families. In the context of the current Cogmed intervention, this would include a brief didactic on neurocognitive health or be more generalized to “brain health” (which could incorporate information about stroke, neurocognitive sequelae and school-based learning). Aligned with the SHARE model, youth could be provided with education on the ways in which SCD predisposes them to neurocognitive sequelae. Information would also be shared on the functional domains impacted (e.g., attention, working memory, processing speed), and the associated impact these skills have on academic achievement. The rationale for a cognitive intervention would then be provided. Ultimately, by helping families and children better understand the risk factors and the basis for this type of intervention, commitment and compliance may be strengthened.
8.2.2 Reducing Programmatic Barriers to Facilitate Compliance

While education about risk factors and treatment rationale is important to promote health behavior, it may not sufficient on its own. Additional effort needs to be taken to reduce the barriers to the computerized CT program that were identified in this study. A particularly important consideration is the dosing schedule for this type of intervention. The Cogmed program is a rigorous intervention and does not allow participants or treatment coaches to manually set or modify the intervention dose. Rather, the duration of the session and the games played is determined electronically based on the child’s task performance. Therefore, the approach is individualized but ultimately inflexible. For children with SCD, a feasible cognitive intervention may need to permit greater flexibility given concerns about children’s lack of time, reduced caregiver support for the intervention and competing medical concerns. Research on the efficacy of computerized CT in other illness groups (e.g., schizophrenia) suggests that the number of sessions, the duration of sessions and the intensity of sessions does not correlate with the therapeutic outcome (Keefe et al., 2011). This provides some evidence to support a modified intervention protocol, which may include briefer but more frequent sessions, or less frequent but longer sessions for pediatric patients with SCD.

An alternative to an adapted dosing schedule may be to embed a computerized CT program within the school day, which might mitigate some of the time demands of the intervention. While offering the program solely as an in-school intervention would
present a range of additional concerns (namely accessibility concerns), doing so could prove useful and feasible, especially for children enrolled in an afterschool program. Given that children are able to carry out the intervention with minimal assistance and on any computer, there would be relatively low cost demands for schools. Indeed, research in children with ADHD has demonstrated good feasibility and efficacy of Cogmed as a school-based intervention (Holmes & Gathercole, 2013; Mezzacappa & Buckner, 2010). In these trials, school staff was trained to administer the intervention and children carried out the training three to five days per week for a total of 20 to 25 sessions. While there are unique variables that may affect children with SCD and impact feasibility of a school-based intervention (e.g., medical factors), at the very least these data suggest that schools may be able to support this type of program. Thus, this type of strategy should be considered in the future.

In addition to the time demands of the current protocol, youth frequently reported feelings of boredom or instances of complaining while completing the study games. This may speak to their overall level of engagement with the Cogmed intervention. A common associated comment made by children was the lack of engaging graphics or contextualized activities. This may speak to the fact that the Cogmed program has not been updated to the same degree as commercially-available computer programs or video games. Other models of cognitive remediation that utilize commercially-available software (e.g., the Neuropsychological and Educational
Approach to Remediation; Medalia & Freilich, 2008) allow patients to access more contemporary games, that may have more vivid graphics or contextually-relevant games while still strengthening working memory, attention and executive skills. Relying on commercially-available programs is not a perfect solution, however, as it increases the burden on the clinician to assess and vet software prior to recommending it as a therapeutic tool. Furthermore, reliance on commercially-available software inevitably leads to questions regarding the validity of the intervention, which is bypassed by using an empirically-supported software package such as Cogmed.

In consideration of the HBM, a final facilitator toward action that is important to consider is the level of support provided to the participants as they complete the study. The literature on the working memory training suggests that children benefit significantly from supportive interactions with their parents or their coach as they complete the study games (Holmes et al., 2010). While comprehensive data on the level/types of support from caregivers was not collected, a snapshot of data from the current study suggests that the majority of caregivers used a more authoritarian approach (i.e., you have to do this) when their child complained about the intervention, rather than relying on praise or empathic encouragement. This is notable, as the literature suggests that the latter (i.e., verbal praise, empathy and reflection) can facilitate motivation. This may also be compounded by the fact that many parents of children with SCD have high levels of stress and burden (Barakat, Patterson, Tarazi, &
Ely, 2007; Barakat, Patterson, Daniel, & Dampier, 2008), which may make it difficult for them to offer consistent and helpful support to their child throughout this type of intervention.

In light of this, future research should consider finding alternative approaches to supporting children throughout this type of intervention. In particular, it may be beneficial to provide direct support to participants through text messages, instant messages, or email. These technological interfaces can be utilized to improve treatment adherence of this intervention.

8.3 Summary

The computerized CT program, Cogmed, was not feasible in the current sample of children with SCD. Children had poor compliance with intervention, which was related to specific barriers including duration of the study and length of sessions, engagement with the program and, to some extent, medical variables and potentially the child’s level of support from caregivers. Using the HBM as a guide (Figure 5) it is theorized that the computerized CT approach could be made more feasible by providing caregivers and children with more information about neurocognitive functioning, the risk factors associated with SCD and the benefits of the intervention. Further, programmatic barriers could be addressed by modifying the dosage schedule, carrying out the program while children are at school, increasing the level of enjoyment/engagement by updating the technology and by providing the children with
more direct support. Other facilitators of compliance include the high ease of use reported by participants and the use of rewards throughout the intervention.

8.3.1 Study Limitations and Future Directions

There are limitations to the current study that are important to recognize. The primary limitation is the small sample size, which makes it difficult to broadly generalize the findings. Thus, many of the effect sizes were large, the results should be considered preliminary and generalized with caution. In addition, given the poor feasibility, it would have been beneficial to collect more precise data pertaining to the children’s and parents’ schedules in an effort to better assess the variance associated with time constraints. Likewise, associated measures pertaining to the degree of caregiver support and other family-level variables would have helped parse out more specific environmental factors related to feasibility. It also bears noting that the study did not assess certain child or caregiver knowledge of risk for cognitive impairment or participant motivation, and thus the relative contribution of such factors can only be hypothesized.

Another limitation of this study is the fact that it only included parent and child informants. In the context of research on cognitive functioning, teachers are particularly valuable informants; they may have more opportunities than parents to observe children throughout the day and assess academic weaknesses that may map on to neurocognitive skills. In addition, teachers could also provide valuable data on behavioral functioning,
such internalizing and externalizing characteristics of children. Alongside data from teachers, objective data from schools, including grades and absences, may have been helpful to obtain a more holistic assessment of child participants in an effort to identify additional factors related to feasibility.

Although there are limitations to this study, the current findings reflect a valuable contribution to the small body of literature on cognitive interventions for children with SCD. Despite enrolling only 18 children in the computerized CT program, it is important to note that this is a larger sample than observed in most behavioral interventions in pediatric SCD. Further, this study is the only one of its kind to assess the feasibility of an empirically-validated cognitive intervention in this population. This type of research is sorely needed given the high risk of cognitive impairment in children with SCD and the significant impact of cognitive functioning on quality of life. Indeed, preliminary findings from Study 1 suggest that this type of intervention could potentially impact children beyond measured improvements on a cognitive battery; such findings present the possibility of improving quality of life among individuals with SCD. This provides further impetus for ongoing research into cognitive interventions in this population.

As previously discussed, another reason to continue this line of work is the unfortunate fact that behavioral interventions and quality of life research have been historically neglected in pediatric SCD. This is a reflection of the fact that children with
SCD were generally underserved and understudied and, even today, face disparities in clinical care and research. The inattention given to this group has resulted in significant gaps in the literature, which impede the identification and development of services and supports that could ultimately improve the everyday lives of children and families affected by this illness. For this reason alone, future efforts ought to continue assessing the feasibility and efficacy of cognitive interventions, among other quality of life initiatives, for children with SCD.
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Biography

Taryn Margaret Allen was born on February 18, 1982 in New Haven, Connecticut. She received her Bachelors of Science in Neuroscience from Trinity College (Hartford, Connecticut) in 2004. In 2008, she received a Masters of Arts in Psychology and Education from Teachers College, Columbia University (New York, New York). In August 2008, she began her doctoral program in Clinical Psychology at Duke University. She received a second Masters of Arts degree in Psychology from Duke University in September 2011. As a doctoral student, Taryn received the Elizabeth Munsterberg Koppitz Fellowship from the American Psychological Foundation, the Sulzberger Fellowship from the Center for Child and Family Policy at Duke University, the NIMH Training Fellowship sponsored by Duke University, the Summer Research Fellowship through Duke University and Travel Fellowships through Duke University (i.e., Graduate School Conference Travel Award, Claire Hamilton Travel Award). She has published the following articles and book chapters:


