Spring 5-2020

Executive Ability Difficulties in Everyday Contexts among Children with Sickle Cell Disease

Neco Johnson
Washington University in St. Louis

WASHINGTON UNIVERSITY IN ST. LOUIS

Psychological and Brain Sciences

Executive Ability Difficulties in Everyday Contexts among Children with Sickle Cell Disease
by
Neco Johnson

A thesis presented to
The Graduate School
of Washington University in
partial fulfillment of the
requirements for the degree
of Masters of Arts

May 2020
St. Louis, Missouri

Table of Contents

List of Figures

List of Tables

<u>Acknowledgments</u>

Abstract of The Master's Thesis

Executive Ability Difficulties in Everyday Contexts

among Children with Sickle Cell Disease

by

Neco Johnson

Master of Arts in Psycholgical and Brain Sciences

Washington University in St. Louis, 2020

Objective: The present study investigated the utility of the Behavior Rating Inventory of Executive Function (BRIEF) in identifying executive ability difficulties in everyday contexts among children with sickle cell disease (SCD).

Method: Participants were 243 children with SCD and 409 typically-developing control children ranging from 5.0 to 18.3 years of age (M=10.5, SD=3.4). The primary outcome, reported executive ability difficulties, was assessed using the Behavior Rating Inventory of Executive Function (BRIEF) Parent Form. IQ was estimated using the Weschler Abbreviated Scale of Intelligence (WASI). Sociodemographic information was obtained from parents, and SCD characteristics were ascertained from medical records.

Results: Independent samples t-tests indicated that children with SCD had poorer scores than typically-developing controls on the BRIEF Global Executive Composite Index. Additional analysis showed that their scores were also poorer than those of controls across both BRIEF indices (Behavioral Regulation, Metacognition) and the 8 individual scales of the BRIEF. Models investigating the contributions of infarct status, age, and parent education on the BRIEF Global Executive Composite, Behavioral Regulation, and Metacognition Indices indicated

significant, independent associations of infarct status and parent education with each BRIEF measure, as well as a significant age by group interaction for the Behavioral Regulation Index. Conclusion: The BRIEF is of utility in identifying executive difficulties among children with SCD.

Part 1: Introduction

Sickle cell disease (SCD) is a broad term used to classify a group of chronic red blood cell disorders that are attributable to congenital hemoglobinopathy. SCD is one of the most common genetic disorders in the United States (Hassel, 2010). Hassell (2010) estimated that 1 of every 2,000 – 2,500 newborns in the United States is diagnosed with SCD. The disorder is predominately inherited by individuals of African ancestry, although a minority of individuals in this population are of East Indian, Mediterranean, and Latin American descent (Center for Disease Control and Prevention, 2017).

The sickle-shaped red blood cells that are characteristic of SCD are the result of a single nucleotide polymorphism in the hemoglobin A beta-globin gene. These cells tend to cluster in blood vessels and restrict the flow of oxygenated blood throughout the body (Redding-Lallinger & Knoll, 2006). As a result, children with SCD are at risk for a variety of medical problems, such as cardiac (e.g., cardiomegaly), pulmonary (e.g., acute chest syndrome), and neurological (e.g., stroke) complications, among others (see Ballas et al., 2012).

Children with SCD are 300 times more likely than typically developing peers to experience strokes, which are cerebral infarcts resulting in focal neurologic symptoms (Earley et al., 1998; Ohene-Frempong et al., 1998). Among children with SCD, those who have experienced stroke tend to perform poorer on assessments of general cognitive ability (i.e., intelligence quotient [IQ]) compared to those who have not (Kawadler, Clayden, Clark, & Kirkham, 2016; Schatz and Buzan, 2006). However, silent cerebral infarcts (SCIs), which are cerebral infarcts that result in observable brain lesions without the focal neurological symptoms

1

associated with stroke, are the most common cerebrovascular complication experienced by children with SCD. The prevalence of SCI increases as children with SCD age, with nearly 40% of children having SCI by the time they reach adolescence (Quinn, 2014). SCI increases the risk for subsequent stroke (DeBaun et al., 2012; Miller et al., 2001), new or exacerbated SCI (Pegelow et al., 2002), and poorer cognitive (Armstrong et al., 1996; Bernaudin et al., 2000; Schatz et al., 2001; Thompson et al., 2003; Wang et al., 2001) and academic outcomes (Schatz et al., 2001).

SCI typically impacts the frontal lobes and leads to poorer executive abilities (Schatz et al., 2001). Executive abilities (e.g., working memory, cognitive flexibility, and inhibitory control) are a set of cognitive processes that promote goal-oriented management of thought and action. Although SCI increases the risk of poorer general cognitive and executive abilities outcomes among children with SCD, there is some evidence that, irrespective of infarct status (infarct vs. no infarct), children with SCD underperform relative to their typically developing peers on assessments of IQ (Andreotti, King, Macy, Compas, & DeBaun, 2015; Kawadler et al., 2016; Noll et al., 2001; Schatz, Finke, & Roberts, 2004; Steen et al., 2005; Yarboi et al., 2015) and executive abilities (Berg et al., 2012; Berkelhammer et al., 2007; Hijmans et al., 2010). Executive abilities are of particular clinical relevance due to their association with social and cognitive development (Blair & Razza, 2007; Eisenberg et al., 2004), academic achievement, independent living, and employment in adulthood (Blair & Razza, 2007; Bull, Espy, & Wiebe, 2008; Diamond & Lee, 2011; Duncan et al., 2007; Espy et al., 2004; Mischel, Shoda, & Rodriguez, 1989; Ponitz, McClelland, Matthews, & Morrison, 2009).

Most previous studies examining executive abilities in children with SCD identified executive difficulties using performance-based measures that were administered in the

2

laboratory. Rating scales measuring executive abilities, such as the Behavior Rating Inventory of Executive Function (BRIEF; Gioia, 2000), have also proven useful in the identification of executive difficulties. However, Stanovich, West and Toplak (2012) found that performance-based and rating-based measures of executive abilities tap into different underlying constructs. Specifically, the authors suggested that results from rating scales are more relevant to a child's ability to accomplish goals in everyday situations.

The BRIEF is easily administered to children and adolescents between 5 and 18 years of age to assesses behaviors related to executive abilities occurring across a variety of settings (e.g., clinics, hospitals, schools). The scale can be completed in 10 to 15 minutes. As such, it is an instrument that may be particularly useful to screen children with SCD for executive ability difficulties that impact their daily lives, thereby facilitating referral for more in-depth evaluation and appropriate intervention.

The objectives of the current study were twofold: (1) to compare the ratings of children with SCD to the ratings of typically developing control children on the BRIEF and (2) to investigate the potential role of socio-economic status (SES; using parent education) in explaining group differences in executive abilities. Based on prior findings of poorer executive abilities in children with SCD, we hypothesized that children with SCD would exhibit greater executive-related behavioral difficulties. Further, we hypothesized that group differences in executive abilities would be at least partly attributable to SES.

Part 2: Method

2.1 Participants

Our initial sample included data from 340 children with SCD and 419 typically-developing children. We excluded 94 children with SCD and 10 control children due to incomplete or unavailable BRIEF data. The excluded children did not differ from included children in any systematic way with regard to demographic variables. We restricted our SCD group to children with a history of SCI or no known history of infarct due to relatively few reports of stroke in our sample (3 participants, 1.2% of SCD sample). 243 children with SCD (45.7% girls) and 409 typically-developing control children (51.1% girls) constituted the final sample for current analyses.

We acquired BRIEF and demographic data for our control group from an openly available NIH dataset. The SCD group was constructed by aggregating existing datasets from studies of children with SCD. Each child with SCD had previously participated in one or more Washington University-affiliated studies aimed at improving our understanding of this understudied condition. The SCI subgroup predominately comprised children who had previously participated in a multisite intervention trial (Silent Cerebral Infarct Transfusion Trial; DeBaun et al., 2014) that included only children with a history of SCI. Eighty-four percent of our SCD group was diagnosed with hemoglobin SS, 6.6% with hemoglobin SC, 7% with hemoglobin S-beta zero thalassemia, and 2.1% with hemoglobin S-beta plus thalassemia. Age ranged from 5 to 17 years ($M = 0.5$, $SD = 2.80$) for children with SCD and 5 to 18 years ($M = 10.6$, $SD = 3.74$) for control children. IQ ranged from 60 to 125 ($M = 92.1$, $SD = 12.8$) for children with SCD and 77 to 158 ($M = 110.8$, $SD = 12.4$) for control children. In terms of race and ethnicity, 100% of the SCD group identified as Non-Hispanic Black or African American,

4

whereas 10.7% of the control group identified as Non-Hispanic Black or African American. All participants and/or guardians provided informed consent in compliance with the human subjects research institutional review boards at collaborating sites.

2.2 Materials and Procedures

Socio-demographic Characteristics

Socio-demographic information, including age, gender, parent education, and race/ethnicity were parent-reported.

The Behavior Rating Inventory of Executive Function (BRIEF)

The BRIEF (Parent Report) is an 86-item measure that assess everyday behaviors associated with 8 executive ability-related domains in children and adolescents ranging from ages 5 to 18 years (Gioia, 2000). Parents report how frequently ("Never", "Sometimes" or "Often") their child exhibited behaviors related to executive abilities (e.g., keeping belongings well organized) over the preceding six months. Responses to questions on the eight non-overlapping clinical scales are used to compute three summary scores: The General Executive Composite Index (GEC), the Behavioral Regulation Index (BRI), and the Metacognition Index (MI). The first is an aggregate of responses to the clinical scales that represents a child's overall executive abilities. The BRI comprises three subscales (i.e., Inhibit, Shift, Emotional Control) and is conceptualized as the "ability to shift cognitive set and modulate emotions and behavior via appropriate behavioral control" (Gioia, 2000). The MI comprises five subscales (i.e., Initiate, Working Memory, Plan/Organize, Organization of Materials, Monitor) and represents a child's ability to "cognitively self-manage tasks and monitor their performance" (Gioia, 2000). The BRIEF was normed and validated in a representative sample of the U.S. population. Age and sex corrected T-scores ($M = 50$, $SD = 10$) were used. Higher scores on the BRIEF represent more difficulty with executive abilities-related behaviors.

Intelligence Quotient (IQ)

IQ was measured using the Wechsler Abbreviated Scale of Intelligence (WASI; Weschsler, 1999). We used the Full Scale Intelligence Quotient (FSIQ), a composite score that includes performance on each of the WASI subtests (i.e., Block Design, Vocabulary, Matrix Reasoning and Similarities) as our estimate of IQ.

Statistical Analyses

All analyses were conducted in R 3.5.1 (R Core Team, 2018). SCI has been shown to compromise cognitive abilities among children with SCD (DeBaun et al., 1998; Schatz et al., 2001; White et al., 2006). Accordingly, we first examined the association between infarct status within our SCD subsamples (SCI vs. no history of infarct) and descriptive (i.e., age, parent education, FSIQ, gender) variables and BRIEF variables (i.e., subscale scores and index scores) using independent samples t-tests for continuous data and Chi-Square tests (or Fisher's exact) for categorical data. We then examined the associations between group status (SCD vs. control) with our descriptive and BRIEF variables. We used Chi-Square tests to examine group differences in rates of impairment at the BRIEF criterion for clinical significance (i.e., $T \geq 65$) for each of the three BRIEF summary scores. We repeated this same procedure at one, two, and three standard deviations above average ($T \geq 60$, $T \geq 70$, $T \geq 80$, respectively) for the GEC. We adjusted for the inflation of type I error inherent to multiple comparisons using Holm's correction and estimated the effect size of significant associations using Cohen's d for continuous variables and Cramer's V for categorical variables. We then regressed each of the BRIEF indices on group status, using children with SCD as the reference group, age (centered), parent education (as a proxy for SES), and the interaction between age and group status. Parent education was coded continuously with 0 representing less than completion of high school, 1 indicating

completion of high school, 2 indicating some college, 3 indicating a bachelor's degree, 4

indicating some graduate school, and 5 indicating a graduate degree. We examined the model for

multicollinearity among our predictor variables via point biserial correlation and variance

inflation factors. Both analyses indicated that multicollinearity was not a concern (all VIF $\leq$

1.35).

Part 3: Results

Preliminary Analyses: Association of Infarct Status with Demographic and BRIEF Variables

Before investigating differences in BRIEF scores between our SCD and control groups, we first examined possible differences in demographic variables and BRIEF ratings between our SCD infarct status subgroups (SCI vs. no infarct). There were no significant between-group differences (all $ts \leq 1.9$, $ps \geq .05$). Thus, we combined the subgroups and completed all subsequent analyses using a total SCD group.

Preliminary Analyses: Total Sample

Table 1 shows results of independent samples t-tests and Chi-square tests comparing our SCD and control groups on descriptive variables. Values represent means (standard deviations) unless otherwise noted. Children with SCD evidenced significantly lower FSIQs than typically-developing control children; $t(491.55) = 17.75$, $p = <.001$, Cohen's $d = 1.47$. Results of a two-sided Fisher's exact test indicated that control children's parents were more likely to report higher levels of education (Cramer's $V = 0.40$). The SCD and control groups were comparable in age and gender.

Table 1. Study Sample by Group

	SCD (n=243)	Control (n=409)	p^a	ES^b
Characteristics				
Age (years), *M(SD)*	10.49 (2.80)	10.55 (3.74)	0.82	0.02
FSIQ, *M(SD)*^{c}	92.14 (12.79)	110.78 (12.44)	<.0001	1.47
Gender, % girl	45.68	51.10	0.21	0.80
Parent Education, %			<.0001	0.40
<HS	12.35	0.73		
HS	23.87	13.20		
Some College	26.34	31.05		
College Degree	24.28	33.01		
Some Graduate Level	0.41	4.89		
Graduate Degree	6.17	17.11		

Refused/Unknown	6.58	0.00

Note. [a]Results from independent sample t-tests and Chi-square or Fisher's exact tests; [b]Effect sizes were estimated using Cohen's d for continuous data and Odds Ratios or Cramer's V for categorical data.

Group Differences in BRIEF Parent Report Ratings

Table 2 shows mean (standard deviation) ratings for the SCD and control groups on the BRIEF indices and subscales. The scores presented in Table 2 are age and gender adjusted T-scores ($M = 50$, $SD = 10$ based on normative data from the general population that accompany the BRIEF). Independent samples t-tests showed that children in the SCD group evidenced more executive abilities-related behavioral difficulties than children in the control group. This was true for the three BRIEF indices as well as each BRIEF subscale. Effect sizes ranged from medium to large other than the small effect sizes observed for the organization of materials and inhibit subscales.

Table 2. BRIEF Parent Report Scores of the Study Cohort by Group

	SCD (n=243)	Control (n=409)	p[a,b]	Cohen's d
General Executive Composite (GEC)	54.53 (10.95)	46.39 (7.98)	<.0001	0.82
Behavioral Regulation Index (BRI)	53.44 (11.56)	45.60 (7.49)	<.0001	0.77
Inhibit	51.81 (10.92)	47.30 (7.40)	<.0001	0.46
Shift	53.52 (10.98)	46.02 (7.82)	<.0001	0.76
Emotional Control	54.00 (11.76)	45.44 (7.88)	<.0001	0.82
Metacognition Index (MI)	54.69 (10.71)	47.14 (8.38)	<.0001	0.76
Initiate	53.41 (9.87)	47.77 (8.46)	<.0001	0.60
Working Memory	57.72 (11.93)	47.79 (8.77)	<.0001	0.91
Plan/Organize	55.21 (11.34)	46.98 (8.45)	<.0001	0.80
Organization of Materials	51.15 (8.88)	49.46 (8.75)	0.02	0.19
Monitor	51.60 (10.59)	46.34 (9.03)	<.0001	0.52

Note. Values represent means (standard deviations). T-scores were adjusted for age and sex. [a]Results from independent sample t-tests; [b]p-values adjusted for multiple comparisons using Holm's correction.

Percent Impaired on the BRIEF

Figure 1 shows the percentage of children from each group for whom parent ratings evidenced diagnostically relevant index ratings (i.e., GEC, BRI, MI). We used Chi-square tests to compare group proportions at the BRIEF criterion for clinical significance (T>=65). The SCD group evidenced significantly higher proportions of elevated scores on all three indices at the BRIEF criterion for clinical significance. We then repeated this procedure at one, two, and three standard deviations above average (i.e., $T \geq 60$, $T \geq 70$, $T \geq 80$, respectively) for the GEC (see Figure 2). Figure 2 shows that the SCD group evidenced significantly higher proportions of elevated scores both cumulatively and at each standard deviation cut off (all $\chi^2 \geq 4.34$, $ps \leq .04$).

Figure 1. Percentage of children with elevated scores on the GEC, BRI, and MI by group.
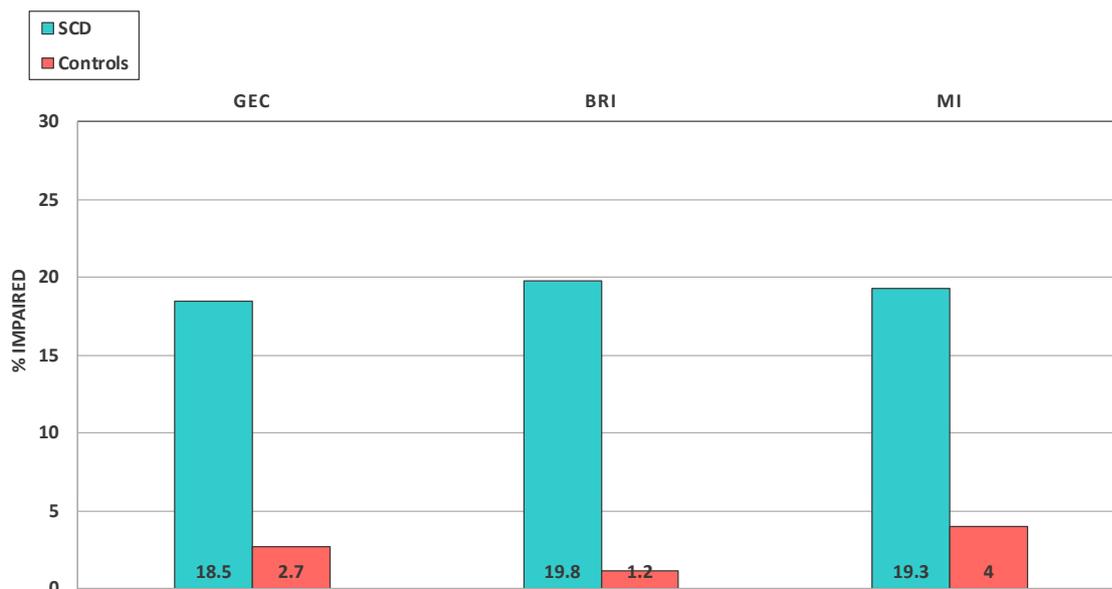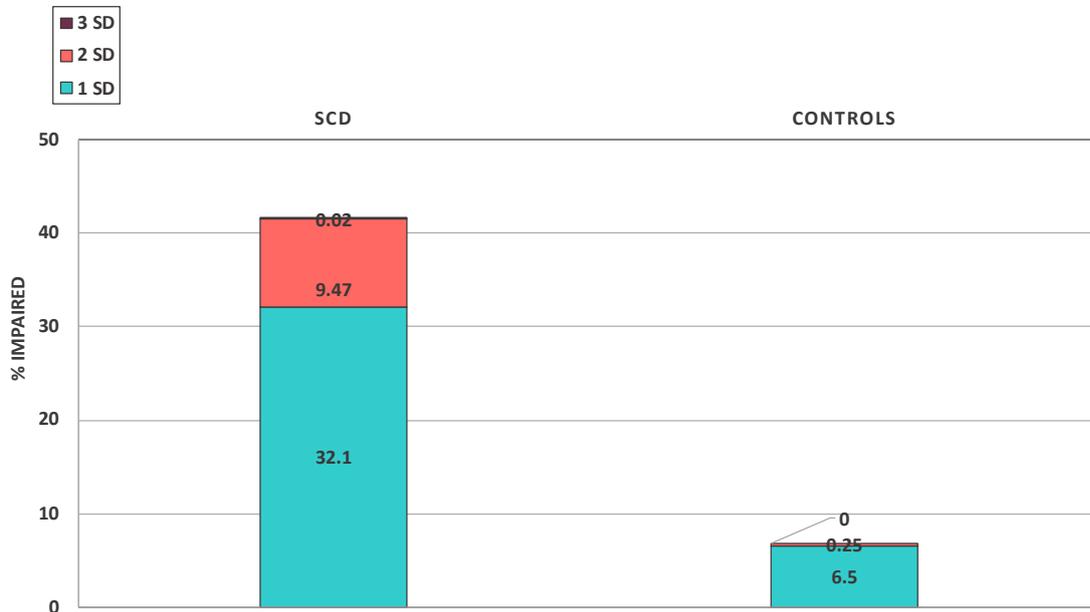
Figure 2. Percentage of children with elevated scores on the GEC at 1, 2, and 3 standard deviations above average by group.

Regression Models

We separately regressed each BRIEF index (GEC, BRI, MI) on group (SCD, control), age, and parent education. The regression model with GEC demonstrated that our predictors accounted for 16.4% of the total variance ($R = 0.16$, $F(4, 631) = 30.84$, $p<.01$). Group was a significant predictor of GEC rating (Estimate = 7.31, $SE = 0.79$, $p<.01$). Parent education also significantly predicted GEC ($SE = 0.28$, $p<.01$); for each 1-unit change in parent education (e.g., 0 [less than HS] to 1 [HS]) there was a 0.82 negative change in GEC. Age (Estimate = -0.08, $SE = 0.12$, $p=.49$) and the age by group interaction (Estimate = 0.46, $SE = 0.25$, $p=.06$) were not significant predictors of the GEC.

The regression model with BRI accounted for 16.0% of the total variance ($R = 0.16$, $F(4, 631) = 29.94$, $p<.0001$). In this model, group was a significant predictor of BRI (Estimate = 7.18, $SE = 0.79$, $p<.01$). Parent education also significantly predicted BRI ($SE = 0.28$, $p<.01$); for each 1-unit change in parent education there was a 0.77 negative change in BRI. The model also

11

indicated a significant age by group interaction (Estimate= 0.57, *SE* = .25, *p*=.02); control children's BRI scores (Age estimate = 0.36, *SE* = 0.22), on average, decreased with older age, whereas older children with SCD (Age estimate = -0.20, *SE* = 0.12), tended to receive higher scores than younger children with SCD.

Results of the regression model with MI indicated that our predictors accounted for 13.9% of the total variance ($R = 0.14$, $F(4, 631) = 25.54$, $p<.01$). Group was a significant predictor of higher MI scores (Estimate = 0.57, *SE* =0.25 $p<.01$). Parent education also significantly predicted MI (*SE* =0.29, $p<.01$). Age (Estimate = 0.04, *SE* = 1.22, *p*=.74) and the age by group interaction (Estimate = 0.35, *SE* = 0.25, *p*=.17) were not significant predictors of the MI.

Part 4: Discussion

The purpose of the present study was to investigate whether executive difficulties in children with SCD could be identified using the BRIEF, an easily administered rating scale measuring executive abilities. Existing literature indicates that children with executive difficulties are at risk for poorer academic achievement (Biederman et al., 2004; Clark, Prior & Kinsella, 2002) and social and cognitive development (Hughes, White, Sharpen, & Dunn, 2000; Moriguchi, 2014; Murphy, Shepard, Eisenberg, & Fabes, 2004), as well as poorer health, socioeconomic, and social outcomes as adults (Moffitt et al., 2011). Although executive difficulties among children with SCD are well documented (see Berkelhammer et al., 2007 for review), there is evidence that the performance-based measures typically used to identify problems with executive abilities may be less relevant than rating scale measures in terms of real-world contexts (Topalk et al., 2012).

Consistent with our primary hypothesis, present findings showed that children with SCD received higher (i.e., poorer) ratings than their typically-developing peers on each of three BRIEF indices, indicating that children with SCD exhibited greater executive ability-related problems. Given the myriad medical complications of SCD (see Ballas et al., 2012), the observed difference in executive abilities may be the result of the pathophysiological characteristics of SCD. For example, the cognitive sequalae associated with SCI could lead to deficits in executive abilities and greater problems with associated behaviors among children with SCD (Berkelhammer et al., 2007).

That said, infarct status was not associated with BRIEF variables, suggesting that the present findings are unlikely to be solely attributable to SCI. It should be kept in mind that the pathophysiology underlying cerebral infarcts in children with SCD is not an all or none

phenomenon. There is a spectrum of pathology, with some children reaching the somewhat arbitrary criteria for SCI whereas others do not. Future studies should more closely explore the relationship between specific aspects of pathophysiology (rather than simply infarct status) and executive abilities in children with SCD.

Notably, in addition to the between-group differences we observed across all BRIEF indices, we observed an age by group interaction in our model on BRI scores. Children in the control group received fewer reports of behavioral regulation problems with older age. Conversely, older children with SCD received higher scores than younger children with SCD. As previously mentioned, these findings could be attributable to the pathophysiology resulting in the increased incidence of stroke and SCI as children with SCD age. That is, increased pathophysiology as children with SCD age may lead to poorer executive abilities, and there is some evidence consistent with this view (Prussien, Jordan, DeBaun & Compas, 2019). Future studies may consider more closely examining the relationship between the pathophysiology and medical complications of children with SCD in relation to age-related changes in executive abilities.

Turning to a more clinical perspective, children with SCD were more likely to receive diagnostically significant ratings across all three BRIEF indices. When compared to the control group, children in the SCD group were nearly seven times more likely to receive diagnostically significant ratings on the GEC. Notably, the SCD group was just under five times more likely to receive diagnostically significant scores on the MI, compared to nearly 17 times more likely on the BRI. As such, behavioral regulation (e.g., impulse control) seems to be an area of particular concern for children with SCD.

14

When the criterion for clinically significant problems with executive abilities was adjusted to represent one, two, and three standard deviations above an average T-score (50), our SCD group again showed greater rates of diagnostically significant ratings. The disparity in diagnostically significant ratings between the groups was most striking when they were compared with the most liberal criterion (i.e., one standard deviation). More than 40% of the children in the SCD group were above the criterion, compared to fewer than 7% of the control children.

We now turn to the contributions of variables other than group and infarct status, including age and parent education (our proxy for socioeconomic status). Findings from our models on BRIEF indices indicated significant, independent relationships between both of our predictors (i.e., age and parent education) and each of the three BRIEF indices. Parent education was consistently negatively associated with BRIEF scores. That is, parents who achieved higher levels of education reported that their children had fewer executive ability problems. However, it is important to keep in mind that the relationship between executive abilities and parent education is general rather than specific. Maternal education influences children's academic and social development (Burchinal, Peisner-Feinberg, Pianta, & Howes, 2002), and higher socioeconomic backgrounds provide greater access to resources and more exposure to stimulating environments (Crosnoe et al., 2010). Thus, this relationship suggests that higher educational attainment, or the associated increase in resources, is beneficial in the development of executive abilities in offspring. Further investigation into the relationship between parent education and socioeconomic status as they relate to children's executive ability development is warranted.

Limitations

Our findings indicated that children with SCD are more likely to receive clinically significant ratings that indicate problems with executive abilities than are their typically-developing peers. However, as referenced when we suggested foci for future studies, we did not examine possible pathophysiological mechanisms (e.g., decreased brain oxygenation), medical complications (e.g., pain), or caregiving variables that may underlie these findings. In addition, because we did not collect self-report of executive ability problems from the children, we were unable to investigate the congruence between child and adult responses. Given existing evidence showing incongruence between parent and child reports (Angold et al., 1987; Mahone et al., 2007), future researchers examining executive abilities using behavior rating scales may wish to collect self and parent reports to assess this relationship.

References

Andreotti, C., King, A. A., Macy, E., Compas, B. E., & DeBaun, M. R. (2015). The association of cytokine levels with cognitive function in children with sickle cell disease and normal MRI studies of the brain. *Journal of Child Neurology*, *30*(10), 1349-1353.

Angold, A., Weissman, M. M., John, K., Merikancas, K. R., Prusoff, B. A., Wickramaratne, P., ... & Warner, V. (1987). Parent and child reports of depressive symptoms in children at low and high risk of depression. *Journal of Child Psychology and Psychiatry*, *28*(6), 901-915.

Armstrong, F. D., Thompson, R. J., Wang, W., Zimmerman, R., Pegelow, C. H., Miller, S., ... & Hurtig, A. (1996). Cognitive functioning and brain magnetic resonance imaging in children with sickle cell disease. *Pediatrics*, *97*(6), 864-870.

Ballas, S. K., Kesen, M. R., Goldberg, M. F., Lutty, G. A., Dampier, C., Osunkwo, I., ... & Malik, P. (2012). Beyond the definitions of the phenotypic complications of sickle cell disease: an update on management. *The Scientific World Journal*, *2012*.

Berg, C., Edwards, D. F., & King, A. (2012). Executive function performance on the children's kitchen task assessment with children with sickle cell disease and matched controls. *Child Neuropsychology*, *18*(5), 432-448.

Berkelhammer, L. D., Williamson, A. L., Sanford, S. D., Dirksen, C. L., Sharp, W. G., Margulies, A. S., & Prengler, R. A. (2007). Neurocognitive sequelae of pediatric sickle cell disease: a review of the literature. *Child Neuropsychology*, *13*(2), 120-131.

Bernaudin, F., Verlhac, S., Freard, F., Roudot-Thoraval, F., Benkerrou, M., Thuret, I., ... & Casse-Perrot, C. (2000). Multicenter prospective study of children with sickle cell

disease: radiographic and psychometric correlation. *Journal of Child Neurology*, *15*(5), 333-343.

Biederman, J., Monuteaux, M. C., Doyle, A. E., Seidman, L. J., Wilens, T. E., Ferrero, F., ... & Faraone, S. V. (2004). Impact of executive function deficits and attention-deficit/hyperactivity disorder (ADHD) on academic outcomes in children. *Journal of Consulting and Clinical Psychology*, *72*(5), 757.

Blair, C., & Razza, R. P. (2007). Relating effortful control, executive function, and false belief understanding to emerging math and literacy ability in kindergarten. *Child Development*, *78*(2), 647-663.

Bull, R., Espy, K. A., & Wiebe, S. A. (2008). Short-term memory, working memory, and executive functioning in preschoolers: Longitudinal predictors of mathematical achievement at age 7 years. *Developmental Neuropsychology*, *33*(3), 205-228.

Burchinal, M. R., Peisner-Feinberg, E., Pianta, R., & Howes, C. (2002). Development of academic skills from preschool through second grade: Family and classroom predictors of developmental trajectories. *Journal of School Psychology*, *40*(5), 415-436.

Centers for Disease Control and Prevention. (2015). Sickle cell disease: data and statistics. *Online at Http://www.cdc.gov/NCBDDD/sicklecell/data.html*.

Clark, C., Prior, M., & Kinsella, G. (2002). The relationship between executive function abilities, adaptive behaviour, and academic achievement in children with externalising behaviour problems. *Journal of Child Psychology and Psychiatry*, *43*(6), 785-796.

Crosnoe, R., Leventhal, T., Wirth, R. J., Pierce, K. M., Pianta, R. C., & NICHD Early Child Care Research Network. (2010). Family socioeconomic status and consistent environmental stimulation in early childhood. *Child Development*, *81*(3), 972-987.

DeBaun, M. R., Armstrong, F. D., McKinstry, R. C., Ware, R. E., Vichinsky, E., & Kirkham, F. J. (2012). Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. *Blood, The Journal of the American Society of Hematology*, *119*(20), 4587-4596.

DeBaun, M. R., Gordon, M., McKinstry, R. C., Noetzel, M. J., White, D. A., Sarnaik, S. A., ... & Telfer, P. T. (2014). Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. *New England Journal of Medicine*, *371*(8), 699-710.

DeBaun, M. R., Schatz, J., Siegel, M. J., Koby, M., Craft, S., Resar, L., ... & Noetzel, M. (1998). Cognitive screening examinations for silent cerebral infarcts in sickle cell disease. *Neurology*, *50*(6), 1678-1682.

Diamond, A., & Lee, K. (2011). Interventions shown to aid executive function development in children 4 to 12 years old. *Science*, *333*(6045), 959-964.

Duncan, G. J., Dowsett, C. J., Claessens, A., Magnuson, K., Huston, A. C., Klebanov, P., ... & Sexton, H. (2007). School readiness and later achievement. *Developmental Psychology*, *43*(6), 1428.

Earley, C. J., Kittner, S. J., Feeser, B. R., Gardner, J., Epstein, A., Wozniak, M. A., ... & Johnson, C. (1998). Stroke in children and sickle-cell disease: Baltimore-Washington cooperative young stroke study. *Neurology*, *51*(1), 169-176.

Eisenberg, N., Spinrad, T. L., Fabes, R. A., Reiser, M., Cumberland, A., Shepard, S. A., ... & Thompson, M. (2004). The relations of effortful control and impulsivity to children's resiliency and adjustment. *Child Development*, *75*(1), 25-46.

Espy, K. A., McDiarmid, M. M., Cwik, M. F., Stalets, M. M., Hamby, A., & Senn, T. E. (2004). The contribution of executive functions to emergent mathematic skills in preschool children. *Developmental Neuropsychology*, *26*(1), 465-486.

Gioia, G. A., Isquith, P. K., Guy, S. C., & Kenworthy, L. (2000). Test review behavior rating inventory of executive function. *Child Neuropsychology*, *6*(3), 235-238.

Hassell, K. L. (2010). Population estimates of sickle cell disease in the US. *American Journal of Preventive Medicine*, *38*(4), S512-S521.

Hijmans, C. T., Fijnvandraat, K., Grootenhuis, M. A., van Geloven, N., Heijboer, H., Peters, M., & Oosterlaan, J. (2011). Neurocognitive deficits in children with sickle cell disease: a comprehensive profile. *Pediatric Blood & Cancer*, *56*(5), 783-788.

Hughes, C., White, A., Sharpen, J., & Dunn, J. (2000). Antisocial, angry, and unsympathetic: "Hard-to-manage" preschoolers' peer problems and possible cognitive influences. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, *41*(2), 169-179.

Kawadler, J. M., Clayden, J. D., Clark, C. A., & Kirkham, F. J. (2016). Intelligence quotient in paediatric sickle cell disease: a systematic review and meta-analysis. *Developmental Medicine & Child Neurology*, *58*(7), 672-679.

Mahone, E. M., & Schneider, H. E. (2012). Assessment of attention in preschoolers. *Neuropsychology Review*, *22*(4), 361-383.

Miller, S. T., Macklin, E. A., Pegelow, C. H., Kinney, T. R., Sleeper, L. A., Bello, J. A., ... & Ohene-Frempong, K. (2001). Silent infarction as a risk factor for overt stroke in children with sickle cell anemia: a report from the Cooperative Study of Sickle Cell Disease. *The Journal of Pediatrics*, *139*(3), 385-390.

Mischel, W., Shoda, Y., & Rodriguez, M. I. (1989). Delay of gratification in children. *Science*, *244*(4907), 933-938.

Moffitt, T. E., Arseneault, L., Belsky, D., Dickson, N., Hancox, R. J., Harrington, H., ... & Sears, M. R. (2011). A gradient of childhood self-control predicts health, wealth, and public safety. *Proceedings of the National Academy of Sciences*, *108*(7), 2693-2698.

Moriguchi, Y. (2014). The early development of executive function and its relation to social interaction: a brief review. *Frontiers in Psychology*, *5*, 388.

Murphy, B. C., Shepard, S. A., Eisenberg, N., & Fabes, R. A. (2004). Concurrent and across time prediction of young adolescents' social functioning: The role of emotionality and regulation. *Social Development*, *13*(1), 56-86.

Noll, R. B., Stith, L., Gartstein, M. A., Ris, M. D., Grueneich, R., Vannatta, K., & Kalinyak, K. (2001). Neuropsychological functioning of youths with sickle cell disease: Comparison with non-chronically ill peers. *Journal of Pediatric Psychology*, *26*(2), 69-78.

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

Pegelow, C. H., Macklin, E. A., Moser, F. G., Wang, W. C., Bello, J. A., Miller, S. T., ... & Younkin, D. P. (2002). Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. *Blood*, *99*(8), 3014-3018.

Ponitz, C. C., McClelland, M. M., Matthews, J. S., & Morrison, F. J. (2009). A structured observation of behavioral self-regulation and its contribution to kindergarten outcomes. *Developmental Psychology*, *45*(3), 605.

Prussien, K. V., Jordan, L. C., DeBaun, M. R., & Compas, B. E. (2019). Cognitive Function in Sickle Cell Disease Across Domains, Cerebral Infarct Status, and the Lifespan: A Meta-Analysis. *Journal of Pediatric Psychology*.

Quinn, C. T. (2014). Breakthrough: new guidance for silent cerebral ischemia and infarction in sickle cell disease. *ASH Education Program Book*, *2014*(1), 438-443.

R Core Team. (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. 2012. *Online at http://www.R-project.org*.

Redding-Lallinger, R., & Knoll, C. (2006). Sickle cell disease--pathophysiology and treatment. *Current Problems In Pediatric and Adolescent Health Care*, *36*(10), 346-376.

Rhoades, B. L., Greenberg, M. T., Lanza, S. T., & Blair, C. (2011). Demographic and familial predictors of early executive function development: Contribution of a person-centered perspective. *Journal of Experimental Child Psychology*, *108*(3), 638-662.

Schatz, J., & Buzan, R. (2006). Decreased corpus callosum size in sickle cell disease: relationship with cerebral infarcts and cognitive functioning. *Journal of the International Neuropsychological Society*, *12*(1), 24-33.

Schatz, J., Brown, R. T., Pascual, J. M., Hsu, L., & DeBaun, M. R. (2001). Poor school and cognitive functioning with silent cerebral infarcts and sickle cell disease. *Neurology*, *56*(8), 1109-1111.

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

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

Thompson Jr, R. J., Armstrong, F. D., Link, C. L., Pegelow, C. H., Moser, F., & Wang, W. C. (2003). A prospective study of the relationship over time of behavior problems, intellectual functioning, and family functioning in children with sickle cell disease: a report from the Cooperative Study of Sickle Cell Disease. *Journal of Pediatric Psychology*, *28*(1), 59-65.

Stanovich, K. E., West, R. F., & Toplak, M. E. (2012). Judgment and decision making in adolescence: Separating intelligence from rationality.

Wang, W. C., Wynn, L. W., Rogers, Z. R., Scott, J. P., Lane, P. A., & Ware, R. E. (2001). A two-year pilot trial of hydroxyurea in very young children with sickle-cell anemia. *The Journal of Pediatrics*, *139*(6), 790-796.

Psychological Corporation. (1999). Wechsler abbreviated scale of intelligence.

White, D. A., Moinuddin, A., McKinstry, R. C., Noetzel, M., Armstrong, M., & DeBaun, M. (2006). Cognitive screening for silent cerebral infarction in children with sickle cell disease. *Journal of Pediatric Hematology/Oncology*, *28*(3), 166-169.

Yarboi, J., Compas, B. E., Brody, G. H., White, D., Rees Patterson, J., Ziara, K., & King, A. (2017). Association of social-environmental factors with cognitive function in children with sickle cell disease. *Child Neuropsychology*, *23*(3), 343-360.