The assessment of executive functions in preschool children with sickle cell anemia

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Abstract

Objective: Children with sickle cell anemia are commonly reported to experience executive dysfunction. However, the development of executive function in preschool-age children without stroke in this patient population has not been investigated so it is unclear when and how these deficits emerge. Methods: This case-control study examines the feasibility of assessing the early development of executive functioning in 22 preschool children years with SCA in the domains of processing speed, working memory, attention, inhibitory control, and cognitive flexibility, as well as everyday function, in comparison to matched control children. Results: A pattern of potential deficits in early emerging executive skills was observed in the domains of inhibitory control and cognitive flexibility. Parents reported no differences for everyday executive function and no significant differences were observed for working memory and processing speed. Conclusions: Results suggest that deficits in everyday executive difficulties, working memory, and processing speed, as commonly reported for older children with sickle cell anaemia, may not yet have emerged at this early developmental stage despite specific deficits in cognitive flexibility and inhibitory control on behavioural measures. The feasibility of using available executive measures with preschool age children to characterise the development of early EF skills is discussed.

Key Words: Cognition; executive function; sickle cell disease; preschool; attention; cognitive flexibility

Introduction

Sickle cell anemia (SCA) is a genetic blood disorder that affects the ability of red blood cells to transport oxygen around the body. Stroke is common in SCA and typically occurs in the frontal cortex. However, for those patients who do not experience stroke, there remains evidence for bilateral cortical thinning and poorer white matter integrity which is thought to result from the effects of chronic hypoxia on the fronto-parietal regions that subsume executive functioning (EF) (Baldeweg et al., 2006).

EF is an umbrella term for a collection of skills that we use to coordinate and control our everyday behaviour. The emergence of EF skills occurs alongside the protracted development of the prefrontal cortex with full maturity not reached until post-adolescence. Basic EF skills, such as attention control, are hypothesised to emerge first and lay down the foundation for more complex and later emerging EF skills such as cognitive flexibility (Anderson, 2002). Improvements in attention control, switching, and fluency, are reported up to six years in typically developing children, with significant gains in planning and organisation in mid-childhood, and rapid development of information processing speed in the preadolescent stage (Anderson, 2002). Children with early brain insult are sometimes described to ‘grow into’ later emerging deficits when impairments are reported to emerge with brain development and as developmental expectations grow to incorporate higher-order skills such as planning, organising, and problem-solving. The severity of EF dysfunction, the most common cognitive deficit in SCA, is related to increasing neurologic morbidity although poor EF remains in this patient population in the absence of neurologic

morbidity (Berg, Edwards, & King, 2012; Berkelhammer et al., 2007; Burkhardt et al., 2017; Hensler et al., 2014; Hollocks et al., 2011; Hijmans et al., 2011; Kral & Brown, 2004; Nabors & Freymuth, 2002; Smith & Schatz, 2016).

It has been recommended that neuropsychological assessment of all children with SCA should include EF measures (Daly, Kral, & Tarazi, 2011). However, until recently, a lack of age-appropriate measures for the preschool population has hindered research (Glass et al., 2012). Previous studies with preschool children with SCA have largely focused on global measures of cognition, showing evidence for early cognitive delay (Drazen, Abel, Gabir, Farmer, & King, 2016; Glass et al., 2012; Tarazi, Grant, Ely, & Barakat, 2007). The lack of focus on EF in preschool children makes it difficult to ascertain the extent of potential EF deficits at this early stage although there is emerging evidence for subtle delays in early working memory and processing speed (Hogan, Telfer, Kirkham, & de Haan, 2012; Schatz & Roberts, 2007). Additional barriers to knowledge of EF development more generally in children and adults with SCA in previous studies include combined sickle cell genotypes and neurological histories, no matched controls, and insufficient descriptions of poor performance or measures (Burkhardt et al., 2017; Ruffieux et al., 2013; Smith & Schatz, 2016). Clinicians, parents and educators tend to underestimate the rate of neurocognitive delay (Glass et al., 2012). Promoting EF at an early stage could reduce the achievement gap often reported for this patient population.

The aim of this study is to better establish the neuropsychological profile of EF in preschool-age children with SCA who have no clinical evidence of neurological

morbidity while determining the feasibility of available EF measures for this age range. It is hypothesised that children with SCA will show EF deficits at this early stage that may not yet be observable in everyday contexts.

Method

Participants

Control children were recruited through the same clinics as patients at Barts NHS Trust (n=11 siblings) or through study advertisement in local boroughs (n=2). 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, normal transcranial Doppler (TCD), no developmental/psychiatric disorders, full-term delivery, and fluent in English. Inclusionary criteria for the matched control group were no history of developmental/psychiatric disorders, full-term delivery, fluent in English, Black British, and socioeconomic status (SES; by postcode to estimate total weekly house income). The participation rate for those introduced to the study was approximately 85%, there were no differences between those who chose not to participate. Reasons for non-participation included unavailability or a lack of response when contacted by the researcher. The 22 patients who participated in the study represented approximately 20% of the children within the same age range and with a diagnosis of SCA registered on the Barts NHS Trust database. Data on other inclusionary criteria for those on the database not participating in the study was not available. All patients had available TCD data with a mean delay between TCD and neuropsychological assessment of 60 days. No patients had abnormal transcranial Doppler recordings

(velocity> 200 cm/s). Five patients were on transfusion and four were on hydroxyurea. No influence of treatment type was observed. Table 1 shows population descriptives.

TABLE 1 HERE

Procedure

NHS ethical approval (13/LO/0962) and site-specific approval was obtained. Participant recruitment occurred from March 2014 - July 2015. Written consent was obtained from guardians. Child assent was obtained. The session took place at UCL Great Ormond Street Institute of Child Health. A revised Scrambled Boxes Working Memory Task was administered, followed by a revised Picture Deletion Task for Preschoolers (DDTP). The Wechsler Preschool and Primary Scales (WPPSI-III-UK) were administered before the EF Scale for Early Childhood and two NIH Toolbox (NIHTB) tasks: Processing Speed and Inhibitory Control. Parents completed the Behavior Rating Inventory of EF-Preschool (BRIEF-P). All tasks, described in the supplementary section, were completed within two and a half hours.

Data Analysis

Statistical analyses were conducted using SPSS version 21.0. Multivariate analysis of variance, independent t-tests, Fisher's exact tests, and chi-square analysis were used with a significance level of $p<.05$.

Results

TABLE 2 HERE

Working Memory

One patient found seven stimuli by the final trial (4.5%), while five patients (22.7%) found eight stimuli, and the rest found all nine. There was no group difference in success rates. Two control children (15.4%) found eight stimuli whilst the rest found all nine stimuli (X^2=.64. p=.72). Multivariate ANOVA found no statistically significant differences between groups for total trials or the number of consecutively correct trials (F2,32=.181, p=.84).

Attention

Four patients and one control child did not pass the practice phase of the DDTP and one control participant did not attempt the DDTP due to administrator error. Three patients did not complete the task so scores for total time, omissions, and commissions, were pro-rated. For those who passed the practice phase, an ANOVA including the individual test phase factors (omissions, commissions, time to completion) found no overall group differences (F1,29=.338, p=.34). There were no group differences for motor speed. Commissions was higher for the patients (p=.04, Table 2). More than 1.5 standard deviations above the combined mean score for omissions/commissions in typically developing children (M=33.1) was considered poorer than average performance in this study. Seven patients performed lower than average in comparison to three controls.

Cognitive Flexibility

An independent t-test found a main effect for group on the switching score, showing poorer cognitive flexibility in patients (t (30)=2.5, p=.02; Table 2). Patients typically reached ceiling on level four of the task in comparison to the controls who typically

reached level five (Table 2). Six patients (30%) did not reach the normed average highest level for their age range in comparison to one control child (8.33%). The task was not administered to two patients and one control due to time restrictions.

Inhibitory Control and Processing Speed

Patients had lower mean scores for inhibitory control (t (30) =.76, p=.38) and processing speed (t(30)=.24, p=.27), but these did not reach significance (Table 2). However, when looking at individual scores, seven (35%) patients were more than 1.5 standard deviations (SD) below the normative mean scores for processing speed in comparison to three (23%) of the controls, while three (15%) patients were more than 1.5 SD below the normative mean for inhibitory control in comparison to none of the controls. Technical issues prevented two patients from completing the measure whilst one control participant did not compete these tasks due to time restrictions.

Parent-reports of Executive Functioning

Multivariate analysis of variance on the five subdomains showed no overall group differences on the BRIEF-P (F1,35=.66, p=.66). There was a pattern of higher mean scores across all subdomains for the patients; however, this did not reach significance (Table 2). Clinically elevated General Executive Composite (GEC) scores were observed for three (14.3%) patients and one (7.7%) control.

Discussion

The aim of this study was to investigate the EF profile of preschool children with SCA. Until recently, the lack of appropriate measures has been a barrier in the characterization of executive development in preschool children with SCA despite widely reported executive deficits in older children (Berkelhammer et al., 2007). This study is the first robust assessment of individual EF domains in preschool-age children with SCA using available EF measures. Through the administration of standardised and lab-based measures, potential strengths and difficulties emerged for the preschool children with SCA. In particular, everyday EF (EF reported by parents as typically observed behaviour in day-to-day real-life contexts), processing speed and working memory were relatively preserved whereas a pattern of specific deficits in cognitive flexibility and inhibitory control emerged on behavioural tasks.

Although more patients failed to retrieve all stimuli on the working memory task, the number of consecutively correct trials was comparable to controls. Contrary to current findings, previous studies have reported working memory deficits (Hijmans et al., 2011; Schatz & Roberts, 2007). There were no significant differences observed between groups on NIHTB Processing Speed, or on the processing speed components of the DDTP (DDTP motor phase/ DDTP completion time) which is also in contrast to findings for school-age children (Burkhardt et al., 2017; Smith & Shatz, 2016). In comparison to normative scores on NIHTB Processing Speed, both the patients and the controls showed poor processing speed, which may reflect the factors that they were matched on such as IQ or SES.

A pattern for difficulties with cognitive flexibility and inhibitory control was observed. The evidence for a specific deficit in cognitive flexibility builds upon previous research that observed poorer cognitive flexibility in older children (Hensler et al., 2014). In the current study, 30% of patients did not reach the average performance level for their age range on the cognitive flexibility task (Fuglestad et al., 2014). Similarly, Hensler and colleagues (2014) reported that 45% of their school-age patients were impaired on a sorting task.

Potential deficits in inhibitory control were noted through the trend for poorer performance on NIHTB Inhibitory Control and the high error rate of DDTP commissions. The small group size that successfully completed the DDTP means that these findings must be interpreted cautiously and further research should address adapting the task further to capture low end performance. However, the higher level of commissions on this task adds weight to the trend for poorer performance on NIHTB Inhibitory Control.

The BRIEF-P GEC was more typical for the current patient population in comparison to previous reports for older children with SCA. Importantly, different subdomain categories on the school-age version of this measure preclude direct comparison with older patient groups. Hollocks and colleagues (2012) observed a higher mean composite score on the BRIEF (M=62.2; SD=13.51) in 8-to-16-year-old children with SCA. Berg and colleagues (2012) also found a higher mean in 8-to-12-year-olds with SCA on both teacher (M=59.1; SD=13.54) and parent (M=52.5, SD=8.7) BRIEF reports. However, Hensler and colleagues (2014) found a more comparable mean to

the current study in their cohort of 8-to-16-year-olds (M=54.3 SD= 14.4). Findings in the current study are also comparable to Kral and Brown (2004) as the group mean was also not in the clinical range in their study of 6-to-16-year-olds.

Everyday EF, as well as specific domains of working memory, attention, inhibitory control, cognitive flexibility, and processing speed, were measured in this study. Interestingly, clinically elevated composite scores on the BRIEF-P captured patients who performed poorly on at least one behavioural task (Table S1). This supports the utility of multi-method assessment of EF rather than a reliance on parent-report only in order to provide a holistic picture of an individual child. Findings on the BRIEF-P reflected a lower level of EF impairment in the patient group than what was observed on the other behavioural tasks. This could be attributed to subtle differences that are less readily observable in everyday contexts at this young age.

Strengths and Limitations

The generalizability of study findings is limited due to the small sample. The small control group limits statistical power. Effect sizes for each comparison have been included to assist with interpretation (Table 2). One strength of this study is the homogeneity of the patient population which overcomes the shortcomings of previous studies by focusing on the HbSS genotype and excluding patients with stroke, as well as a narrow age range. Group differences carry more weight as they are matched for age, ethnicity, gender, and SES, reducing the likelihood of spurious effects. This stringent approach allows us to elucidate differences due to disease without the influence of previously reported confounding factors. Including control groups matched for ethnicity and SES is important as children with SCA are often from a

minority group and face socioeconomic disadvantages known to influence EF (Yarboi et al., 2017). For example, the low group mean for the controls on NIHTB Processing Speed allowed us to better interpret findings that may have otherwise been construed as patients performing significantly poorer than peers. Order of administration may have impacted performance on tasks due to factors such as fatigue however this was controlled for with the comparison group.

Finally, incomplete batteries for some participants and the lack of large-scale normative data for some of the lab-based tasks, although widely used in developmental research, should also be considered in the interpretation of results. Further validation of the lab based EF measures, particularly the Scrambled Boxes task and the DDTP, are required in large populations and patient populations with well-known EF deficits. The failure of seven patients to pass the practice phase or complete the DDTP indicates that further task development is required in order to prevent floor effects in children with poorer attention control. Adapting the scoring system so that performance on the practice phase is incorporated could be one potential avenue to capture the range of performance at this level.

Conclusion

The findings of the current feasibility study inform researchers and clinicians on the potential impact of SCA in EF development and support early EF assessment. Recent research has highlighted a relation between poorer EF and increasing age and disease progression in older children and adults with SCA (Hijmans et al., 2011; Ruffieux et al., 2013; Vichinsky et al., 2010). Further research is necessary to develop valid EF measures for preschool children and to delineate the developmental trajectory of early EF in preschool children with SCA.

Conflict of Interest

None of the authors have potential conflicts of interest to be disclosed.

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Table 1. Participant characteristics

Variable	**Patients M (SD) n=22**	**Controls M (SD) n=13**	**P-value**
Male, n	13	5	.31
Age	4.8 (0.9)	4.9 (0.9)	.35
FSIQ	98.6(11.4)	100.9(10.4)	.55
SES			.56
Level 1	3	3	
Level 2	3	1	
Level 3	9	3	
Level 4	3	3	
Level 5	4	4	
Black British, n	22	13	-

FSIQ, full-scale intellectual quotient; SES, socioeconomic status. Office for National Statistic website data was used to analyse SES based on postcode to estimate total weekly house income on a scale from 1 (up to £520) to 5 (over £791). FSIQ=Full scale Intellectual Quotient.

Table 2. Means (M) and Standard Deviations (SD) on executive measures

EF Domain	Measure	Individual Scores	Patients Mean (SD)	Controls Mean (SD)	P-value (d)	Statistical Test
Parent-report	BRIEF-P	GEC	53.95 (13.9)	50.69 (11.2)	.29 (0.3)	MANOVA
		ISCI	54.19 (13.2)	49.30 (11.3)	.18 (0.4)	
		EMI	54.05 (13.3)	50.69 (12.6)	.37 (0.3)	
		FI	52.67 (14.16)	48.15 (9.1)	.18 (0.4)	
		Inhibit	52.19 (11.8)	50.30 (11.1)	.83 (0.2)	
		Shift	50.66 (11.4)	48.31 (9.0)	.11 (0.2)	
		Emotional Control	54.38 (14.17)	48.30 (10.4)	.04 (0.5)	
		Working Memory	54.43 (12.3)	51.61 (11.5)	.39 (0.2)	
		Plan/organise	52.86 (13.9)	49.31 (13.1)	.37 (0.3)	
Inhibitory control and Processing Speed	NIHTB	Inhibitory Control	92.38 (22.6)*	98.45 (21.8)*	.38 (0.3)	T-test
		Processing Speed	80.28 (12.71)*	85.9 (14.9)*	.27 (0.4)	T-test

EF Domain	Measure	Individual Scores	Patients Mean (SD)	Controls Mean (SD)	P-value (d)	Statistical Test
Attention	DDTP	Commissions	77.9 (111.2)	13.6 (22.7)**	.04 (0.8)	MANOVA
		Omissions	22.9 (16.8)	26.7 (30.4)**	.73 (0.1)	
		Time to Complete	12.1 (4.9)	11.06 (4.2)**	.52 (0.2)	
		Motor Speed	51.9 (13.7)	46.6 (8.3)**	.54 (0.5)	
Cognitive Flexibility	EF Scale for Early Childhood	Switching score	46.6 (14.4)*	56.9 (9.7)*	.02 (0.8)	T-test
Working Memory	Scrambled Memory Task	Total Number of Trials	14.68 (3.92)	14.64 (3.99)	.98 (0.0)	MANOVA
		Consecutively Correct Trials	5.63 (2.21)	5.28 (1.49)	.67 (0.2)	

*Two patients and one control child did not complete the NIH toolbox tasks and the EF scale for Early Childhood. **One control child did not complete the DDTP. BRIEF-P=Behavior Rating Inventory of Executive Function. GEC=Global Executive Composite. FI= Flexibility Index. ISCI=Inhibitory Self-Control Index. EMI=Emergent Metacognition Index. NIHTB=NIH Toolbox. DDTP= Doggie Deletion Task for Preschoolers. SD=Standard Deviation. d= Effect size.

EF Measures

Working Memory

A revised version of the Scrambled Boxes Working Memory Task (Diamond, Prevor, Callender, & Druin, 1997) was developed with 40 typically developing preschool children at the London Babylab, University College London (Downes, 2016) due to lack of consistent administration, design, and scoring parameters in previous studies (Schoemaker et al., 2012; Wiebe et al., 2011). The revised task shows good convergent validity. Nine boxes were chosen rather than six at pilot phase as ceiling effects were observed with the latter number of boxes. The number of consecutively correct trials is related to parent ratings of working memory on the BRIEF-P (N=27) (Downes, 2016). The examiner instructs the child to find all of the toys in the least amount of trials. Children are permitted to open only one box per trial. Nine boxes are scrambled according to a predetermined protocol during a 10-second inter-trial interval. The task continues until a maximum of 20 trials are administered or until the child finds all of the toys. The total retrieved stimuli within 20 trials are coded along with the number of consecutively correct trials and the total number of trials. Working memory for this task is considered impaired if the child does not receive all of the stimuli in the maximum number of trials.

Attention

The DDTP is a modified version of a cancellation task previously used to measure attention (Byrne, Bawden, DeWolfe, & Beattie, 1998). The task was revised at the London Babylab, University College London, with five typically developing preschool children in order to make it more age appropriate for this age range before validation with 26 children. Previous research found that the original version of the task was appropriate for typically developing four and five-year olds but not for three year olds or children with disorders that affect executive development, despite the fact that the objective of this task is to detect difficulties in these children (Parker, 2005). Parker (2005) concluded that further work was required to standardize the administration in order to make the task a more reliable and valid. The main modifications of the task in the current version from previous versions include updated stimuli, an in-depth script and examiner instructions, and the addition of objective instructions to administer “cues” to participants who go off-task for upwards of 20 seconds, as well as instructions for scoring incomplete attempts.

The utility of the final version was then investigated with 26 typically developing children showing good convergent validity (Downes, 2016). The child undergoes a training phase (2 x 6 array of shapes) and a practice phase (two pages with targets ([30]: triangle) and distracters ([90]: circle, square, diamond, and octagon) arranged in a 10 × 6 array), to ensure that they can hold and use the bingo stamper successfully and can understand the task instructions, before the test phase (8 pages with 10 × 6 arrays of targets (N=120 standing dogs) and distracters (N=360 four identical dogs varying in position only). The aim is to stamp the target stimuli as cued by the image on the top of the page. The test phase was modified so that the examiner can cue if a child remains off-task for greater than a 20 second block and terminate the task if a child remains off-task for greater than a 20 second block on a second occasion. Finally, the child completes the motor speed phase where they start at the top left side dog stimulus stamp all the dogs until the end, going as fast as they can.

The variables in this measure are omissions, commissions, time to completion, and motor speed. Number of omissions and commissions are combined during the test phase to obtain the mean rate of errors in typically developing children so that the number of patients and controls performing greater than 1.5 standard deviations below the average score of typically developing children can be computed. Time to completion is the time taken to complete the test phase and motor speed is the time taken to stamp every stimulus on the motor speed phase. Impairment on this task is defined as failing the practice phase or obtaining a score greater than 1.5 calculated SD above average on the combined rate of omissions and commissions.

Parent-reports of Executive Functioning

The BRIEF-P is a standardized rating scale that measures everyday EF with high internal reliability and validity (Sherman & Brooks, 2010). The researcher scored the BRIEF-P using a computerized scoring program which showed no rater negativity and inconsistency. Raw scores were converted to standardized T-scores (Mean=50; SD=10). T-scores over 65 (greater than 1.5 standard deviation above the mean) are considered clinically significant.

Cognitive Flexibility

The EF Scale for Early Childhood assesses cognitive flexibility across seven levels with increasing difficulty (Beck, Schaefer, Pang, & Carlson, 2011; Carlson & Schaefer, 2012).

This graded measure of EF incorporates three tasks; categorization (Carlson, Mandell, & Williams, 2004), dimensional change card sort (Diamond, Carlson, & Beck, 2005) and integrated/advanced dimensional change card sort (Zelazo et al., 2003). It requires the participant to sort cards according to one rule for the first half of each level and then switch to a new rule for the second half of the level. The dependent variables are the number of correct trials and the highest level at which the child passes both pre-and post-switch trials. Children who did not reach the average level for their age were considered to have impaired cognitive flexibility (Fuglestad et al., 2014).

Inhibitory Control and Processing Speed

The NIHTB measures of inhibitory control and processing speed taps these domains using standardised computerized tasks free from experimenter bias (Zelazo et al., 2013). The inhibitory control task is administered as an age-appropriate Flanker task where flankers face the same direction for congruent trials and a different direction for incongruent trials. The processing speed task involves pressing a target button in response to on-screen pictures that are the same or different. Standardised age-adjusted scores of less than 85 for both tasks are considered atypical performance based on normative data.

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Table S1. Pattern of individual 'impaired' scores across the seven executive measures

Patient	BRIEF-P	NIHTB-IC	NIHTB-PS	DDTP	WM	EF Scale
A						x
B						
C				x	x	
D						
E	x		x		x	
F			x	x		x
G	x	x	x	x		
H				x	x	x
I						x
J			x	x		
K		x				
L			x	x		
M		x	x		x	
N						
O				x	x	
P						
Q			x			x
R				X		x
S	x			x		
T				x	x	
U						

V

BRIEF-P=Behavior Rating Inventory of Executive Function. NIHTB-IC=NIH Toolbox task of inhibitory control. NIHTB-PS=NIH Toolbox task of Processing Speed. DDTP= Doggie Deletion Task for Preschoolers. WM= Scrambled Boxes Working Memory Task. EF Scale=Executive Function Scale for Early Childhood.