**Executive performance on the preschool executive task assessment in children with sickle cell anemia and matched controls**

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**Abstract**

Executive deficits are commonly reported in children with sickle cell anemia. Earlier identification of executive deficits would give more scope for intervention, but this cognitive domain has not been routinely investigated due to a lack of age-appropriate tasks normed for preschool children. In particular, information relating to patient performance on an executive task that reflects an everyday activity in the classroom could provide important insight and practical recommendations for the classroom teacher at this key developmental juncture as they enter the academic domain. The performance of 22 children with sickle cell anemia was compared to 24 matched control children on the Preschool Executive Task Assessment.Findings reveal that children with sickle cell anemia are performing poorer than their matched peers on this multi-step assessment. In particular, children with sickle cell anemia required more structured support to shift focus after a completed step, as reflected by poorer scores in the quantitative Sequencing and Completion domains. They also required more support to stay on task, as seen by poorer ratings in the qualitative Distractibility domain.

**Key Words:** Executive function, Neuropsychological assessment, Preschool, Sickle cell disease, Sickle cell anemia, Neurodevelopmental disorders

**Abbreviations:** PETA=Preschool Executive Task Assessment; SCA=Sickle Cell Anemia; EF=Executive Functioning

**Introduction**

Sickle cell disease is the most common hereditary disorder in the United Kingdom, with over one in 2,000 infants diagnosed. It is a genetic blood disorder in which the hemoglobin in red blood cells, which transport oxygen around the body, is abnormal. Sickle cell anemia (SCA), the most commonly occurring and severe form of sickle cell disease, is associated with an elevated risk of stroke. Up to 40% of children with SCA experience stroke by mid-adolescence (Armstrong et al., 1996; Bernaudin et al., 2000), and the fronto-parietal regions are most frequently affected (Ohene-Frempong et al., 1998). Even in the absence of stroke, there is evidence for developmental differences resulting from chronic hypoxemia in frontal and parietal regions (Baldeweg et al., 2006). The fronto-parietal network, which is vulnerable to damage in SCA, is known to play a role in mediating executive functions (EF).

The interactive specialization account postulates that EF development is dependent upon connectivity between different brain regions (Johnson, 2011). This account may be particularly applicable to SCA. White matter integrity is affected in older children even when there is no evidence of stroke, and white matter connections are important to integrate information between different brain regions in circuits related to EF (Charlton et al., 2006). The cognitive profile of children with SCA who show decreases in general cognition over time as well as specific EF deficits has been compared to patients with early treated phenylketonuria who also show a similar pattern of reduced microstructural white matter integrity (Antenor-Dorsey et al., 2013).

EF deficits are the most frequently reported cognitive deficits in school-age children and adolescents with SCA, even when there is no evidence for neurological morbidity (Berkelhammer et al., 2007; Hijmans et al., 2011; Nabors & Freymuth, 2002; Noll et al., 2001). The executive system is responsible for combining different faculties in order to execute cognitive control in high level processes such as making plans and solving problems (Welsh & Pennington, 1988). Most SCA studies have focused on evaluating EF deficits in school-aged or older patients. SCA researchers have highlighted the difficulty in ascertaining the extent of earlier executive deficits due to the lack of age-appropriate measures (Schatz & Roberts, 2007; Smith & Schatz, 2016). The available literature for preschoolers and toddlers with SCA without stroke reports lower IQ scores and developmental quotients, and poorer school readiness (Glass et al., 2012; Steen et al., 2002; Tarazi, Grant, Ely, & Barakat, 2007; Thompson et al., 2003).

The lack of focus on EF research in preschool children with SCA is reflected in the literature. To the authors’ knowledge, only three published studies have included children with SCA younger than school age to investigate aspects of EF development. Infants with SCA tested at nine and 12 months (n=14) showed preliminary evidence for a delay in the development of early markers of EF on classical ‘A not B’ and object retrieval tasks (Hogan, Telfer, Kirkham, & de Haan, 2012). Schatz and Roberts (2007) found some evidence for poorer working memory in children with high-risk sickle cell disease (including HbSS) at 12-18 and 32-40 months on a delayed memory task. Using an event-related potential task, it was found that three to five year olds with SCA (n=12) showed neurophysiological differences in attention control (Downes et al., 2017), another early emerging domain of EF (Anderson, 2002).

A performance-based assessment that can inform a targeted intervention is an invaluable resource in the assessment of patients with potential EF deficits (Burgess et al., 2006). Berg and colleagues (2012) observed several differences between school-age children with SCD and a matched comparison group in task performance on an ecologically valid task of executive functioning, which led them to emphasize the importance of performance-based tasks in obtaining a holistic picture of a child’s ability. Ecological performance-based tasks that mirror everyday multi-step tasks provide the opportunity to translate practical individualized recommendations for support into the classroom environment (Downes et al., 2017).

This study investigates whether executive deficits can be observed on an ecological level in preschool-age children with SCA, the most common and, typically, the most severe form of SCD using a newly developed task (Downes et al., 2017). Based on the previous study findings, it is hypothesized that children with SCA will require more support to complete the task and show specific difficulties in organisation and initiating/completing the task. Earlier detection of potential executive deficits on an ecological level could lead to the implementation of earlier targeted scaffolding and support on everyday tasks with the goal of improving school readiness and reducing the achievement gap reported for this patient population (Schatz, 2004; Smith & Schatz, 2016).

**Method**

Patients were informed of the study by their consultant haematologist during their regular clinical visit if they met the following inclusionary criteria; aged between 36 and 72 months, HbSS genotype, no history of stroke or known neurological issues, no history of developmental or psychiatric disorders, full-term delivery, and fluent in English. Twenty-two patients with SCA whose parents identified as Black British and had normal transcranial Doppler readings at their most recent clinical appointment (Mean age 4.8, SD=.94; Mean FSIQ=98.6 (SD=11.4); Mean VIQ=99.9 (SD=12.6); Mean PIQ=97.8 (13.1); 13 males) were recruited at Barts NHS Trust. Inclusionary criteria for the control group were; aged between 36 and 72 months, no history of developmental or psychiatric disorders, full-term delivery, fluent in English, Black British ethnicity, and matched for SES (by postcode). Twenty-four ethnicity, age, gender, and SES matched comparison children (Mean age 4.8, SD=.92; Mean FSIQ=101.5 (SD=11.8); Mean VIQ=103.8 (SD=14.9); Mean PIQ=100.9 (14.9); 10 males) were recruited through the same clinics as the patients (n=13) as well as schools in the same boroughs of East London where the patients reside (n=11). Ethical approval was obtained from the National Health Service and UCL Great Ormond Street Institute of Child Health (Ref: 13/LO/0962). The Preschool Executive Task Assessment (PETA; Downes et al., 2017) and the Wechsler Preschool and Primary Scale (WPPSI-III-UK; Wechsler, 2002) were administered. The WPPSI-III-UK is a standardized IQ measure used to obtain full scale IQ (FSIQ), performance IQ (PIQ), and verbal IQ (VIQ). The PETA is an ecological executive function task developed for preschool children which requires the participant to follow a picture recipe book in order to create a caterpillar from a box of supplied ingredients. The task encapsulates a multistep everyday activity that the child might be expected to do in the classroom and requires the administrator to follow a structured cueing system for scoring each step where a child may require a basic level of cueing (verbal guidance) up to examiner completion. Total Cues (TC) is the number of cues required throughout. Total Score (TS) is the total weighted number of cues the participant obtains with the weight of cue dependent on the level of support that is required at each step. Completion time is the time taken for the child to complete the task. Qualitative scores for Working Memory, Organization, Emotional Lability, and Distractibility are based upon a descriptive guide in the manual. The quantitative domains (Initiation, Sequencing, Meta-Cognition, Judgment/Safety, Completion) are scored based upon number of cues required during specific steps that tap into these abilities. Extended details for PETA administration and scoring can be found in Downes and colleagues (2017).

 The PETA always followed a break after the administration of the core subtests of the WPPSI-III-UK. Raw scores on the PETA were converted to z scores based on the normative data in Downes and colleagues (2017). MANOVA, independent t-tests and chi-square analyses were used to investigate group differences.

**Results and Discussion**

No group differences were observed on the WPPSI-III-UK for full scale IQ, or verbal IQ and performance IQ. A MANOVA that included the quantitative PETA scores (Initiation, Sequencing, Meta-Cognition, Judgment/Safety, Completion) found a significant difference between the patients and the matched controls (F1,45=2.5, p=.05). Inspection of individual quantitative subdomains revealed that the patients performed poorer on the domains of Completion and Sequencing (Table 1). A trend for poorer performance was observed for TC (t(44)=-1.6, p=.11), but not for Completion Time (t(44)=-.50, p=.62). Although non-significant, patients had a higher mean TS and required more cues on average for the Meta-Cognition and Judgment/Safety domains. Chi-square analyses on the qualitative examiner-rated domains (Working Memory, Organization, Emotional Lability, Distractibility) and Highest-Level domain (see Table 2) revealed significant group differences for Distractibility only (X=10.18, p=.002).

 (TABLE 1 HERE)

(TABLE 2 HERE)

It was expected that executive deficits would be observable on an ecological level in children with SCA. Poorer performance was observed across the quantitative subdomains for the patients. Poorer patient scores in the Completion, Sequencing, and Judgment/Safety domains particularly drove this group difference although there was only a trend for poorer performance in the overall TS and TC. In the examiner-reported qualitative subdomains, there were significant differences observed for Distractibility only.

The lack of significant differences in the composite TS and TC scores between the patients and the matched controls indicate that differences in EF in specific domains may not yet translate to easily observable differences in everyday EF at this early developmental stage. The medium effect size for TC indicates that there was a tendency for patients to obtain more cues throughout the task. This means that the patients required more cues to stay on task and the administrator was required to provide more scaffolding through the sequence of steps. Despite the lack of significant group differences on the macro level of the task, there were notable differences in specific quantitative and qualitative domains that were also observed when performance was compared with normative scores.

Significant group differences were observed for Organization, Initiation, and Completion in Berg and colleagues’ (2012) cohort of eight to 12 year olds on the Children’s Kitchen Task Assessment, which uses similar scoring and cueing guidelines. Of these three domains, only significant group differences for the Completion domain were found in the current cohort. Differences in study findings could be due to the differences in task design or could be influenced by a younger and more homogenous population in the current study. Berg and colleagues included children who had a history of neurological morbidity and also included a patient with a different genotype whereas the current study excluded children with other sickle genotypes and children with a known history of neurological morbidity. However, the shared group difference between studies for difficulties in task completion is particularly interesting as it is a component of EF that has not previously been investigated in the sickle cell literature. Similar to the older children in the previous study, the patients in the current study also required more cues to complete the task. Maintaining intentions, or goal-directed behavior, is the management of behavior, including the activation and inhibition of actions, in order to reach goal completion. This skill is often impaired in disorders that affect the frontal lobes (Levine et al., 2000).

The findings of this study build upon previous reports that have called for early neuropsychological assessment in children with SCD before they enter the school system (Glass et al., 2013). Reported group differences on EF domains in the current study are strengthened due to the fact that the groups are matched on a number of factors, reducing the likelihood of spurious differences being uncovered. The importance of recruiting children matched for age, gender, ethnicity, and SES in studies of cognitive and behavioral development is strongly emphasized in the sickle cell literature (Richard & Burlew, 1997) and is a particularly important caution for research concerning EF development. Children with SCA have been described to be at a “double disadvantage” (Hijmans et al., 2011) due to the fact that they are often from a minority group and face socioeconomic disadvantages that have been shown to influence EF development (Noble, Norman, & Farah, 2005; Sarsour et al., 2011). In particular, previous research has shown that PETA performance is related to SES, gender, age and VIQ-all factors that were controlled for in the current study (Downes et al., 2017). Despite strong inter- and intra- rater reliability reported for the PETA, one limitation to be considered in the current study was that the administrator was not blinded to group status which could have biased the qualitative rankings (Downes et al., 2017). Another limitation to be noted is that data is still accumulating for the validity of the PETA domains, however initial published data suggests that performance on the task is linked with proxy-rated executive function on the widely used Behavior Rating Inventory of Executive Function (Gioia, Isquith, Guy, & Kenworthy, 2000).

Children with SCA do not typically receive neuropsychological evaluations as part of their standard of care and there has been a lack of focus on EF development in this patient group in the preschool years despite well-established EF deficits by school age (Schatz, 2004). A future focus on early EF assessment and intervention could improve outcomes for young children with SCA both inside and outside of the classroom (Schatz, Finke, Kellett, & Kramer, 2002). A particular focus on ecological assessment is important in order to identify and address real issues that a young child may encounter when engaging in multi-step classroom activities.

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 **Tables**

**Table 1.** Group comparisons on the quantitative domains of the PETA between the patients, the matched controls, and the London norms (Downes et al., 2017)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable****M (SD) /[Range]**  | **Patient****(n=22)** | **Matched Controls****(n=24)** | **P\* (d)** | **London Mean Norms**  |
| Total Score | 63.18 (48.2) | 47.54 (31.2) | .195 (0.4) | 46.6 (38.3) |
| Total Cues  | 34.32 (18.2) | 26.71 (13.3) | .111 (0.5) | 26.3 (15.8) |
| Completion Time | 16.2 (3.3) | 15.5 (4.7) | .618 (0.2) | 13.96 (3.9) |
| Initiation  | 2.32 (2.7)  | 2.33(2.4)  | .984 | 2.6 0-9 |
| Sequencing  | .82 [0-3] | 1.5 [0-5] | .034 | 1.87 0-7 |
| Meta-cognition  | 5.05 [1-9] | 3.96 [1-9] | .132 | 4.27 0-9 |
| Judgment/Safety  | 1.18 [0-6] | .54 [0-5] | .122 | .43 0-5 |
| Completion | 2.77 [0-7] | 1.21 [0-6] | .003 | 1.1 0-6 |
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\**p*<.05 \*\* *p* <.01 \*\*\* *p* <.005

**Table 2.** Group comparisons on the qualitative domains of the PETA between the patients, the matched controls, and the London norms (Downes et al., 2017)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Variable****Percentage of group (%)** | **Patient** | **Matched** | **P\* (d)** | **London Mean Norms** |
| Working Memory*Poor**Typical**Very Good* | 13.668.218.2 | 4.55045.5 | .123 | 115138 |
| Organization *Poor**Typical**Very Good* | 22.736.440.9 | 27.331.840.9 | .924 | 173845 |
| Emotional Lability*Poor**Typical**Very Good* | 13.668.218.2 | 18.2 54.527.3 | .645 | 66232 |
| Distractibility*Poor**Typical**Very Good* | 27.354.518.2 | 045.554.5 | .002 | 134641 |
| Highest Level of Support *Verbal Guidance**Gestural Guidance**Direct Verbal**Physical Assistance**Examiner Completes* | 013.636.436.413.6 |  020.841.729.28.3 | .825 | 4.919.541.523.211 |
| Self-talk*Yes* | 41.2% | 47.4% | .485 | 48.8% |