

The role of family function in the development of executive functions in preschool children with sickle cell anemia

Michelle Downes PhD, Michelle de Haan PhD, Paul T Telfer MD, Fenella J Kirkham MD

Michelle Downes, School of Psychology, University College Dublin +35317168541

Michelle de Haan, Developmental Neurosciences, UCL Great Ormond Street Institute of Child Health +4420 7905 2755

Paul T Telfer, Department of Hematology, Barts Health NHS Trust +442032460338

Fenella J Kirkham, Developmental Neurosciences, UCL Great Ormond Street Institute of Child Health +4420 7905 2968

Address correspondence to:

Michelle Downes, Assistant Professor in Developmental Psychology, School of Psychology, Newman building, University College Dublin, Dublin 4, Ireland.

Michelle.downes@ucd.ie

ORCID ID 0000-0002-9317-0644

@DrMDownes

Running Head: Executive development in sickle cell disease

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Abstract

Executive functions are compromised in children with sickle cell anemia. There is limited research on the development of executive functions in preschool children with sickle cell anemia and the factors that contribute to executive dysfunction. We looked at the relation between biomedical and environmental factors, including family functioning and socioeconomic status, and executive functions in 22 preschool children with sickle cell anemia. We found that family functioning was the strongest predictor of executive outcomes in young children with sickle cell anemia with no evidence for an influence of disease severity at this early stage.

Keywords: executive function, family functioning, sickle cell, preschool, sleep

Introduction

Sickle cell anemia (SCA) is the most common and, typically considered the most severe, form of sickle cell disease (SCD). It is a genetic blood disorder that results in chronic hypoxia and often leads to overt and covert stroke. Despite the growing body of literature showing evidence for specific deficits in executive functioning (EF) in children with SCA who have not experienced stroke, there is a limited understanding of the underlying etiology of these deficits (Downes et al., 2018; 2019). To date, research has largely focused on the general neurocognitive outcomes of overt or covert stroke in this patient population (Van Der Land et al., 2014; White, Salorio, Schatz, & DeBaun, 2000), and to a lesser extent, on the relation between cognition and indicators of disease severity including cerebral blood flow velocity (CBFV) (Kral & Brown, 2004; Sanchez, Scahtz, & Roberts, 2010), hemoglobin levels, and anemia severity (Hijmans et al., 2011; Steen et al., 2005; Steen et al., 2003).

Even in the absence of stroke, there is evidence for cortical thinning and compromised white matter integrity, thought to be a result of chronic hypoxemia, in fronto-parietal brain regions of patients with SCA (Baldeweg et al., 2006). The fronto-parietal network, which is vulnerable to damage in SCA, subsumes EF. EF is an umbrella term for a collection of cognitive skills that are applied in everyday life to control behavior, solve problems and make decisions (Welsh & Pennington, 1988). Anderson's developmental model of EF incorporates four inter-connected EF domains of attention control, cognitive flexibility, goal setting, and information processing, that are proposed to develop at different rates (Anderson, 2002). Attention control refers to self-regulation and inhibition of distractions. Cognitive flexibility allows one to divide as well as shift attention between stimuli, and appropriately

altering behavior in response to errors. Goal setting involves initiation, planning and organization and information processing, involves attending to a task quickly and efficiently.

Although there is some evidence for an association between high CBFV, which is thought to indicate a greater risk for stroke, and poorer cognitive functioning, findings have been inconsistent (Armstrong et al., 2013; Hogan, Pitten Cate, Vargha-Khadem, Prengler, & Kirkham, 2006; Kral & Brown, 2004; Sanchez, Schatz, & Roberts, 2010). One study reported that children with SCD who had abnormal CBFV performed poorer on executive tasks than those with CBFV within the conditional range. Additionally, children within the conditional range performed poorer than children with CBFV in the normal range (Kral et al., 2003). Some studies have reported potential effects of CBFV on memory and IQ (Bernaudin et al., 2000; Ruffieux et al., 2013). However, other studies have found no relation between CBFV and cognitive development (Aygun et al., 2011; Kral et al., 2006; Onofri et al., 2012; Strouse et al., 2006). Low hemoglobin levels have also been described as a potential predictor of poorer cognitive functioning (Bernaudin et al., 2000; Brown, Buchanan, et al., 1993; Hijmans et al., 2011; Kral et al., 2006; Steen, Xiong, Mulhern, Langston, & Wang, 1999; Swift et al., 1989; Vichinsky et al., 2010). Recently, studies have looked at the neurocognitive effects of treatments such as transfusion and hydroxyurea, suggesting potential cognitive benefits for treated children (DeBaun et al., 2014; Puffer, Schatz, & Roberts, 2007) while a handful of studies have looked at alternative biomedical factors such as oxygen saturation levels (SpO₂), height-for-age and body mass index (Kirkham et al., 2001; Knight, Singhal, Thomas, & Serjeant, 1995; Puffer, Schatz, & Roberts, 2014).

Overall, findings for a relation between biomedical markers of disease severity and neurocognitive outcomes are inconsistent, which has led researchers to explore the role of other factors in neurocognitive development. For example, a recent study in 24 children with SCA and co-occurring sleep disordered breathing found that those who received a sleep intervention showed improved processing speed (Marshall et al., 2009). Higher rates of sleep disordered breathing, which causes nocturnal hypoxia (low SpO₂), a pathological process that also occurs in patients with SCA, is reported for children with SCA and is associated with executive dysfunction in the general population as well as in those with SCD (Beebe & Gozal, 2002; Hollocks et al., 2011). There has also been an emerging focus on socio-environmental factors, such as socioeconomic status (SES), which some studies have found to be more predictive of neurocognitive dysfunction than biomedical factors (King et al., 2014; Tarazi, Grant, Ely, & Barakat, 2007; Yarboi et al., 2015).

Poor family environment, characterized by conflict and unsupportive or inconsistent environments, may be conducive to stress, which can impact the development of the prefrontal cortex, and has been associated with poorer physical and mental health outcomes in typically developing children (Fishbein, Hyde, Coe, & Paschall, 2004; Repetti, Taylor, & Seeman, 2002; Skosnik, Chatterton, Swisher, & Park, 2000). Low SES, usually measured through family income and parental education and occupation status, has been shown to have negative implications for health and cognitive outcomes in children and is known to particularly affect the executive system in comparison to other cognitive domains (Bradley & Corwyn, 2002; Noble, Norman, & Farah, 2005). Theories such as the Family Stress Model and the Investment Model

suggest that SES may impact child development in an indirect way; through parental behavior and family processes (Conger, Conger, & Martin, 2010). Accumulating evidence shows that positive family functioning, such as the provision of stimulating experiences in the home environment, lower maternal stress, and positive parenting practices can act as a protective factor against the impact of poor SES on cognitive development, particularly EF, in typically developing children and patient populations (Coscia et al., 2001; Laliberte Durish et al., 2017; Linver, Brooks-Gunn, & Kohen, 2002). Children with SCA often face issues associated with lower SES and ethnic minority status in addition to the burden of a chronic condition (Barakat, Lash, Lutz, & Nicolaou, 2006). A recent report found that SCA patients in the most socio-economically deprived areas were most likely to have greater disease-related morbidity and mortality (AlJuburi et al., 2013).

King and colleagues (2014) argue that cognitive outcomes in children with SCA are best accounted for by multivariate models that include both biomedical and socio-economic factors. Indeed, Yarboi and colleagues (2015) found that maternal financial stress, which was related to depressive symptoms, was the strongest predictor of performance across all cognitive domains, including EF in a study of school-age children with SCD. Several studies in the SCA literature have linked the SES proxy of parental education to cognitive outcomes. In one study of school-age children with SCA, a regression model that incorporated parental education as well as hemoglobin oxygen saturation and silent stroke predicted FSIQ, with parental education as the strongest independent predictor (King et al., 2014). Smith and colleagues also reported parental education as an important determinant of academic achievement in children with SCA, alongside IQ, transfusion status, and quality of life (Smith, Patterson, Szabo, Tarazi, & Barakat, 2013). It has been postulated that parental

education may be the most important aspect of SES, as a higher parental educational level could act as a protective factor for cognitive development (Brown, Buchanan, et al., 1993; Davis-Kean, 2005).

Research in SCA has largely focused on socioeconomic factors such as income and maternal education rather than potentially modifiable psychosocial factors such as family functioning and parental stress (Schatz & McClellan, 2006). Thompson and colleagues investigated disease-related and psychosocial factors contributing to cognitive development and found that a learned-helplessness style of parenting was found to have an adverse association with neurocognitive outcomes in young children with SCD (Thompson, Gustafson, Bonner, & Ware, 2002). The same group also found that improvements in behavioral control over nine years were related to better family functioning (Thompson et al., 2003). A more recent paper reported that family functioning predicted ADHD symptoms over and above SES in a group of school age children with SCD (Bills, Schatz, Hardy, & Reinman, 2019).

There has only been one previous investigation that focused on predictors of neuropsychological functioning that looked specifically at preschool children with SCD. Tarazi and colleagues (2007) found that SES was a more pertinent target than disease-related factors for neuropsychological deficits. Environmental factors, including SES and parental stress, were most strongly associated with memory/attention, language, and visuospatial skills than disease variables in their cohort. However, they did not include any specific measures of EF. A greater understanding of the complex relationship between executive dysfunction in children with SCA and disease-related and socio-environmental factors could inform the

development of targeted assessment and intervention at this early developmental stage, where EF is most malleable. This, in turn, could have far-reaching influences on facets of daily life, leading to improved school readiness and academic attainment as well as improved social functioning, quality of life, and adaptation to disease management (Allen, Anderson, Rothman, & Bonner, 2016; Jones, 2013; Tarazi et al., 2007).

Despite the importance of focusing on early executive development in order to control for factors that may influence findings later, such as missed school, and a greater opportunity to promote development at this early stage, there remains a lack of research investigating predictors of cognitive development in preschool children with SCA. While some studies have found that socio-environmental predictors are more predictive of neurocognitive outcomes than disease-related factors (Brown, Buchanan, et al., 1993; Tarazi et al., 2007) in school-age children, others have shown evidence for the influence of markers of disease severity (Kral & Brown, 2004; Sanchez et al., 2010). This study aims to explore predictors of executive development in preschool children with SCA. EF was chosen as the cognitive domain of focus in the current study as it is a greater predictor of school readiness than IQ, math or reading ability (Diamond & Ling, 2016). Additionally, it has been demonstrated that the gap in EF ability between children with SCA and their peers increases from preschool to school age (Prussien et al., 2019). As this cognitive domain can be promoted with early intervention at this stage of development (Diamond & Lee, 2011), it is important to determine what factors interventions for children with SCA should target in order to lessen the widening EF gap.

Based on previous research, it is hypothesized that environmental factors will have a greater influence on executive outcomes at this young age than biomedical factors. It is expected that sleep and family functioning will have a particular influence on executive outcomes due to a strong case for associations between executive development and these factors in typically developing preschool children (Bernier, Beauchamp, Bouvette-Turcot, Carlson, & Carrier, 2013; Karpinski, Scullin, & Montgomery-Downs, 2008) and an emerging literature in older children with SCD (Hollocks et al., 2011).

Methods

Participants

NHS ethical approval was obtained (13/LO/0962) and site-specific approval was obtained from UCL Great Ormond Street Institute of Child Health and Barts NHS Trust. Patients were informed of the study by their consultant haematologist during their clinical visit if they met the following inclusionary criteria: aged between 36 and 72 months, HbSS genotype, no history of stroke/known neurological issues, CBFV described as normal by haematologist, no developmental/psychiatric disorders, full-term delivery, and fluent in English. Twenty-two children with SCA aged between 3.0 and 5.99 years of age ($M=4.8$, $SD=0.9$) were recruited through Barts NHS Trust between March 2014 and July 2015. Written consent was obtained from guardians. All children provided assent and were in a clinically stable condition at the time of testing. Five patients were on blood transfusion and four were on hydroxyurea. No influence of treatment type was observed.

Measures

Medical

CBFV was measured using a transcranial doppler as part of patient clinical care. CBFV measures were obtained within nine months of neuropsychological assessment with a mean delay of 60 days. Maximum CBFV was calculated as the maximum reading from the right and left middle carotid artery. Hemoglobin levels were obtained on the most recent hospital visit or the day of neuropsychological assessment if not available. The number of hospital admissions for the previous year was obtained from medical records. End-tidal carbon dioxide (CO₂) and daytime oxygen saturation (SpO₂) levels were collected on the day of neuropsychological testing by the researcher using capnography and pulse oximetry measures, respectively. CO₂ data points were unavailable for two patients due to non-administration on day of testing as a result of time restrictions and a blocked nasal airway. Disease severity was indicated by a history of complications associated with SCA including dactylitis, splenomegaly or splenic sequestration, or regular transfusion of hydroxyurea treatment, obtained through review of medical records.

Socio-environmental

Environmental factors included maternal education and SES. Maternal education was a categorical variable ('at least some college' or 'secondary school only'). SES was represented by average weekly net income based on residential postcode, estimated through the UK Office for National Statistics methods. Children were divided into five SES categories, from very low to very high: £791+ (5), £671-£790 (4), £591-670 (3), £521-£590 (2), and up to £520 (1). Levels of positive family environment were measured by administering the Family Environment Scale (FES) questionnaire to parents (questionnaire was incomplete for one participant). The FES Summary Score

consisted of the addition of scores on the subdomains of cohesion, expressiveness, active/recreational, and organization and the inverse of conflict and control. This composite score has been previously used in children with SCA and other chronic conditions. A higher score reflects a more positive family environment (Barakat, Patterson, Tarazi, & Ely, 2007; Perrin, Ayoub, & Willett, 1993).

Neuropsychological

Executive

Parents completed the Behaviour Rating of Executive Function-Preschool (BRIEF-P) questionnaire (Gioia, Espy, & Isquith, 2003). Participants completed the Scrambled Boxes Working Memory Task (Diamond, Prevor, Callender, & Druin, 1997), revised versions of the Deletion Task for Preschoolers (DDTP)(Byrne, Bawden, DeWolfe, & Beattie, 1998), the EF Scale for Early Childhood (Carlson & Schaefer, 2012), the NIH Toolbox Tasks of Inhibitory Control and Processing Speed (Zelazo et al., 2013), and the Preschool Executive Task Assessment (PETA) (Downes, et al., 2017). See Downes and colleagues (2018; 2019) for extended task descriptions and scores.

Sleep Behavior

Parents completed the Children's Sleep Habits Questionnaire (Owens, Spirito, & McGuinn, 2000). Higher sleep composite scores reflect a higher burden of sleep problem behaviors associated with obstructive sleep apnea.

Intelligence

Full scale IQ was obtained by administering the core subtests of the Wechsler Preschool and Primary Scale of Intelligence-third version (Wechsler, 2002).

Data Reduction and Analysis

Executive Composite Scores

Individual neurocognitive test scores were grouped based on the four domains in Anderson's theoretical developmental model of EF (Cognitive Flexibility= EF Scale for Early Childhood-Total Correct, Scrambled Boxes Working Memory, PETA Learning, BRIEF Shift, Brief Working Memory; Goal Setting=PETA Initiation, PETA Meta-cognition, PETA Completion, BRIEF Plan/Organise; Attention Control= NIH Inhibitory Control, DDTP Omissions, DDTP Commissions, BRIEF Inhibit; and Information Processing=NIH Processing Speed, DDTP Completion Time, PETA Time to Complete). Similar to data reduction procedures adopted by Noble and colleagues, individual test scores were used to create composite scores within each of the four domains (Noble et al., 2005). Test scores were converted to z-scores based on the SCA group continuous raw scores, and the composite score was defined as the average z-score across tasks within a particular domain. ($z\text{-score} = (\text{score} - \text{mean}) / \text{standard deviation}$). In the few cases of missing scores on individual tasks, composite scores were replaced with a mean z-score of 0 (mean for the group), to create representative composite scores. Lower composite scores on these executive domains reflect better EF. Finally, a general EF score was calculated as the average score of all individual tasks. Inter-correlations between individual task scores and the corresponding domain composite score, and between individual task scores and the general EF score are displayed in Table 1. The overall general EF score was compared with the BRIEF general executive composite score and the PETA total score (the two other indicators of 'general' EF, one parent-report and one behavioral, that were not included in the generated composite score) in order to establish its validity and was significantly correlated with both tasks ($r = .52$ and $r = .73$, respectively).

Statistical Analyses

Bivariate correlational analysis was used to determine what variables were to be excluded in the regression analyses. As several tests were carried out, a Bonferroni correction was applied to any estimated p-values to reduce the potential for a Type I error in correlations. Normality of the distribution of each of the four executive domains and the general EF domain was tested, by plotting data as histogram. A series of hierarchical regression analyses were carried out with each of these variables as the dependent outcome. Factors were entered into the model based on the amount of focus they have received in the sickle cell literature (King et al., 2014). Age (Step 1) was entered into the model first. Disease variables (CBFV, max CBFV, SpO₂, hemoglobin, number of hospital admissions; Step 2) were then entered, as they have been traditionally associated with executive outcomes in the wider literature, followed by environmental variables (maternal education, SES category; Step 3), the FES composite score (Step 4) and sleep composite score (Step 5), as it was hypothesized that these factors would contribute to the model over and above age and disease status. Hemoglobin was eventually removed as an independent variable from the model due to multicollinearity with the FES score in Step 4 ($r=.496$, $p=.019$) and the sleep composite variable in Step 5 ($r=.532$, $p=.011$). Multicollinearity between hemoglobin and sleep scores has previously been reported for older children with SCD (Hankins et al., 2014). The variable of number of hospital admissions in the previous year was also removed due to multicollinearity with SES level in Step 3 and the sleep composite variable in Step 5. CO₂ was removed due to multicollinearity with CBFV in Step 2. FSIQ was not included as predictor in regression analyses as it did not correlate with executive variables and it was not a factor of interest. Given these considerations, the final regression model had five levels. Post hoc analyses were

conducted to further explore significant predictors of EF. A significance level of $P < .05$ was used. Effect sizes were reported. A regression coefficient greater than 0.8 was interpreted as large, < 0.8 and > 0.5 as moderate, and minimum value accepted to represent a possible association as .2, and a large R^2 was interpreted as .64, moderate as .25, and minimum acceptable value for an association as .04 (Ferguson, 2009).

Results

Predictors of Overall Executive Function

Group means for variables of interest are displayed in Table 2. The hierarchical regression model significantly accounted for variability in outcomes at stage one for the general EF domain ($F_{1,19} = 6.1$, $p = .024$, $R^2 = .252$; Table 3). Introducing the medical and environmental variables in stage two and three did not substantially alter the R^2 value; however, adding the family functioning variable in stage three explained an additional 18.2% of the variation in EF, and this change in R^2 was significant ($F_{6,19} = 3.8$, $p = .022$, $R^2 = .634$). Finally, the addition of the sleep composite score to the regression model did not contribute a significant difference to R^2 change but the model remained significant ($F_{7,19} = 3.5$, $p = .027$, $R^2 = .673$). When all variables were included in the model, it was found that a more positive family environment was the strongest predictor of better general EF in this young cohort ($-.48$, $p = .02$). Taken together, the variables accounted for 67.3% of the variance in EF.

Exploring Predictors of Individual Executive Function Domains

No factors independently contributed to information processing as an outcome variable and no steps contributed to a significant change in variability.

Age did not significantly account for variation in outcome at stage one in the cognitive flexibility domain. Neither the medical nor environmental variables independently accounted for variation in outcomes at stage one and two. The addition of the family functioning variable in stage four significantly contributed to the model, with a significant R² change of 20% ($F_{1,13} = 3.2$, $p = .04$, $R^2 = .60$; Table 4). The addition of the sleep composite score in stage five did not contribute a significant difference to R² change but the model remained significant ($F_{1,12} = 3.4$, $p = .03$, $R^2 = .67$). When all variables were included in the model, it was found that a more positive family environment was a significant predictor of better cognitive flexibility ($-.49$, $p = .02$).

The hierarchical regression model was significant at stage one for goal setting ($F_{1,18} = 10.3$, $p = .005$, $R^2 = .365$; Table 5). Introducing the medical, environmental, and family variables did not show a significant R² change, however adding the sleep variable in stage five explained an additional 10% of the variation in goal setting, and this change in R² was significant ($F_{1,12} = 3.2$, $p = .038$, $R^2 = .649$).

Age did not contribute significantly to the model for attention control at stage one. Stage one and stage two showed that neither the medical nor environmental variables contributed to the model. The addition of the family functioning variable in stage four significantly contributed to the model, with significant R² change of 45.6% ($F_{1,13} = 7.9$, $p < .001$, $R^2 = .785$; Table 6). The addition of the sleep composite score in stage five did not contribute a significant difference to R² change but the model remained significant ($F_{1,12} = 6.7$, $p = .002$, $R^2 = .796$). When all variables were included in the

model, it was found that a more positive family environment ($-.77, p < .001$) and higher SES ($-.55, p = .02$) were significant predictors of better attention control.

Discussion

This study examined the influence of disease-related and environmental factors on the development of EF in preschool children with SCA. Analyses looked at the contribution of these factors to 'general EF,' a summary of performance across a range of EF measures, as well as their contribution to four specific EF domains; attention control, cognitive flexibility, information processing, and goal setting. The neurocognitive development of children with SCA is subject to several risk factors even when there is no history of stroke. Previous studies have highlighted the role of disease factors such as chronic pain and school absences as well as the impact of poor parenting and lower SES on neurocognitive development (King et al., 2013; King et al., 2014; Schatz, Finke, & Roberts, 2004; Thompson et al., 2002; Wang et al., 2001). Findings from the current study reveal a strong relation between family functioning and EF, except for the domains of information processing and goal setting.

Although these analyses reveal family functioning as an important variable in the development of EF, the influences of biomedical and socio-environmental factors on specific aspects of EF are likely to be interrelated, and must be considered in future investigations (King et al., 2014). Distinct executive components may be impacted in different ways by disease-related and socio-environmental factors (Bradley & Corwyn, 2002; Rochette & Bernier, 2014). The varying influence of the predictor variables on the different EF composite scores suggests that EF is not a unitary construct, even in these early years, as Anderson's model suggests. Anderson (2002) also hypothesize that the domain of attention control becomes established earlier in

development, laying a foundation for the other three interrelated domains to develop. This could contribute to an explanation for why a positive family environment was a particularly strong predictor for this domain, as these skills are more malleable at a stage when the child may spend more time in the family context, and may have cascading effects on the other EF domains over time.

Another important predictor for attention control was SES, which could interact with family functioning in the context of executive development. Research has shown that low SES can have an impact on health and family relations over time (Matthews & Gallo, 2011) and this could have an even greater cumulative impact on children with SCA. Family environment may have more of an impact on the cognitive outcomes of children from lower SES families. Low SES environments may cause parents to feel socially isolated and have an impact on family management, affecting parent-child relations (Wilson, 1991). One study looked at the effects of home environment and maternal intelligence for typically developing African-American preschool-age children and school-age children, noting that the effects of home environment on cognition was stronger in the younger children, potentially having less of an impact on older children who are spending more time outside the home environment (Luster & Dubow, 1992). Devine and colleagues (1998) did not find a significant influence of family functioning on IQ or adaptive behavior in their study of school age children with SCD; however, they used different predictor and outcome variables, as well as combining children with different genotypes and including those with a history of stroke. They used a caregiver adjustment questionnaire as their family functioning variable, which arguably only looks at one domain of family environment in comparison to the family environment scale and, crucially, their cognitive battery did

not contain any executive measures. Family functioning and SES both contributed significantly to attention control in this model, however further investigation of how family functioning mediates the influence of SES on the development of EF and self-regulation in children with SCA over time is important to establish if models such as the Family Stress Model and the Investment Model are similarly supported in this patient population in line with previous reports for typically developing children (Hackman, Gallop, Evans, & Farah, 2015; Masarik & Conger, 2017).

Surprisingly, no effects were seen for maternal education or for daytime oxygen saturation on any of the EF domains in the current study. Unexpectedly, sleep only played a role when added to the model for goal setting, however was not significant as an individual predictor. Another unexpected finding was the lack of predictors for information processing that could potentially be better explained by variables not included in the current study. Poor processing speed has been associated with the degree of white matter damage visible on MRI in older children (Armstrong et al., 1996; Van Der Land et al., 2014), which might remain relatively intact in this younger age group, although covert infarction is reported to be highly prevalent by school age (DeBaun et al., 2012). Imaging was not included in the current protocol due to participant age but it may be feasible to examine white matter integrity in young unsedated children in future studies (DeBaun & Kirkham, 2016). The lack of influence of CBFV on EF domains should be interpreted with caution as children with abnormal TCD were excluded from the current study and so variability of this predictor is limited by the inclusion criteria.

The sample size warrants caution for the over-interpretation of regression analyses due to the reduced power based upon the number of predictors included (Cohen,

1992). However, the predictors were reduced in number while still maintaining a ‘totality’ approach by including the physical and psychosocial experiences that may influence EF development in this exploratory investigation (Anderson, Northam, & Wrennall, 2014). Measures were taken during the statistical analysis stage to reduce the impact of multiple predictors in a small population. Instead of a multiple linear regression, where all variables are entered at once, a multilevel regression was chosen to reduce the noise created by multiple predictors (Gelman & Hill, 2006). A theory-driven hierarchical regression model was adopted so that the order of variable entry was based upon the extant literature. The small sample size was due to strict inclusionary (e.g. HbSS only) and exclusionary criteria and a narrow age range. Finally, the creation of executive composite domain scores from a number of behavioral measures also increased power and measurement precision in the analyses (Gibbons et al., 2012). A final limitation to be noted is the lack of data on a healthy control group, such as sibling controls, which restricts the findings of the current study.

Implications for future research and practice

Disease and environmental factors cannot be easily disentangled in the determination of their impact on development as there are likely many bidirectional and interactive relations (Gustafson, Bonner, Hardy, & Thompson, 2006). There is emerging evidence for the important role of family functioning in executive development, which has even been reported as a mediator for SES and other factors (Sarsour et al., 2011). Children with SCA may be more susceptible to the impact of poor family functioning and stressful home environments due to increased vulnerability related to having a chronic disease (Brown, Kaslow, et al., 1993; Thompson et al., 2002) and

family functioning may mediate any impact of SES and disease severity on cognitive development (Sarsour et al., 2011). Poor SES has even been associated with a higher incidence of pediatric obstructive sleep apnea (Spilsbury et al., 2006). However, as family functioning is reported as a mediator for poor SES, there is a potential for the development of psychosocial interventions with the goal of promoting cognitive and behavioral development. Similar to the bidirectional relations demonstrated in the research literature for parenting and EF development in typically developing children, family functioning could also be influenced by child EF and this should be considered in future research as this could have implications for the development of interventions (Blair et al., 2014; Merz, Landry, Montroy, & Williams, 2016).

Early screening for EF deficits has been championed in the sickle cell literature (Daly, Kral, & Tarazi, 2011). Recent evidence has emphasized the important role of EF for this patient population. Findings show poorer EF related to lower quality of life and depressive symptoms in children with SCD (Allen et al., 2016; Prussien et al., 2017). However, it is still not an established routine for preschool children with SCA to undergo neuropsychological assessment, despite preschool children having a high risk of first stroke occurrence (Armstrong et al., 1996; DeBaun et al., 2012) and a greater executive burden due to the adaptive requirements of their disorder (Tarazi et al., 2007).

Recent research demonstrates a clear increase of EF deficits in children with SCD from the preschool to the school-age period (Prussien et al., 2019). Support is growing in the developmental literature more generally for interventions that reduce stress and improve a child's social and emotional development (with the goal of

promoting EF) over interventions that train specific EF skills (Diamond & Ling, 2016), and this may be a promising route for children with SCA given the findings of the current study. A targeted family-focused intervention in the early years for families of children with SCA may have a positive impact on early executive development. Previous research has shown family function to be associated with rates of behavioral problems in children with SCA, but not in their typically developing siblings (Brown, Buchanan, et al., 1993; Thompson et al., 1999). Parents of adolescent patients with SCA tend to report more negative home environments than parents of preschool age children, a decline in family functioning that could be addressed with intervention (Barakat et al., 2007). However, given the possible bi-directionality of the association of family function and EF deficits in children, the next step is to undertake experimental research to confirm the role of family functioning in the development of EF skills through intervention.

Family intervention programs are costly to implement, both in terms of funding and time, but could have long-term benefits for EF and other health and education outcomes, such as quality of life and self-management, in children with SCA (Ludwig et al., 2018; Psihogios et al., 2018). Daniel and colleagues recently implemented the first family-based intervention in families of school age children with SCD that aimed to improve academic performance over a six-month period (Daniel et al., 2015). However, they did not find any improvements over time, which can partly be attributed to a high rate of attrition. Nevertheless, they still conclude that with the right intervention, a focus on family functioning for children with SCA is a worthwhile avenue for the future. The findings of this study show that there may be added value in implementing intervention at an earlier stage of EF development.

Conclusions

In recent years, researchers in SCA have shifted their attention to a more biopsychosocial model of child development (Gustafson et al., 2006; King et al., 2014). In the current study, we looked at predictors of EF in preschool age children with SCA for the first time and found that positive family functioning was associated with better executive performance in preschool children with SCA. There was a lack of evidence for associations between disease factors and EF. Overall, the results of this study could inform the identification of children with SCA who are most at risk of EF issues. Future studies should focus on family-based interventions that aim to promote early EF development in children with SCA.

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List of Tables

Table 1. Inter-correlations between individual tasks and composite scores

Variable		General EF
	Attention Control	.717**
NIH Flanker	-.571**	-.286
DDTP Omissions	.204	-.174
DDTP Commissions	.507*	.612**
BRIEF-P Inhibit	.625**	.631**
	Information Processing	.704**
NIH pattern comparison	-.654**	-.432*
DDTP time to complete	.750**	.474*
PETA Total Time	.777**	.621**
	Cognitive Flexibility	.633**
EF scale for Early Childhood	-.386	-.539**
Working Memory Consecutive Score	-.442*	-.409*
PETA learning score	-.680**	-.238

BRIEF Shift	.693**	.246
BRIEF Working Memory	.746**	.444*
	Goal Setting	.903**
PETA Initiation	.657**	.626**
PETA metacognition	.856**	.655**
PETA Completion	.765**	.651**
BRIEF-Plan/organize	.213	.320

*not significant after Bonferroni correction **remains significant after Bonferroni correction

Table 2. Summary of Patient Characteristics and Neuropsychological Functioning

Variable	Mean	SD
FSIQ	98.6	11.4
CBFV	157.1	26.0
SpO2	97.1	1.2
Hemoglobin	8.9	1.7

End-tidal pCO ₂ *	37.2	4.0
No. hospital admissions in the previous year	1	1.1
SES (based on postcode)	3.1	1.3
FES score**	114.4	25.0
Sleep score	21.4	11.7
BRIEF GEC	54.0	13.9
PETA TS	63.2	46.2

*datapoint missing for two participants

**datapoint missing for one participant

Table 3 Summary of stepwise regression analysis for variables predicting general executive functioning

Variable	β coefficient	p-value	R ²
Step 1			.252
Age	-.50	.024	
Step 2			.269
Age	-.51	.032	
CBFV	.01	.967	
SpO ₂	.128	.560	
Step 3			.45

Age	-.54	.023	
CBFV	-.11	.626	
SpO2	.32	.174	
Income	-.503	.058	
Maternal Education	-.304	.208	
Step 4			.634
Age	-.34	.101	
CBFV	-.06	.769	
SpO2	.23	.253	
Income	-.53	.025	
Maternal Education	-.15	.492	
FES	-.49	.024	
Step 5			.673
Age	-.41	.06	
CBFV	-.02	.92	
SpO2	.13	.57	
Income	-.33	.23	
Maternal Education	.04	.89	
FES	-.48	.02	
Sleep	.29	.26	

*p<.05

Table 4 Summary of stepwise regression analysis for variables predicting cognitive flexibility

Variable	β coefficient	p-value	R²
Step 1			.009
Age	-.093	.697	
Step 2			.089
Age	-.139	.577	
CBFV	-.281	.265	
SpO2			
Step 3			.400
Age	-.244	.286	
CBFV	-.481	.05	
SpO2	.084	.727	
Income	-.470	.086	
Maternal Education	-.602	.025	
Step 4			.600
Age	-.040	.847	
CBFV	-.427	.044	
SpO2	-.010	.960	
Income	-.493	.040	
Maternal Education	-.436	.062	
FES	-.512	.024	
Step 5			.665

Age	-.129	.534
CBFV	-.379	.062
SpO2	-.151	.493
Income	-.236	.390
Maternal Education	-.200	.445
FES	-.492	.024
Sleep	.384	.148

Table 5 Summary of stepwise regression analysis for variables predicting goal setting

Variable	β coefficient	p-value	R²
Step 1			.365
Age	-.604	.005	
Step 2			.371
Age	-.587	.011	
CBFV	.068	.741	
SpO2	-.042	.837	
Step 3			.488
Age	-.592	.011	
CBFV	-.013	.952	
SpO2	.125	.573	
Income	-.417	.098	
Maternal Education	-.198	.388	
Step 4			.545
Age	-.483	.043	
CBFV	.016	.937	
SpO2	.075	.733	
Income	-.429	.085	
Maternal Education	-.109	.640	
FES	-.273	.225	
Step 5			.649

Age	-.595	.014
CBFV	.077	.692
SpO2	-.101	.653
Income	-.107	.699
Maternal Education	.186	.489
FES	-.248	.230
Sleep	.481	.083

Table 6 Summary of stepwise regression analysis for variables predicting attentional control

Variable	β coefficient	p-value	R²
Step 1			.034
Age	-.184	.437	
Step 2			.041
Age	-.197	.442	
CBFV	-.023	.927	
SpO2	.083	.740	
Step 3			.329
Age	-.233	.333	
CBFV	-.174	.474	
SpO2	.321	.217	
Income	-.626	.036	
Maternal Education	-.402	.137	
Step 4			.785
Age	.075	.624	
CBFV	-.092	.523	
SpO2	.179	.249	
Income	-.660	.001	
Maternal Education	-.151	.354	
FES	-.773	.000	

Step 5			.796
Age	.037		.816
CBFV	-.072		.627
SpO2	.120		.483
Income	-.551		.020
Maternal Education	-.052		.798
FES	-.765		.000
Sleep	.162		.421
