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Executive Abilities and Academic Achievement in Children with Sickle Cell Disease
by
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A dissertation presented to
The Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

August 2019
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ABSTRACT OF THE DISSERTATION

Executive Abilities and Academic Achievement in Children with Sickle Cell Disease

by

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Doctor of Philosophy in Psychological and Brain Sciences

Washington University in St. Louis, 2019

Professor Desiree White, Chair

Academic achievement is crucial to a child's psychosocial and occupational success (Davaoudzadeh et al., 2015; Margari et al., 2013). In children with sickle cell disease (SCD), a genetic disorder resulting in abnormal hemoglobin and significant neurologic sequelae, poor academic achievement is common (Wang et al., 2001). Studies of typically-developing children have revealed links between academic achievement and neuropsychological abilities, particularly higher order executive abilities that are mediated primarily by frontal brain regions (Altemeier et al., 2006; Bull & Scerri, 2001). In children with SCD, there is a wealth of evidence that executive abilities are impaired (Berkelhammer et al., 2007), but very little research has been conducted in which academic achievement has been examined within the context of specific cognitive domains, including executive abilities. The present study was designed to investigate relationships among *executive performance* (assessed using a composite of performance-based measures), *executive behavior* in daily life (assessed using parent ratings), and *academic achievement* (assessed using performance-based measures) in children with SCD. Existing data collected during a longitudinal study (baseline and 2-year follow-up) of 38 children with SCD were examined. Results indicate a significant, positive relationship between baseline executive

performance and executive behavior, and these two measures were simultaneously associated with concurrent academic achievement. Of note, executive performance did not explain variance in academic achievement above and beyond executive behavior, but executive behavior did predict unique variance. However, neither baseline executive performance nor baseline executive behavior predicted follow-up academic achievement. Our findings suggest that measures of executive behavior should not be overlooked in the context of pediatric SCD, and that additional investigation of potential screening tools for academic outcomes in this population is warranted.

1. Background

Sickle cell disease (SCD) refers to a group of hereditary blood disorders that are associated with chronic morbidity and increased mortality. With over 90,000 affected individuals in the US alone, SCD is one of the most common monogenic disorders worldwide (Brousseau et al., 2010; Weatherall et al., 2005). SCD typically occurs in individuals of African descent, but it also presents in individuals of Hispanic, Mediterranean, and Indian descent (Bou-Maroun, 2017; Hassell, 2010). Newborn screening for SCD gained federal support in the 1970s and became increasingly common across US hospitals in the decades that followed (National Sickle Cell Anemia Control Act, 1972; Newborn Screening Committee, Council of Regional Networks for Genetics Services, 1998). Despite early detection and intervention, SCD remains associated with significant health and economic costs. Notably, the life expectancy of individuals with this complex disease is greatly reduced, with one investigation of individuals with the most severe form of the disease (i.e., *Hb SS*) reporting a median age of death of 42 years for men and 48 years for women, which is approximately 25 to 30 years younger than expected in the general African-American population (Platt et al., 1994). National healthcare surveys indicate that complications arising from pediatric SCD contribute to at least 75,000 hospitalizations per year, with annual costs rising from \$500 million to over \$900 million over the past 20 years (Bou-Maroun, 2017; Davis et al., 1997).

From a genetic perspective, SCD arises from a substitution of the amino acid valine for glutamic acid at the sixth position of the beta-globin gene, which codes for a protein that contributes to the formation of hemoglobin (Ashley-Koch et al., 2000). This genetic variant is known as sickle hemoglobin (*Hb S*). More than 100 million individuals worldwide are carriers of this sickle cell

trait (American Society of Hematology, 2012), possessing one copy of the sickle hemoglobin variant and one copy of the normal beta-globin gene (*Hb AS*). SCD is expressed in individuals who possess either the autosomal recessive variant known as sickle cell anemia (*Hb SS*) or heterozygous combinations of sickle hemoglobin and other beta-globin variants, such as C-type (*Hb SC*), beta-zero thalassemia (*Hb Sβ⁰*), or beta-plus thalassemia (*Hb Sβ⁺*).

Regardless of specific genetic variations, all phenotypes of SCD are characterized by the production of abnormal hemoglobin. Hemoglobin within red blood cells transports oxygen to the organs of the body. In individuals with SCD, the release of oxygen causes hemoglobin molecules to form long tubules and, in turn, red blood cells become abnormally sickled in shape (Ashley-Koch et al., 2000). These sickled blood cells are rigid and more prone to hemolysis, which causes chronic anemia (Sickle Cell Disease Guideline Panel, 1993). Sickled cells are also susceptible to adherence to blood vessel walls, leading to occlusion of the microvasculature (Sickle Cell Disease Guideline Panel, 1993). These vaso-occlusions are the hallmark complication of SCD, contributing to a wide array of medical sequelae, including acute episodes of pain and fatigue (Fosdal, 2015), chronic pain and anemia (Mousa & Qari, 2010), and organ and tissue damage resulting from reductions in blood flow and oxygen saturation (Serjeant, 1993). Children with the most common SCD genotype, *Hb SS*, experience more frequent and severe symptoms than children with other SCD variants, such as *Hb Sβ⁺* or *Hb SC* (Austin et al., 2007).

Importantly, reduced blood flow and oxygen saturation have the greatest impact on major organs, including the brain. Cerebrovascular accident (CVA) is one of the most common causes of mortality and morbidity in children with SCD (Serjeant, 1993) and includes ischemic stroke,

hemorrhagic stroke, and transient ischemic attack. In SCD, CVA most often occurs within the distribution of the anterior cerebral artery or the anterior distribution of the middle cerebral artery, including the white matter of the frontal lobes (Buchanan et al., 2004; Moser et al., 1996; Prengler et al., 2002; Serjeant, 1993). When clinically-apparent neurologic symptoms (e.g., motor or language abnormalities) of CVA are detected, the event is referred to as “overt stroke.” In a longitudinal study of a cohort of over 4,000 children with SCD, 6% of children experienced overt stroke (Ohene-Frempong et al., 1998). However, neuroimaging studies have indicated that most CVAs in children with SCD are not accompanied by overt neurological symptoms, a phenomenon that has been termed “silent stroke” (Kral et al., 2001). Silent stroke, as typically detected by magnetic resonance imaging (MRI), occurs in an estimated 21% of children with *Hb SS* or *Hb Sβ⁰* and 6 to 8% of children with *Hb SC* (Pegelow et al., 2002; Wang et al., 2001). Critically, cognitive impairment has been associated with the presence of silent stroke (Christ et al., 2007) and abnormal cerebral blood flow (Kral & Brown, 2001) in children with SCD, which will be explored in detail in the following sections.

1.1 Cognition in SCD

Given the neurologic sequelae, it is perhaps unsurprising that cognition is compromised in children with SCD. Poorer performance on cognitive tasks has been associated with the presence of CVA, but it is important to note that even children with normal-appearing neuroimaging experience cognitive impairment (Schatz et al., 2002; Schatz & McClellan, 2006; Steen et al., 2003). At the broadest level, SCD has been associated with deficits in general intellectual ability, as quantified by the intelligence quotient (IQ; mean = 100, SD = 15 in the general population) (Swift et al., 1989; Wang et al., 2001). Individuals with recent overt stroke experience a loss of

up to 14 to 17 IQ points (Hijmans, Fijnnvandraat et al., 2011; Rennie & Panepinto, 2008), whereas losses of 5 to 14 IQ points have been observed in children with normal-appearing MRI or silent stroke (Berkelhammer et al., 2007; Kral et al., 2001). Steen and colleagues (2005) compared the IQ of children with SCD (ages 6 to 18 years) to that of African-American controls from the Wechsler Intelligence Scale for Children-III (WISC-III) normative sample and found that children with SCD who had normal-appearing MRI scored approximately 13 IQ points lower; moreover, the IQ of the SCD group significantly decreased as a function of increasing age, likely reflecting the chronic morbidity of the disease.

Impairments have been also observed in specific cognitive domains, including visuospatial abilities (Grueneich et al., 2004; Schatz et al, 2009), memory (Wasserman et al., 1991), and language (Brown et al., 2000). Although researchers have posited several potential contributing factors to account for these findings, including anemia, ischemia, and sleep disordered breathing (e.g., Hijmans, Grootenhuis, et al., 2011; Hollocks et al., 2012; Köbel et al., 2017), the precise mechanisms underlying cognitive impairment in SCD remain unclear. However, of particular relevance to this study are impairments in executive abilities, which will be discussed in the next section.

1.2 Executive Abilities in SCD

The term *executive abilities* refers to higher-order cognitive abilities that are largely mediated by frontal brain regions, including working memory, inhibition, and set shifting. These abilities provide coordination and integration of other aspects of cognitive and behavioral performance (Anderson, 2002; Diamond, 2013). Attention, another area of cognition that is at least partially mediated by the frontal lobes, is highly correlated with executive abilities in children (Friedman

et al., 2007) and, as such, will be categorized with executive abilities in the current study. Longitudinal studies of typically developing children have shown that some aspects of executive abilities, such as working memory, emerge during preschool years and continue to develop throughout adolescence and into young adulthood (Best & Miller, 2010; Huizinga et al., 2006). Other skills, including inhibition and shifting, demonstrate rapid growth during early childhood and increasingly slowed growth during late childhood and adolescence (see Romine & Reynolds, 2005 for a meta-analysis).

Children with SCD generally demonstrate impairments in executive abilities, with the strongest evidence for impairments in working memory, inhibition, and sustained attention (Berkelhamer et al., 2007). First turning to working memory, results are generally indicative of impairment but are somewhat mixed depending on the nature of the task administered to assess working memory. For example, results from a Dutch study of 41 children with SCD and mixed neurologic history (overt stroke = 3) indicated that working memory performance assessed using a visuospatial n-back task was impaired compared with that of typically-developing controls, whereas working memory performance assessed using a verbal digit span task was intact (Hijmans et al., 2011). In addition, findings from working memory tasks across SCD subgroups point to heterogeneity in the degree to which executive abilities are impaired. For example, using a visuospatial working memory task, Schatz and Roberts (2007) showed that toddlers with SCD and no history of overt stroke who had more severe SCD (*Hb SS*) made significantly more errors than their peers with less severe SCD (*Hb SC*). In an older sample of children with SCD, Brandling-Bennett et al. (2003) examined working memory in 31 participants, including 10 children with CVA affecting frontal brain regions as evidenced by MRI, and 21 children with normal-appearing MRI and no history of overt stroke. They found that both groups performed

comparably on a relatively simple working memory task (i.e., digit span forward), but the CVA group performed more poorly on a slightly more complex working memory task (i.e., digit span backward), suggesting difficulty in manipulating but not storing information for the CVA group.

Results from studies investigating inhibition and sustained attention have been more mixed. In the aforementioned Dutch study (Hijmans et al., 2011), a stop task assessing inhibition showed that SCD and control groups performed comparably in terms of reaction time and accuracy. In contrast, an investigation of inhibition that used a similar method of group classification to that of Brandling-Bennett et al. (2003) demonstrated that children with SCD who had neuroimaging evidence of CVA affecting frontal brain regions made more errors on an inhibitory control task than children with SCD and normal-appearing MRI (Christ et al., 2007). Interestingly, group differences in error rate on this task appeared to be driven by CVA status but not differences in SCD genotype, as children with *Hb SS* in the normal-appearing MRI group performed comparably to other normal-appearing MRI participants but worse than children with *Hb SS* in the CVA group. In addition, a study of sustained attention showed that children with SCD with no history of overt stroke made significantly fewer correct responses on a computerized vigilance task than sibling controls (Brown et al., 1993).

Overall, empirical studies of cognition in children with SCD provide mixed evidence, but findings are generally indicative of impairment in executive abilities (Berkelhamer et al., 2007). Factors contributing to the inconsistency across results most likely include task heterogeneity and samples with mixed history of CVA. Furthermore, the developmental trajectories of executive abilities in SCD are poorly understood. Given these limitations, additional research regarding the role of executive abilities in children with SCD is warranted.

1.3 Academic Achievement in SCD

Coupled with impairments in cognition in children with SCD are difficulties in academic achievement, which are commonly assessed using standardized measures such as the Woodcock-Johnson Tests of Achievement (WJ) or the Wide Range Achievement Test (WRAT). In general, children with SCD tend to score more poorly on tests of basic reading and math skills (e.g., word and phoneme decoding, one-step math calculations) than typically-developing or sibling controls (Armstrong et al., 1996; Fowler et al., 1988; Schatz et al., 2001). Among subgroups of children with SCD, the presence of overt and silent stroke is associated with particularly poorer achievement scores (Armstrong et al., 1996; Cohen et al., 1994; Schatz et al., 2001).

Although academic achievement generally improves with age in typically-developing children (Williamson et al., 1991), evidence from a large longitudinal study of school-age children with SCD (the Cooperative Study of Sickle Cell Disease) indicated that the developmental trajectory of academic achievement is negatively affected. Wang et al. (2001) found that children with *Hb SS* and normal-appearing MRI (n = 170) experienced a loss of 0.9 standard points in math achievement and 0.5 verbal IQ points each year over a 10-year time span. While children with *Hb SS* and silent stroke scored approximately 9 to 10 standard points poorer on reading and math achievement tests at baseline than children with *Hb SS* who had normal-appearing MRI, the rate of change in IQ and achievement did not significantly vary between these two subgroups. Age-related changes in reading achievement were not observed despite changes in verbal IQ, which may reflect an uncoupling of the association between IQ and reading abilities observed in other longitudinal studies of poor readers (Ferrer et al., 2010). Other studies of children with *Hb SS* have since replicated findings of age-related declines in IQ (e.g. Steen et al., 2005), but trajectories of academic achievement within SCD have not been as thoroughly investigated.

Importantly, poor academic achievement has been associated with other poor academic outcomes for individuals with SCD (Ladd et al., 2014; Schatz et al., 2001; Schatz, 2004). Although children with SCD utilize special education services more than their peers, they continue to experience higher rates of grade retention and school attrition (Dyson et al., 2010; Epping et al., 2013; Fowler et al., 1985; Schatz et al., 2001). In a retrospective review of medical and school records from 197 African-American children who received care for SCD at a midwestern clinic, 24% were retained at least 1 grade in their lifetime, and 34% received special education services (Epping et al., 2013). These percentages were significantly higher than normative rates for national, state, and local African-American students. In addition, it was found that silent stroke was related to grade retention within their sample, and both overt and silent stroke were related to receipt of special education services (Epping et al., 2013).

Risk for poor academic outcomes in children with SCD is likely increased by interactions with psychosocial and environmental factors. Many children with SCD are from lower socioeconomic status (SES) backgrounds (King et al., 2014), and the negative effects of low SES and financial stress on academic achievement and other academic outcomes in SCD have been well documented (Fowler et al., 1988; King et al., 2014; Ladd et al., 2014; Schatz, 2004; Yarboi et al., 2015). Children with SCD also tend to attend schools with limited resources (Radcliffe et al., 2006), which may complicate implementation of appropriate academic interventions. They also experience higher rates of absenteeism, with an average of 20 to 40 missed school days per year (Ogunfowora et al., 2005; Peterson et al., 2005; Shapiro et al., 1995). The negative impact of these factors on academic outcomes is indisputable, but much more research is needed to

identify contributing intermediary mechanisms that contribute to poor academic achievement and academic outcomes in individuals with SCD.

1.4 Rationale for Current Study

Little research has been conducted in individuals with SCD regarding the relationship between academic achievement and performance in specific cognitive domains, although poorer academic achievement in SCD has been correlated with poorer general intellectual ability (Swift et al., 1989; Wang et al., 2001). Schatz et al. (2004) examined general intellectual ability, as measured by composite scores from 6 tests selected to represent the Gf-Gc model of cognition (McGrew & Flanagan, 1998), in 70 children with SCD who had no history of stroke based on neurologic examination. Results showed that general intellectual ability was associated with academic achievement, whereas disease-related risk factors such as days of illness and anemia severity were not.

In typically-developing children, executive abilities assessed using performance-based measures (i.e., *executive performance*) have been implicated as critical for academic success. Both reading and math achievement have been associated with performance on laboratory tasks assessing inhibition (Altemeier et al., 2008; Swanson, 1999), set shifting (Altemeier et al., 2008; deJong, 1998), working memory (Bull & Scerif, 2001; Espy et al., 2004; McLean & Hitch, 1999; Siegel & Ryan, 1989), and attention (Christopher et al., 2012; Claessens & Dowsett, 2014; St. Clair-Thompson & Gathercole, 2006) in children and adolescents. Moreover, greater activation of frontal brain regions that support executive performance has been associated with the development of reading and math abilities (Ashkenazi et al., 2013; Schlaggar et al., 2002; Semrud-Clikeman, 2005). Executive performance has also been identified as a partial mediator

between SES and math achievement in typically-developing children (Lawson & Farah, 2017), suggesting that executive abilities may play an especially important role in an economically diverse population such as SCD.

Executive abilities in daily life (i.e., *executive behavior*), typically assessed using behavior rating questionnaires completed by parents or teachers, have also been shown to predict academic achievement in typically-developing children (Samuels et al., 2016; Toll et al., 2010). Examples of executive behavior in children include planning ahead for assignments, avoiding careless errors on schoolwork, refraining from impulsive outbursts, and flexibly moving from one activity to another. Although executive behavior is studied less frequently in children with SCD, existing evidence indicates that parents and teachers rate executive behavior in children with SCD as worse than in healthy peers (Berg et al., 2012), and among children with SCD, executive behavior is associated with cerebral blood flow velocity, a marker of stroke risk (Kral & Brown, 2004; Kral et al., 2003). Administration of questionnaires that assess executive behavior generally requires less time and resources to administer than performance-based measures, and thus may be especially practical in the context of a medical clinic given concerns with patient fatigue and time constraints. In addition, some researchers have suggested that executive behavior ratings may better capture the complex, integrative nature of executive abilities and be of greater ecological validity than performance-based measures (Waber et al., 2006). For these reasons, it has been recommended that measures of executive behavior be included alongside measures of executive performance as part of a typical neuropsychological battery for pediatric SCD care in both comprehensive and brief follow-up examinations (Daly et al., 2011).

Several studies of typically developing children have investigated relationships between ratings on one popular measure of executive behavior, the Behavior Rating Inventory of Executive

Function (BRIEF; Gioia et al., 2000), and academic achievement, although results have been mixed (e.g., Clark et al., 2010; Locascio et al., 2010). Lack of convergence may reflect the use of different types of behavioral raters across studies (i.e. self, parent, or teacher), as well as a focus on different domains of academic achievement. For example, Dekker et al. (2017) examined the relationship between parent and teacher ratings on the BRIEF, scores from performance-based tasks assessing executive abilities, and scores from math and spelling achievement tests in first and second grade students. Teacher ratings of working memory and shifting explained variance in spelling scores above and beyond scores from performance-based tasks assessing executive abilities; teacher ratings, however, did not explain variance in math scores, and parent ratings explained variance in neither spelling nor math scores. In contrast, Ten Eycke and Dewey (2016) examined parent ratings on the BRIEF in relation to executive performance and academic achievement in a sample of 405 healthy children (aged 5 to 18 years) with heterogeneous motor, attentional, and academic skills. Results revealed that reading and math scores were significantly associated with both BRIEF parent ratings and scores from performance-based executive measures. Measures of executive behavior also appear to be associated with academic outcomes other than achievement. For example, in a 4-year longitudinal study conducted with middle-schoolers, BRIEF teacher ratings predicted both current and annual grade point averages in humanities, math, and science above and beyond individualized education plan (IEP) and free lunch (a marker of SES) status (Samuels et al., 2016).

While it appears that executive performance and executive behavior may both relate to academic achievement, evidence suggests that executive performance and executive behavior likely reflect different aspects of the executive abilities construct. This notion is partially supported by Faradi

et al. (2014), which reported evidence of distinct neuroanatomical correlates of BRIEF working memory scores (associated with cortical thickness of posterior parahippocampal gyrus) and performance-based measures of working memory (associated with hippocampus and amygdala volumes). Additionally, a meta-analysis of 20 studies investigating executive abilities in children and adults showed that less than 25% of the correlations examined between scores from performance-based executive tasks and ratings of executive behavior were statistically significant (Toplak et al., 2013). Of the original 20 studies, 13 specifically compared BRIEF ratings with performance-based executive scores in children or young adults (including clinical and nonclinical samples), and only 19 % of the 182 correlations examined in this subset of studies were statistically significant. It should be noted that many of the reported correlations in this subset were between BRIEF indices (which average across subscales and theoretical constructs) and individual scores from specific performance-based tasks; thus, it is possible that examining BRIEF indices in relation to a composite measure of executive performance (that averages across tasks and theoretical constructs) may yield different results. Toplak and colleagues (2013) have suggested that the two types of measures may assess distinct levels of cognitive analysis, an algorithmic level and a reflective level. Specifically, performance-based measures may better assess the efficiency with which we process information (algorithmic level), while behavioral rating scales may better assess our success with goal and decision making (reflective level). Given the high complexity of completing an academic task (e.g., reading a passage, solving a math problem), it is conceivable that both levels of cognitive analysis, and thus measures of both executive performance and executive behavior, may relate to success with an academic task in children with SCD.

1.5 Specific Aims

The present study was designed to investigate relationships among *executive performance* (assessed using performance-based measures), *executive behavior* in daily life (assessed using parent ratings), and *academic achievement*, (specifically *reading and math achievement*, assessed using performance-based measures) in children with SCD. Existing data collected during a longitudinal study (baseline and 2-year follow-up) were examined, with the ultimate goal of identifying measures to screen for risk of poor academic outcomes. Overall, identifying both early predictors of academic achievement and screening measures of academic risk will facilitate recommendations for in-depth cognitive evaluations and interventions in educational settings to increase the likelihood that children with SCD reach their full academic potential. The specific aims and hypotheses of the current study are as follow:

Aim 1: To determine the relationship between executive performance and executive behavior in children with SCD. We hypothesize that baseline executive performance will be significantly and positively associated with baseline executive behavior in children with SCD when both aspects of executive abilities are analyzed at the composite level.

Aim 2: To determine the relationship between executive performance, executive behavior, and reading and math achievement in children with SCD. We hypothesize that baseline executive performance and baseline executive behavior will be significantly associated with baseline reading and math achievement in children with SCD.

Aim 3: To determine whether executive performance predicts reading and math achievement above and beyond executive behavior in children with SCD. We hypothesize that both baseline executive performance and baseline executive behavior will be unique predictors of follow-up academic achievement. Given the author's interest in the potential utility

of cost-effective evaluations within a clinic setting, the primary question was whether more costly measures (i.e. performance-based measures) provide unique information regarding academic outcomes above and beyond less costly measures (i.e. parent rating scales). We hypothesize that baseline executive performance will significantly predict academic achievement at baseline and follow-up above and beyond baseline executive behavior, consistent with the notion that the different types of executive measures quantify slightly different aspects of functioning.

Aim 4: To determine whether executive performance, executive behavior, and academic achievement remain stable over time in children with SCD. We hypothesize that executive performance and executive behavior will remain stable over time at the mean level, when assessed across middle childhood and early to mid-adolescence. Given evidence from a relatively large, longitudinal study of SCD (Wang et al., 2001), we hypothesize that math achievement but not reading achievement will decrease over time.

2. Methods

2.1 Participants

Data from children with SCD were collected at Washington University in St. Louis between 2006 and 2012 as part of a longitudinal study of neuropsychological performance in children with SCD. Although 65 children were initially considered for inclusion in the study, 27 were excluded due to lack of baseline executive performance data. Thus, the final sample included 38 children aged 7 to 16 years ($M = 11.8$, $SD = 2.8$), with grade levels ranging from kindergarten to 11th grade ($M = 5.6$, $SD = 3.0$). At the time of enrollment, all children were followed by the Pediatric Sickle Cell Disease Program in the Division of Pediatric Hematology and Oncology. No child had a reported history of a vascular disorder unrelated to SCD (e.g., congenital heart defect). Nearly half of our participants were diagnosed with the most severe and common variant of SCD, *Hb SS* ($n = 18$; 47.4%); other genetic variants were *Hb SC* ($n = 12$; 31.6%), *Hb S β^0* ($n = 7$; 18.4%), and *Hb S β^+* ($n = 1$; 2.6%). Medical records, including MRI results evaluated by a neuroradiologist, indicated that 94.7% of children had normal-appearing MRI, with 5.3% having evidence of past silent stroke. Mean number of hospitalizations in the past year was 1.6 ($SD = 2.4$).

Additional demographic and educational information were obtained from a parent questionnaire and medical records. Participants included 16 boys and 22 girls whose parents all identified as Black or African-American. At the time of enrollment, 34.2% of the children utilized special education services (IEP or 504 plan, $n = 13$), and 18.4% had repeated at least one grade in their lifetime ($n = 7$). History of grade retention and use of special education services were both coded as binary variables (0 = no, 1 = yes) for the purpose of this study.

2.2 Procedure

The Institutional Review Board of Washington University in St. Louis approved the study protocol (IRB # 201101836). Consent was obtained from parents or guardians of children, and children's assent was obtained when appropriate. A neuropsychological battery lasting approximately 2.5 hours was then administered to each child by a trained psychometrician or psychology graduate student. Parents completed a behavior rating scale related to their child. All procedures were completed at St. Louis Children's Hospital or the Developmental & Behavioral Assessment Unit of the Washington University Intellectual and Developmental Disabilities Research Center in a private, quiet room. Participants returned for follow-up approximately 2 years later, at which time study procedures were repeated. After each study visit, participants received gift certificates or monetary remuneration.

2.3 Study Measures

2.3.1. General Intellectual Abilities

The *Wechsler Abbreviated Scale of Intelligence, Second Edition* (WASI-II) is a standardized measure of general intellectual ability (i.e., IQ). Two subtests from the WASI-II may be used to estimate IQ. Specifically, the *Vocabulary* subtest is an untimed measure of word knowledge, whereas *Matrix Reasoning* is an untimed measure of perceptual reasoning. Administration time was approximately 25 minutes. Summary scores from the 2 subtests were used to estimate IQ, the variable of interest. The IQ was reported as a standard score with a mean of 100 and a standard deviation of 15. Although IQ was examined to characterize the general intellectual ability of the sample, it was not included in primary statistical analyses due to empirically-supported concerns regarding methodological issues with controlling for IQ when examining

cognitive outcomes in children with neurodevelopmental disorders (e.g., Dennis et al., 2009). The primary concern was that including IQ as a covariate in statistical models for Aims 2 or 3 would fail to elucidate our primary questions of interest regarding the specific relationships between executive abilities and academic achievement, given the well-established, high degree of association between IQ and academic achievement (Mayes et al., 2009). For the sake of consistency with studies of IQ, cognitive abilities, and academic outcomes in typically developing children (e.g. Bull & Scerif, 2001), secondary analyses were performed which included IQ and other educational variables of interest in the models.

2.3.2. Executive Performance

Subtests from the *Delis-Kaplan Executive Function System* (D-KEFS) and the *Conners' Continuous Performance Test, Second Edition* (CPT-2) were administered to assess executive performance.

Turning first to the D-KEFS, this battery includes a variety of verbal and nonverbal subtests to assess executive abilities across developmental stages. Relevant to the proposed study are variables from the following 3 subtests: *Verbal Fluency Test*, *Color-Word Interference Test*, and *Trail-Making Test*. The Verbal Fluency Test required that children generate as many words as possible in 1 minute upon hearing stimulus cues. The variable of interest in the current study was *Category Switching Accuracy*, which reflected the total number of words correctly generated when children were asked to switch between 2 semantic categories (fruits, furniture). The Color-Word Interference Test is a modified Stroop task which contains a condition (Condition 3) requiring that children inhibit the automatic reading of words and instead name the ink colors in which words are printed. The best indicator of inhibition from this subtest is the *Inhibition vs*

Color Naming Contrast Score. This variable of interest represented the difference between the time to complete Condition 3 and the time to complete an earlier condition (Condition 1) requiring rapid naming of colored squares. The Trail-Making Test is a timed subtest requiring that children rapidly draw lines connecting numbered and/or lettered dots. We focused on the condition of this subtest (Condition 4) requiring that children switch between connecting numbered and lettered dot sequences. Our variable of interest was the *Trails 4 vs 5 Contrast Score*, which represented the difference between the time to complete Condition 4 and the time to complete a condition (Condition 5) requiring rapid connection of open dots. Combined administration time for these 3 D-KEFS subtests was approximately 25 minutes. All subtests were administered using standard formats, and computer software was used to calculate standard T scores based on normative data, with lower T scores indicating poorer executive performance.

The CPT-2 is a computerized measure of visual, sustained attention. Children were instructed to press a keyboard button when a target stimulus appeared on a computer monitor and withhold the button press when a non-target stimulus appeared. Administration of the CPT-2 occurred using the standard format and required approximately 20 minutes for completion. The variable of interest was *Response Variability*, which is a measure of consistency in response time. Computer software was used to calculate transformed T scores based on normative data, with lower T scores indicative of poorer executive performance.

In statistical analyses, executive performance was reflected by an *Executive Performance Composite* T score, which was an average T score across all main executive performance variables of interest (i.e., CPT Response Variability, Verbal Fluency Test Category Switching Accuracy, Color-Word Interference Test Inhibition vs Color Naming Contrast Score, and the

Trail-Making Test Trail 4 vs 5 Contrast Score). The role of individual measures was examined in secondary analyses.

2.3.3. Executive behavior

The *Behavior Rating Inventory of Executive Function* (BRIEF) is a rating scale assessing executive behaviors in daily life. It includes 86 items that comprise 8 clinical scales. Parents were asked to indicate how often their child displayed a given behavior in the past 6 months by endorsing one of three responses: “Never,” “Sometimes,” or “Often.” Administration required approximately 10 minutes. Summary scores from the 8 clinical scales were converted to T scores based on normative data, from which a single *Global Executive Composite* (GEC) was obtained. The GEC was the primary variable of interest, and lower T scores indicated poorer executive behavior.

In secondary analyses, two additional composite scores from the BRIEF were examined. The *Behavior Regulation Index* (BRI) comprises 3 of the clinical scales and reflects set shifting and modulation of behavior and emotions. The *Metacognition Index* (MI) comprises the remaining 5 clinical scales and reflects planning, organization, initiation, and working memory. Like the GEC, both indices are reported as T scores, with lower scores indicating poorer executive behavior.

2.3.4 Academic Achievement

Subtests from the *Woodcock-Johnson Tests of Achievement, Third Edition* (WJ-III) were administered. Relevant to the proposed analyses were the following 4 subtests: *Letter-Word Identification*, a phonemic decoding test; *Reading Fluency*, a timed sentence reading test;

Calculation, a pencil-and-paper test of broad mathematical abilities; and *Math Fluency*, a timed test of simple arithmetic solution. Administration of the 4 subtests required approximately 20 minutes. For each subtest, the total number of correct responses was scored on the basis of age-based normative data, which provides standard T scores (mean = 50, SD = 10) as a component of the WJ-III. A *Reading Achievement Composite* was created by averaging T scores from Letter-Word Identification and Reading Fluency, and a *Math Achievement Composite* was created by averaging T scores from Calculation and Math Fluency. Each composite represented the academic achievement variables of interest in our study, with lower T scores indicating poorer achievement.

2.4 Statistical Analyses

In primary analyses, executive performance was represented by the Executive Performance Composite, executive behavior was represented by the BRIEF GEC, and reading and math achievement were represented by the Reading and Math Achievement Composites. To provide a clinical context for our findings, means and SDs of all composite and individual subtest variables were calculated, and one-sample t-tests were used to compare scores to those of age-matched normative samples from the standardized measures. To increase statistical rigor, findings from t-test, correlation, and regression analyses were considered statistically significant if either $p < .01$ or $p < .05$ with medium (e.g., $d = 0.50$, $r = 0.30$, or $\Delta R^2 = 0.09$) or large (e.g., $d = 0.80$, $r = 0.50$, or $\Delta R^2 = 0.25$) effect size according to Cohen's conventions (1988). Age was not included in statistical analyses because preliminary results revealed no significant interactions with age. Due to our use of age-corrected normative scores, age was not expected to have significant direct effects on scores of executive abilities or academic achievement.

Aim 1: To determine the relationship between executive performance and executive behavior in children with SCD. Pearson correlation was used to determine the strength of the relationship between baseline executive performance (i.e., Executive Performance Composite) and baseline executive behavior (i.e., BRIEF GEC). Secondary analyses examining individual executive performance and executive behavior variables were conducted only if executive performance was significantly related to executive behavior.

Aim 2: To determine the relationship between executive performance, executive behavior, and academic achievement in children with SCD. Two linear regression analyses were used to determine the variance in baseline academic achievement (Reading and Math Achievement Composites, examined separately) accounted for by baseline executive performance (i.e., Executive Performance Composite) and baseline executive behavior (i.e., BRIEF GEC), which were entered simultaneously:

$$\text{Baseline Reading Achievement} = (\text{Baseline BRIEF GEC} + \text{Baseline Executive Performance Composite})$$

$$\text{Baseline Math Achievement} = (\text{Baseline BRIEF GEC} + \text{Baseline Executive Performance Composite})$$

Secondary analyses controlled for IQ and educational variables of interest, including utilization of special education services and history of grade retention. Four separate linear regressions (i.e. two models each for baseline reading achievement and baseline math achievement) were performed which included either IQ or both educational variables in the first step of the model, followed by baseline executive performance and baseline executive behavior in the second step.

Aim 3: To determine whether executive performance predicts academic achievement beyond executive behavior in children with SCD. Four hierarchical linear regressions were used to determine the variance in baseline and follow-up academic achievement (i.e., baseline

and follow-up Reading and Math Achievement Composites, modeled separately) accounted for by baseline executive performance (i.e., Executive Performance Composite) after accounting for baseline executive behavior (i.e., BRIEF GEC):

$$\text{Baseline Reading Achievement} = \text{Baseline BRIEF GEC} + \text{Baseline Executive Performance Composite}$$

$$\text{Baseline Math Achievement} = \text{Baseline BRIEF GEC} + \text{Baseline Executive Performance Composite}$$

$$\text{Follow-up Reading Achievement} = \text{Baseline BRIEF GEC} + \text{Baseline Executive Performance Composite}$$

$$\text{Follow-up Math Achievement} = \text{Baseline BRIEF GEC} + \text{Baseline Executive Performance Composite}$$

Secondary regression analyses examined the variance in baseline and follow-up achievement predicted by baseline executive behavior after accounting for baseline executive performance.

Aim 4: To determine whether executive performance, executive behavior, and academic achievement remain stable over time in children with SCD. Repeated measures t-tests were used to examine change in executive performance (i.e. baseline and follow-up Executive Performance Composites), executive behavior (i.e., baseline and follow-up BRIEF GECs), and academic achievement (i.e., baseline and follow-up Reading and Math Achievement Composites). Secondary linear regression analyses examined whether baseline executive behavior and executive performance predicted the change in reading and math and achievement over time.

3. Results

First turning to descriptive statistics, Table 1 displays summary statistics for baseline IQ, executive performance, executive behavior, and academic achievement variables, as well as results of one-sample t-tests comparing performance of our SCD sample to that of normative samples. Significantly poorer scores were identified for children with SCD for IQ, the Executive Performance Composite (as well as Trails 4 vs 5 Contrast Score of the Executive Performance Composite), the MI of the BRIEF, and Reading and Math Achievement Composites (as well as Reading and Math Fluency of the Achievement Composites). From a clinical perspective, all scores fell within 1 SD of the normative mean and were within the broad average range, suggesting that observed executive and academic difficulties were relatively mild in this sample. Although not depicted in Table 1, children with more severe SCD genotypes (*Hb SS* and *Hb Sβ⁰*, $n = 25$) did not significantly differ from children with less severe genotypes (*Hb SC* and *Hb Sβ⁺*, $n = 13$) in terms of baseline age, IQ, executive performance, executive behavior, or academic achievement.

Table 1: Baseline summary statistics and results from one-sample t-tests comparing IQ, executive performance, executive behavior, and academic achievement scores from children with SCD to that of normative data.

| | <i>M (SD)</i> | <i>t</i> | <i>d</i> |
|--|---------------|----------|----------|
| <i>IQ</i> | 93.5 (14.0) | -2.87* | -0.45 |
| <i>Executive Performance Composite</i> | 46.8 (6.7) | -3.00* | -0.38 |
| <i>Response Variability</i> | 45.6 (11.5) | -2.36 | -0.41 |
| <i>Category Switching Accuracy</i> | 52.4 (10.5) | 1.43 | 0.24 |

| | | | |
|--------------------------------------|-------------|--------|-------|
| <i>Inhibition vs Color Naming</i> | 47.1 (9.9) | -1.81 | -0.29 |
| <i>Trails 4 vs 5</i> | 41.9 (12.6) | -3.96* | -0.71 |
| <i>BRIEF GEC</i> | 47.1 (9.4) | -1.92 | -0.30 |
| <i>BRI</i> | 48.5 (10.2) | -0.89 | -0.15 |
| <i>MI</i> | 46.0 (8.7) | -2.82* | -0.42 |
| <i>Reading Achievement Composite</i> | 45.2 (8.7) | -3.41* | -0.51 |
| <i>Letter-Word Identification</i> | 46.8 (10.0) | -1.96 | -0.32 |
| <i>Reading Fluency</i> | 43.6 (8.6) | -4.60* | -0.69 |
| <i>Math Achievement Composite</i> | 44.0 (9.0) | -4.08* | -0.63 |
| <i>Calculations</i> | 46.7 (10.5) | -1.92 | -0.32 |
| <i>Math Fluency</i> | 41.6 (9.4) | -5.46* | -0.87 |

Notes: IQ reported as standard score, with mean = 100, SD = 15; all other scores reported as T scores, with mean = 50, SD = 10; * indicates statistically significant finding (i.e., either $p < .01$ or $p < .05$ with medium or large effect size.)

Aim 1: To determine the relationship between executive performance and executive behavior in children with SCD. As predicted, the Pearson correlation coefficient indicated a significant positive relationship ($r = 0.41$, $p < .05$) between baseline executive behavior and baseline executive performance as measured by the baseline Executive Performance Composite and the BRIEF GEC, respectively. Pearson correlations from secondary analyses are presented in Table 2. Of the two baseline BRIEF indices, the MI was significantly correlated with the baseline Executive Performance Composite, but the BRI was not. Analyses of the individual baseline executive performance variables revealed that only the Trails 4 vs 5 Contrast Score was significantly correlated with baseline executive behavior, including BRIEF GEC, BRI, and MI.

Table 2: Correlations between executive performance and executive behavior.

| | <i>Executive Performance Composite</i> | <i>Response Variability</i> | <i>Category Switching Accuracy</i> | <i>Inhibition vs Color Naming</i> | <i>Trails 4 vs 5</i> | <i>BRIEF GEC</i> | <i>BRIEF BRI</i> | <i>BRIEF MI</i> |
|--|--|-----------------------------|------------------------------------|-----------------------------------|----------------------|------------------|------------------|-----------------|
| <i>Executive Performance Composite</i> | --- | | | | | | | |
| <i>Response Variability</i> | 0.66* | --- | | | | | | |
| <i>Category Switching Accuracy</i> | 0.58* | 0.24 | --- | | | | | |
| <i>Inhibition vs Color Naming</i> | 0.45* | 0.19 | -0.10 | --- | | | | |
| <i>Trails 4 vs 5</i> | 0.67* | 0.16 | 0.27 | 0.07 | --- | | | |
| <i>BRIEF GEC</i> | 0.41* | 0.20 | 0.14 | 0.11 | 0.47* | --- | | |
| <i>BRIEF BRI</i> | 0.28 | 0.03 | 0.13 | 0.04 | 0.43* | 0.91* | --- | |
| <i>BRIEF MI</i> | 0.43* | 0.32* | 0.11 | 0.13 | 0.42* | 0.89* | 0.70* | --- |

Note: * indicates statistically significant finding.

Aim 2: To determine the relationship between executive performance, executive behavior, and reading and math achievement in children with SCD. Results from the linear regressions for Aim 2 are presented in Table 3. Consistent with our hypotheses, baseline executive

performance and baseline executive behavior (entered simultaneously) accounted for significant variance in both baseline Reading Achievement (21%) and baseline Math Achievement (31%).

Secondary regression analyses controlled for the effect of IQ and educational variables of interest (not shown). When IQ was entered alone into the first step of the model, it significantly accounted for 51% of the variance in reading achievement and 26% in math achievement. When executive performance and executive behavior were then entered simultaneously into the second step of the model, they no longer accounted for a significant proportion of variance in reading achievement. However, they did significantly account for 45% of unique variance in math achievement.

Separate models were used to control for the effect of our educational variables. When history of grade retention and utilization of special education services were entered simultaneously into the first step of the model, they did not account for significant variance in either reading or math achievement. Executive performance and executive behavior were then entered into the second step of the model. Together, they significantly accounted for 27% of unique variance in reading achievement and 39% of unique variance in math achievement.

Table 3: Results from linear regressions for Aim 2 assessing relationships among baseline executive performance, executive behavior, and reading and math achievement.

| | <i>Parameter</i> | <i>B</i> | <i>R²</i> | <i>F</i> |
|-------------------------|-------------------------|----------|----------------------|----------|
| <i>Baseline Reading</i> | BRIEF GEC | 0.31* | 0.21* | 4.61* |
| | + Executive Performance | 0.27 | | |
| <i>Baseline Math</i> | BRIEF GEC | 0.38* | 0.31* | 7.54* |
| | + Executive Performance | 0.36 | | |

*Note: * indicates statistically significant finding.*

Aim 3: To determine whether executive performance predicts reading and math achievement beyond executive behavior in children with SCD. Results from the linear regressions for Aim 3 are presented in Table 4. The baseline BRIEF GEC significantly accounted for 17% of the variance in baseline Reading Achievement and 25% of the variance in baseline Math Achievement. When added to the model, the baseline Executive Performance Composite did not account for additional, significant variance in baseline Reading or Math Achievement. Neither the BRIEF GEC nor the Executive Performance Composite were significant predictors of follow-up Reading or Math Achievement.

Secondary regression analyses (not shown) were used to examine the reverse; that is, whether executive behavior predicts reading and math achievement above and beyond executive performance. When entered in the first step, the baseline Executive Performance Composite significantly predicted 11% of the variance in baseline Reading Achievement and 18% of the variance in baseline Math Achievement. When entered in the second step of the model, the baseline BRIEF GEC significantly accounted for 21% of the variance in baseline Reading Achievement and 31% of the variance in baseline Math Achievement above and beyond executive performance. Consistent with primary analyses, neither the BRIEF GEC nor the Executive Performance Composite were significant predictors of follow-up Reading or Math Achievement.

Table 4: Results from linear regressions for Aim 3 assessing relationships among executive performance, executive behavior, and reading and math achievement.

| <i>Parameter</i> | <i>B</i> | ΔR^2 | ΔF |
|------------------|----------|--------------|------------|
|------------------|----------|--------------|------------|

| | | | | |
|--------------------------|-----------------------|-------|-------|--------|
| <i>Baseline Reading</i> | BRIEF GEC | 0.31* | 0.17* | 7.58* |
| | Executive Performance | 0.27 | 0.04 | 1.53 |
| <i>Baseline Math</i> | BRIEF GEC | 0.38* | 0.25* | 11.45* |
| | Executive Performance | 0.36 | 0.06 | 2.98 |
| <i>Follow-up Reading</i> | BRIEF GEC | -0.05 | 0.00 | 0.00 |
| | Executive Performance | 0.16 | 0.02 | 0.46 |
| <i>Follow-up Math</i> | BRIEF GEC | 0.11 | 0.05 | 1.11 |
| | Executive Performance | 0.45 | 0.11 | 2.57 |

Note: * indicates statistically significant finding.

Aim 4: To determine whether executive performance, executive behavior, and academic achievement remain stable over time in children with SCD. Table 5 displays sample size, means, and standard deviations of scores that were available for given tests at both baseline and follow-up, as well as results of repeated measures t-tests. Due to fatigue and time constraints, some children did not complete all tests at both timepoints, leading to variations in sample size. With two exceptions, results from repeated measures t-tests showed that scores from tests of executive performance and executive behavior remained stable over approximately 2 years. The exceptions were CPT-2 Response Variability (on which participants performed significantly better at follow-up) and Letter-Word Identification (on which participants performed significantly worse at follow-up). Pearson correlations indicated that changes in executive performance and executive behavior were not significantly related to baseline age or IQ.

Secondary regression analyses were performed to determine whether baseline executive performance and executive behavior predicted the change in reading and math achievement.

When entered simultaneously into the models, Executive Performance Composite and baseline BRIEF GEC did not predict the change in reading or math achievement. Additionally, changes in reading and math achievement were not related to other baseline variables of interest, including Trails 4 vs 5 Contrast, BRIEF MI, IQ, age, grade retention, and use of special education.

Table 5: Results from repeated measures t-tests comparing baseline and follow-up executive performance, executive behavior, and academic achievement.

| | <i>n</i> | <i>Baseline</i> <i>M (SD)</i> | <i>Follow-up</i> <i>M (SD)</i> | <i>t</i> | <i>d</i> |
|------------------------------------|----------|----------------------------------|-----------------------------------|----------|----------|
| <i>Executive Performance</i> | 19 | 46.5 (7.4) | 47.9 (6.4) | 1.27 | 0.20 |
| <i>Response Variability</i> | 33 | 42.5 (9.7) | 48.6 (10.8) | 3.31* | 0.59 |
| <i>Category Switching Accuracy</i> | 21 | 52.1 (10.4) | 55.9 (10.4) | 1.62 | 0.37 |
| <i>Inhibition vs Color Naming</i> | 38 | 47.1 (9.9) | 47.6 (6.2) | 0.25 | 0.06 |
| <i>Trails 4 vs 5</i> | 38 | 41.9 (12.6) | 45.7 (9.7) | 1.84 | 0.34 |
| <i>BRIEF GEC</i> | 38 | 46.1 (10.9) | 47.3 (10.3) | 0.74 | 0.11 |
| <i>BRI</i> | 38 | 48.3 (11.2) | 50.9 (8.5) | 1.75 | 0.26 |
| <i>MI</i> | 38 | 44.5 (11.2) | 47.7 (7.3) | 2.05 | 0.34 |
| <i>Reading Achievement</i> | 34 | 46.7 (7.2) | 44.9 (7.0) | -2.45 | -0.25 |
| <i>Letter-Word Identification</i> | 34 | 48.9 (8.6) | 46.1 (8.9) | -2.77* | -0.32 |
| <i>Reading Fluency</i> | 34 | 44.4 (7.4) | 43.7 (8.0) | -0.68 | -0.09 |
| <i>Math Achievement</i> | 35 | 43.5 (8.9) | 42.0 (9.8) | -1.52 | -0.17 |
| <i>Calculations</i> | 35 | 45.9 (10.7) | 44.3 (10.1) | -1.34 | -0.15 |
| <i>Math Fluency</i> | 35 | 41.1 (8.7) | 39.7 (10.7) | -1.19 | -0.14 |

*Note: Scores are reported as T-scores, with mean = 50, SD = 10; * indicates statistically significant finding (i.e., either $p < .01$ or $p < .05$ with medium or large effect size.)*

4. Discussion

Previous studies have demonstrated that cognition and academic achievement are compromised in children with SCD (Berkelhammer et al., 2007; Kral et al., 2001), but there have been few investigations of associations between cognition and academic achievement in children with SCD, and those that exist typically examined cognition at only the broadest level (i.e., general intellectual ability; Schatz et al., 2004; Swift et al., 1989; Wang et al., 2001). Executive abilities represent specific aspects of cognition that play important roles in academic outcomes in typically-developing children (Altemeier et al., 2008; Espy et al., 2004), and a growing body of research has revealed impaired executive abilities in children with SCD (Brandling-Bennett et al., 2003; Christ et al., 2007; Hijmans et al., 2011). However, the relationship between executive abilities and academic achievement has not been examined in this population of children.

The present study was conducted to fill this significant gap in the SCD literature through examination of relationships between executive abilities and academic achievement. Aim 1 of our study was designed to shed light on whether executive performance (based on scores from tasks assessing executive abilities in the laboratory) was associated with executive behavior (based on parent ratings of executive abilities in daily life from the BRIEF) in children with SCD. In Aim 2 we determined whether executive performance and behavior, in combination, were associated with academic achievement (based on scores from the WJ-III) in these children. In Aim 3 we evaluated whether executive performance was related to academic achievement after accounting for the relationship between executive behavior and academic achievement. In addition, given limited longitudinal studies in children with SCD, we evaluated whether earlier executive behavior and performance were predictors of later academic achievement. Finally, in

Aim 4, we determined whether executive performance, executive behavior, and academic achievement remained stable over time in children with SCD.

Turning first to Aim 1, our findings supported the hypothesis that executive behavior is significantly associated with executive performance in children with SCD. This result provided validation that, at a global level, parent ratings of executive abilities are related to scores from traditional, performance-based measures of executive abilities in children with SCD. As such, it is possible that relatively brief parent ratings, which are easily obtained during clinic visits, may be of utility in screening for broad impairment in executive abilities. Secondary analyses indicated that the MI (i.e. Metacognition Index) of the BRIEF may be especially useful in this regard. This was not, however, the case for the BRI (i.e. Behavior Regulation Index) of the BRIEF, which contains different items from the MI and comprises a smaller proportion of items on the BRIEF. While the BRI scales (i.e. Inhibit, Shift, and Emotional Control) are thought to assess the child's ability to appropriately modulate their emotions and behavior, the MI scales (i.e. Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor) are thought to assess the child's ability to cognitively self-manage performance (Gioia et al., 2000).

This finding of stronger associations between executive performance and the BRIEF MI (relative to the BRI) appears consistent with existing literature. The present author's examination of the studies included by Toplak and colleagues (2013) in their meta-analysis revealed that most of the significant correlations reported between BRIEF ratings and scores on performance-based tasks included the MI or its subscales (see Anderson, V.A., Anderson, P., et al., 2002; Bodnar et al., 2008; Brown et al., 2008; Mangeot et al., 2002; McAuley et al., 2010; Parrish et al., 2007; Toplak et al., 2008). Of note, 11 out of 13 of these studies utilized clinical samples from a

variety of pediatric populations (e.g. spina bifida, traumatic brain injury, epilepsy) that may experience comparable levels of functional impairment as the sickle cell population. Toplak and colleagues (2013) proposed that measures of executive performance and executive behavior rarely correlate because they capture different cognitive levels of analysis. While performance-based measures are thought to assess cognitive efficiency within an optimized setting, behavioral ratings measure perceived success with goal pursuit in a real-world setting. Our data and existing literature suggest that for clinical populations, the MI is relatively better at approximating cognitive efficiency, the same level of cognitive analysis thought to be assessed by performance-based tasks of executive abilities.

Secondary analyses for Aim 1 also indicated that the relationship between executive behavior and performance was largely driven by the Trails 4 vs. 5 Contrast Scores. In fact, this measure of cognitive flexibility and set shifting was the only individual measure of executive performance which related to executive behavior. This finding is also consistent with the meta-analysis which showed that only 19% of all reported correlations between BRIEF ratings and scores on performance-based tasks assessing executive abilities were statistically significant in typically-developing children and adolescents (Toplak et al., 2013). It is unclear why the Trails 4 vs 5 Contrast Score, but not scores from other executive measures that purport to capture flexibility (e.g., D-KEFS Category Switching Accuracy), was associated with executive behavior. Various versions of the Trail Making Test have been noted for their sensitivity to brain dysfunction but criticized for their limited specificity and sensitivity to mild executive impairment. The D-KEFS version of the Trail Making Test was designed with these criticisms in mind. By incorporating greater visual scanning demands, as well as including stimuli which make it more challenging to shift attention, sensitivity to mild executive impairment was increased, even in individuals with

brain dysfunction who had relatively high premorbid IQ (Delis, Kaplan, & Kramer, 2001). Therefore, it is possible that the executive behavior reported by parents on the BRIEF (which was lower than the normative sample but still in the average range) was only associated with performance on the D-KEFS Trail Making Test because it was more sensitive to mild executive behavior difficulties than the other measures.

Turning to Aim 2, we found that executive performance and behavior, in combination, were significantly associated with both reading and math achievement in children with SCD. These results are consistent with a larger study of healthy, developmentally heterogeneous children (Ten Eycke & Dewey, 2016) and offer support for the notion that the skills assessed by our performance-based measures and behavioral ratings are both related to successful execution of academic skills. As suggested by Ten Eycke and Dewey (2016), who referenced the executive abilities framework proposed by Toplak et al. (2013), this finding is not surprising when considering the importance of efficient, cognitive performance (algorithmic level, assessed by performance-based tasks) as well as regulated, goal-oriented behavior (reflective level, assessed by ratings of executive behavior) to academic success.

For Aim 3 we examined the contributions of executive performance and executive behavior to academic achievement using a hierarchical approach. Results showed that concurrent executive behavior was related to both reading and math achievement. Concurrent executive performance, however, was not related to academic achievement (neither reading nor math) after accounting for the contributions of concurrent executive behavior. Furthermore, secondary analyses indicated that concurrent executive behavior continued to predict unique variance in reading and math achievement above and beyond executive performance. These findings indicate that

ratings from brief measures of executive behavior may be indicative of difficulties in academic achievement, and that supplementing these ratings with scores from measures of executive performance may provide us with redundant information regarding academic achievement.

This should not, however, be interpreted as a recommendation to discard measures of executive performance from pediatric SCD care, as this study does not include an evaluation of how specific types of scores or combinations of scores from performance-based tasks may differentially predict academic achievement. For example, Best and colleagues (2011) observed different developmental patterns in children's completion time and accuracy on performance-based measures of executive abilities, including evidence of a trade-off between increasing accuracy and slower task completion time with increasing age. The variables selected from our executive performance tasks reflect a combination of speed and accuracy that cannot easily be teased apart. It is possible that "pure" speed variables may better relate to performance on academic fluency tasks, while "pure" accuracy variables may better relate to performance on untimed academic tasks. Further, executive performance has been shown to relate to other important functional outcomes related to school readiness, such as social skills, in children with SCD (Hensler et al., 2013). Existing guidelines for neuropsychological care of children with SCD recommend that developmental monitoring of neuropsychological functioning include brief measures of executive performance as well as behavior rating scales, such as the BRIEF (Daly et al., 2011). Based on our data, the D-KEFS Trail Making Test appears worth considering as an option for a brief measure of executive performance. That said, neither executive performance nor behavior were predictors of later (at 2-year follow-up) academic achievement. Thus, although our measure of executive behavior provided us with unique information regarding concurrent academic achievement in children with SCD, it was not of use in predicting future

academic achievement or the change over time in academic achievement. As such, findings from the BRIEF may be of utility as a screener for difficulties in present- but not future-day academic achievement.

Finally, in relation to Aim 4 we found that executive behavior, executive performance, and academic achievement remained stable over a 2-year period. With two exceptions (Response Variability from the CPT-2 and Letter-Word Identification from the WJ-III), this was the case not only when examining composite measures but also individual indices of executive behavior, individual scores from tasks assessing executive performance, and individual scores from academic achievement subtests. Longitudinal studies of typically developing children demonstrate a slowed growth trajectory of executive abilities during middle childhood and adolescence, particularly with regard to inhibitory control and shifting (Romine & Reynolds, 2005). The stability of executive behavior and executive performance observed in our sample may reflect a more extreme slowing of this developmental trajectory. Of particular interest, scores for math achievement also remained stable over time, which contradicts findings by Wang et al. (2001) who identified a yearly decrease of almost 1 standard point in math, but not reading, in children with SCD and normal-appearing MRI. It should be kept in mind that their sample included 350 children who were tested an average of 2.9 times. Because our sample was substantially smaller and children were assessed only twice, it is possible that our study lacked statistical power to detect findings consistent with those of Wang and colleagues.

It is important to acknowledge additional limitations to our study. Our study design was retrospective rather than prospective, as previously collected data from an extensive cognitive and behavioral test battery were examined. It is possible that a prospective design using clinical

and experimental measures of greater sensitivity and specificity to mild executive difficulties would have yielded different results. For example, the battery did not include a direct and challenging task assessing working memory, which has been implicated in investigations of cognitive impairment in children with SCD (Berkelhammer et al., 2007) and studies of academic achievement in typically-developing children (Bull & Scerif, 2001; Siegel & Ryan, 1989). In addition, it would be of interest to collect data using additional measures of executive behavior (e.g., self or teacher report) and academic achievement (e.g., school records), which may better reflect daily functioning. Use of performance-based tasks that better simulate complex, real-world executive functioning may also provide useful insight into how a child might perform when faced with a novel task in a classroom or other setting. For example, Berg and colleagues (2012) compared executive performance between 22 children with SCD and mixed stroke status (silent = 5, overt = 4, none = 13) and 22 healthy controls using the Children's Kitchen Task Assessment (CKTA; Rocke et al., 2008), which requires children to make play dough by following a recipe and receiving structured cueing from the examiner. Although children with SCD received the same total number of cues to complete the task as healthy children, they received lower scores for organization, initiation, and knowledge of completion from blinded raters. Such tests are rarely developed and validated with clinical samples in mind, but results could theoretically provide unique information about how a child performs with more complex demands. Finally, given the number of analyses we performed, we increased the rigor of our criteria for statistical significance. This, combined with our relatively small sample size (although larger than many studies of children with SCD), limited statistical power.

Overall, our findings provide preliminary evidence of an association between executive abilities (assessed with measures of executive performance and behavior) and academic achievement in children with SCD. Parent ratings of executive behavior corresponded with academic achievement in a way that was unique from scores on executive performance tasks, indicating that these measures should not be overlooked in the context of pediatric SCD care as screening or monitoring tools. In addition, our findings indicate that executive behavior and performance are associated with concurrent, but not future, academic achievement. While our sample demonstrated largely consistent performance across time on measures of executive abilities and academic achievement, it remains important to weigh evidence of declines in academic achievement observed elsewhere (Wang et al., 2001). Thus, additional research is clearly needed to identify predictors of future academic outcomes in children with SCD, including not only academic achievement but also academic attainment, so that interventions may be implemented as early as possible.

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