Effect of Age, Cerebral Infarcts, Vasculopathy and Haemoglobin on Cognitive Function, in Tanzanian Children with Sickle Cell Anaemia

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Abstract

Background: Developmental difficulties in many cognitive domains are common in children with sickle cell anaemia (SCA). Children with stroke are most affected but delayed or atypical cognitive function has been reported in children with SCA and silent infarcts (SCI), vasculopathy, and normal brain MRI. However, very few studies of cognition have been conducted in Africa, a continent with 75% of the SCA burden. We therefore investigated cognitive profiles in Tanzanian children with SCA and examined the impact of age, SCI, vasculopathy, and haemoglobin concentration (Hb).

Methods: Children aged 6-16 years with and without SCA were eligible for this cross-sectional study. Cognitive assessment was performed using Raven's Matrices, assessing fluid, non-verbal intelligence and subtests from the Wechsler Intelligence Scales for Children (WISC-IV), assessing processing speed (PS), perceptual reasoning (PR), and working memory (WM) as these tests are less culture-bound. Magnetic resonance imaging (MRI) and angiography (MRA) were also completed to assess the presence of SCI and vasculopathy. Hb was collected in both SCA children and their non-SCA siblings.

Results: Seventy-three children with SCA and 71 healthy siblings ($Mean_{ages}$ 11.9, SD=2.8 and 11.1, SD=2.9 years respectively) were recruited. Compared with healthy siblings, children with SCA had lower PS ($Mean_{diff}$ 7.35 points; p=.002). Older children had higher performance scores on all tests in relation to their ages. Lowest cognitive scores were observed on the PS subtest, where patients with SCI (SCI+) had lowest mean values as compared to children with no SCI (SCI-) and healthy siblings (i.e., SCI+ < SCI- < healthy siblings, p=0.028). On post-hoc analysis the difference was between SCI+ and healthy siblings SCI+ < non-SCA siblings (p = 0.015); there was no difference between SCI+ and SCI- patient groups. PS was significantly lower in SCA patients with no vasculopathy as compared to healthy siblings. The mean difference from healthy siblings was -8.352 and -0.752 points for VASC- and VASC+ respectively (p=0.004). There was a significant positive effect of Hb on PSI (p=0.001) in both patients and controls and a trend level significant positive effect of Hb on PR (p=0.050) and WM (p= 0.051).

Conclusion: In this Tanzanian study, cognitive performance was reduced in children with SCA with or without SCI on MRI or vasculopathy. Cognitive performance improved with increasing age. Lower Hb was associated with lower cognitive performance in both patients with SCA and their non-SCA siblings. SCI and vasculopathy do not appear to have an impact on cognitive function.

Introduction

Neurological manifestations of sickle cell anaemia (SCA) include overt stroke, silent cerebral infarction (SCI), and cognitive difficulties.[1] Stroke and SCI occur in 11%[1] and 21-40%[2–4] of children, respectively, and are associated with difficulties in various cognitive domains,[5] including executive function and processing speed.[6–10] In a meta-analysis of studies from African countries, the overall prevalence of overt stroke was 4.2%, along with 10.1% who had increased stroke risk related to conditional and abnormal transcranial Doppler (TCD) velocities.[11] However, on this continent less is known about the prevalence of SCI and the effect of SCI on cognition.

In Tanzanian studies, prevalence of SCI is as high as 27% to 43% in children with normal and non-normal TCD respectively.[12,13] Vasculopathy on MR angiography (MRA) may affect up to 64% of individuals with SCA.[14] The overall prevalence of vasculopathy in children with no prior stroke in a recent Tanzanian study was 18%,[13] with all grades associated with abnormal white matter integrity,[15] but there are few data on the effect of vasculopathy identified on MRA on cognition, although associations with TCD have been observed.[16]

Previous research has demonstrated that children with SCA have lower cognitive functioning compared to non-SCA children in multiple domains including general intelligence (IQ), executive function, and processing speed. Although there are few data comparing developmental trajectories between children with SCA and controls, cognitive difficulties apparently increase with age.[8,17,18] There is evidence that children with SCA and overt stroke experience the most profound cognitive difficulties.[17] However, children with SCA and SCI and those without evidence of infarction on MRI appear to also be at risk of difficulties.[8,17,19–21] In African countries, there is a dearth of research on structural brain abnormalities and cognition in children with SCA, even though 75% of the disease burden is there,[22] due to fewer MRI scanners and other resources to conduct these types of studies. In a previous study in Tanzania,[23] reduced IQ and executive function (Rey-Osterrieth Complex Figure Test) were observed in children with SCA compared to their siblings, but MRI data were not available.

Although research investigating cognitive dysfunction in children with SCA is relatively robust, the aetiology of developmental cognitive difficulties is not well understood. Possible explanations include large vessel disease, which has been associated with overt stroke[24–26] and SCI,[3,27,28] but may independently play a role in cognitive functioning in children with SCA, for example related to focal reduction in cerebral perfusion.[29] Other potential causes include the burden of chronic disease, less access to resources, or subtle pathological changes in the brain associated with disease severity. Studies have also shown that age and sex are significant predictors of cognitive function in this patient group.[8,17,30] Further, some studies have shown that overt stroke, SCI, lower haemoglobin concentration (Hb), higher white cell and platelet counts (thrombocytosis) are also associated with lower performance on cognitive tests in children with SCA.[7,31,32] Hypoxia, resulting from chronic anaemia, may also contribute to cognitive deficits.[19]

Given that cognition remains poorly understood in African patients with SCA, we examined several domains in children with SCA and their non-SCA siblings. To provide the best comparison with previous work, we used non-verbal Wechsler subscales (i.e., processing speed, perceptual reasoning and working memory), alongside the Raven's Progressive Matrices,[33] a non-verbal measure of fluid intelligence which has been used in African children with SCA.[34] No tests are completely culture-free, especially tests in which normative information has been derived from high resource Western populations, but the tests chosen require less culturally bound knowledge and are less reliant on language abilities. Using these tests, we aimed to:

1. Compare cognitive performance and cognitive trajectories between SCA patients and controls.

2. Explore whether presence of SCI, vasculopathy, and/or severe anaemia represent risk factors for cognitive difficulties.

Materials and Methods

Recruitment of Participants

We conducted a cross-sectional hospital-based study at Muhimbili National Hospital in Dar Es Salaam, an urban area in Tanzania with the large Muhimbili sickle cell program cohort of 5300 patients with SCA[35]. All interactions with patients were conducted in Swahili, which is the primary language in the region. Between 1st June 2016 and 30th October 2019, patients were recruited whilst attending a specialised SCA clinic for a study of cerebral infarcts and vasculopathy[13] by Swahili-speaking research assistants. Patients with SCA who met eligibility criteria were selected consecutively from the list of recruited patients. Participants with prior stroke and history of seizures or other chronic illness, e.g. renal or cardiac diseases, were excluded. Healthy siblings of selected patients were invited to complete cognitive assessment and MRI. Cognitive data were collected in both patients and healthy siblings from February to October 2019. Formal ethics approval was obtained from the Muhimbili University of Health and Allied Sciences Institutional Review Board (MUHAS-IRB Ref.2014-11-03/AEC/Vol.IX/32). Individual written consent was obtained from parents/guardians; assent was obtained from participants aged 7 years and above.

Image Acquisition and Classification

MR images were acquired at Muhimbili National Hospital on a 1.5T Philips scanner (Achieva; Philips, Best, the Netherlands) using a 16-channel phased-array head coil. The acquired images included: an axial turbo spin-echo (TSE) T2-weighted sequence (TR/TE of 3,000/120 ms; slice thickness, 5 mm), a coronal TSE T2- weighted sequence (3,000/120 ms; slice thickness, 5 mm), and an axial FLAIR sequence (TR/TE, 6000/120; inversion time, 2000 ms; slice thickness, 5 mm). A time-of-flight MRA sequence with source and maximum intensity projection was acquired for evaluation of vasculopathy. Clinical images were evaluated by two neuroradiologists (MJS and DS) for diagnosis and verification of subject conditions. A time-of-flight MRA with source and maximum intensity projection was also acquired. Images were evaluated by two Neuroradiology experts (MJ and DS) for identification of SCI and grading of vasculopathy. In the case of any disagreements, the final diagnosis was reached by consensus.

The SCI definition developed for the Silent Infarct Transfusion Trial (SITT) was used: a lesion measuring at least 3mm in greatest linear dimension, visible in at least 2 planes on T2-

weighted and FLAIR images.[36] Participants with and with no SCI were grouped as SCI+ and SCI- respectively. Vasculopathy on MRA was graded according to severity of signal loss 0 (none [normal]); 1 (minor signal attenuation – mild vasculopathy); 2 (obvious signal attenuation, but presence of distal flow - moderate vasculopathy); 3 (signal loss and no distal flow- severe vasculopathy).[13,14] We determined vasculopathy as the worst recorded in any vessel. Participants with and with no vasculopathy were grouped as VASC+ and VASC- respectively.

Cognitive assessment

One of two trained psychologists (M.K and R.M) administered the cognitive testing in a quiet room in the child and adolescent psychiatric unit at the hospital on days that the clinic was not held so as to avoid disruptions and school absences. During the testing parents or guardians were allowed to stay in the room as observers. Tests were administered in the Swahili language and patients were allowed to go for breaks when required. For example, for the Letter Number Sequencing subtest, the Latin alphabet was used (A, B, C), with numbers in Swahili (e.g., Moja, mbili, tatu). Swahili number translations were also used for the Digit Span subtest. The assessment lasted between 2 and 3 hours. Tests were administered and double scored by trained psychologists (R.J.M and D.K) who were blinded to disease status. In the event of disagreement, the opinion of a third assessor (M.K) was sought.

Participants were examined using the Wechsler Intelligence Scale for Children ® - Fourth UK Edition (WISC-IV) for children ages 6 to 16 years. We assessed three non-verbal domains from the WISC-IV using tests that are less dependent on cultural context: 1) the Processing Speed Index (**PSI**) assessed using Coding and Symbol Search subtests; 2) the Perceptual Reasoning Index (**PRI**) assessed using the Block Design, Picture Concepts and Matrix Reasoning subtests; and 3) the Working Memory Index (**WMI**) assessed using the Digit Span, and Letter-Number Sequence subtests. Normative scores were based on the WISC-IV US standardisation sample (WISC-IV^{US}) and were used in analyses.

Fluid intelligence was assessed using the Raven's Standard Progressive Matrices (RSPM),[33] a widely used intelligence test for typically developing (TD) children as well as for children with neurodevelopmental conditions. RSPM has previously been used in research with

children in Nigeria[30] and sub-Saharan Africa,[37] including those with SCA.[34] The trials are arranged in progressively increases of difficulty. Raw scores were used in analyses.

Demographic and clinical questionnaires were used to interview the families of all participants. Haemoglobin was obtained at time of recruitment and isoelectric focusing was used to screen siblings for sickle cell disease.

Data analyses

The statistical package for social science (SPSS) version 25 (IBM Corp, Armonk, NY) was used for data analyses. Shapiro-Wilk tests were used to assess variables for significant deviations from a normal distribution. Continuous variables were compared using two-sided Student's *t*-tests. Categorical variables were compared using a χ^2 test or Fisher's exact test.

Analyses of variance (ANOVA) were also used to compare demographics and cognition between non-SCA siblings and two patient groups : i) patients without SCI (SCI-) and those with SCI (SCI+), ii) patients without vasculopathy (VASC-) and those with vasculopathy (VASC+). Across all analyses, *P* values of <0.05 was considered statistically significant.

Analyses of covariance (ANCOVA) were conducted to examine children's performances on cognitive tasks with chronological age as the predictor to compare TD control siblings and children with SCA. Data on cognitive tasks (dependent variable) and chronological age (CA; independent variable) were used to plot cross sectional developmental trajectories for both groups.

Results

Participants

One hundred and forty-four participants aged 6-16 years of age agreed to participate in the present study and underwent cognitive testing. Of these participants, there were 73 patients with SCA (69 from previous MRI study, 2 siblings who were diagnosed at the time of screening and 2 SCA patients who did not have MRI data) ($Mean_{age}$ 11.9, SD=2.8 years) and 71 non-SCA siblings ($Mean_{age}$ 11.1, SD=2.9 years). Twenty-nine had been admitted with a painful crisis and six with fever, but none had had a documented chest crisis. None of the children with SCA were prescribed hydroxyurea. Sixty-nine patients with SCA and 39 non-

SCA siblings controls had MRI/MRA. None of the non-SCA siblings had SCI or vasculopathy. There were no extreme outliers for cognitive function scores (Figure 1).

There were no significant differences between patients with SCA with and without MRI data in regards to age, sex, baseline haemoglobin or cognition (i.e., PSI, PRI, and WMI). A trend level significance was observed for Raven's matrices (p=0.05). There was also no difference between non-SCA-siblings with and without MRI data with regards to age, sex, baseline haemoglobin or cognition (i.e., Raven's matrices, PSI, PRI, and WMI. There were no differences in any of the cognitive tests between those with normal haemoglobin (HbAA) and those with sickle cell trait (HbAS).

MRI/MRA

On MRI, 21/69 (30.4%) patients with SCA and 2/41 non-SCA siblings (4.8%) had SCI, and 9/69 (13%) patients with SCA had vasculopathy. Among patients with vasculopathy, 4 (5.8%) had grade 1 (mild vasculopathy) and 5 (7.2%) had grade 2 (moderate vasculopathy). None of the sibling controls had vasculopathy. There were no differences in age between non-SCA siblings and patients with SCA overall or when stratified by SCI and vasculopathy status, but patients with SCA had lower mean haemoglobin concentration (Table 1).

Cognitive Profiles

Compared with their TD siblings, patients with SCA had lower PSI (mean difference 7.35 points; *p*=.002) and there was a trend for a lower WMI (mean difference 4.15 points; *p*=.089). There were no significant differences in performance between patients with SCA and siblings for the Raven's or for PRI (Table 2).

Age-related changes in cognitive profiles

ANCOVA analyses demonstrated significant developmental change for all cognitive tasks and in both groups. Older children with and without SCA performed better on all cognitive tests than younger children with and without SCA. Of these cognitive tests, significant group differences were observed for Coding and Cancellation subtests, which are measures of processing speed (Figure 3).

Raven's Progressive Matrices (RSPM) Raw scores were significantly related to chronological age (CA) in both groups, with performance scores improving with age (TD siblings: $F(1, 69) = 35.079$, $p < .001$, $R^2 = .34$,; SCA: $F(1, 71) = 10.265$, $p = .002$, $R^2 = .13$). No significant group difference in developmental changes was found ($F(1,141) = 1.973$, $p = .162$, $\eta^2 = .014$) (Figure 2A).

Block Design subtest. Block Design raw scores were significantly related to chronological age in both groups (TD sibs, $F(1, 69) = 51.033$, $p < .001$, $R^2 = .43$,; SCD:, $F(1, 71) = 23.817$, $p < .001$, $R^2 = .14$), with performance scores improving with age. Older children had higher Block Design raw scores than younger children in both groups and no significant group difference in developmental changes was found ($F(1,141) = .229$, $p = .633$, $\eta^2 = .002$) (Figure 2B).

Digit Span subtest. Digit Span raw scores were significantly related to CA in both groups (Control group sibs:, $F(1, 69) = 33.400$, $p < .001$ $R^2 = .33$,; SCD:, $F(1, 71) = 14.196$, $p < .001$, $R^2 = .17$), with performance scores improving with age. Older children had higher Digit Span raw scores than younger children and there was no significant group difference in developmental changes ($F(1,141) = .223$, $p = .637$, $\eta^2 = .002$) (Figure 2C).

Picture Concept subtest. Picture Concept raw scores were significantly related to CA in both groups (Control group sibs: $F(1, 69) = 33.254$, $p < .001$, $R^2 = .33$,; SCD: $F(1, 71) = 23.754$, $p < .001$, $R^2 = .25$), with performance scores improving with age. Older children had higher Picture Concept raw scores than younger children. No significant group difference in developmental changes was found ($F(1,141) = .112$, $p = .739$, $\eta^2 = .001$) (Figure 3A).

Coding subtest. Coding raw scores were significantly related to CA in both groups (Control group sibs: $F(1, 69) = 13.521$, $p < .001$ $R^2 = .16$,; SCD: $F(1, 71) = 13.768$, $p < .001$, $R^2 = .16$) with performance scores improving with age. Although children in the SCA group showed improvement in performance in relation to age, it was significantly at a slower rate showing a significant group difference with the TD sibling group ($F(1,141) = 8.811$, $p = .004$, $\eta^2 = .059$) (Figure 3 B).

Symbol Search subtest. Symbol Search raw scores were significantly related to CA in both groups (Control group sibs: $F(1, 68) = 33.514$, $p < .001$ $R^2 = .33$,; SCD: $F(1, 71) = 11.706$, $p = .001$, $R^2 = .25$,). Older children with and without SCD had higher Symbol Search raw scores than younger children with and without SCD. No significant group difference in developmental changes was found ($F(1,140) = 3.126$, $p = .079$, $\eta^2 = .022$) (Figure 3C).

Cancellation subtest. Cancellation raw scores were significantly related to CA in both groups (Control group sibs: $F(1, 69) = 36.583$, $p < .001$ $R^2 = .35$,; SCD: $F(1, 70) = 29.189$, $p < .001$, $R^2 = .29$). A significant group difference in developmental changes was found ($F(1,140) = 6.816$, $p = .010$, $\eta^2 = .046$); while younger children in both groups had similar scores, there was a slower rate of improvement in older children with SCA (Figure 3D).

Comparison of cognitive function related to SCI and vasculopathy status

ANOVA revealed that patients without SCI and with SCI had lower PSI when compared with non-SCA siblings (Figure 4). Generally there was a significant difference in PSI when the three groups where compared, that is non-SCA, patients with no SCI (SCI-) and patients with SCI (SCI+). The mean difference from healthy siblings was -4.303 points for SCI- and -9.377 SCI+ patients' groups ($p = .028$). On post hoc analysis the significant difference was between SCI+ <non-SCA siblings (P = 0.015). There was no difference between SCI- and SCI+ patients groups. Lower scores for Ravens (p =.710), PSI (p=.118) and WM (p=.111) were also observed in SCI- and SCI+ patient groups, with SCI+ having the lowest scores. However, none of these observed differences were statistically significant (Table 3). The same trend was observed when comparing patients with vasculopathy, patients without vasculopathy and non-SCA siblings. We found a significant difference for PSI, with the mean difference from non-SCA siblings at -8.35 and -0.75 points for patients with no vasculopathy (VASC-) and patients with vasculopathy (VASC+) respectively ($p = 0.004$). There was also a difference in Raven's ($p= .60$), PR ($p = .26$) and WM ($p = .26$), but it did not reach statistical significance (Table 4). There was no difference between VASC- and VASC+ patient groups.

Haemoglobin concentration and cognitive function

In patients and non-SCA siblings, after correcting for the effects of age, sex and SCI, there was no effect of haemoglobin on Raven's, PSI, PRI or WMI, but a significant positive effect of Hb on PSI was observed after removing sex and SCI from the model (Table 5, Figure 5A). An identical analysis was performed in a sub-set comprised of patients with SCA only (n=73); there was no significant effect of haemoglobin on Raven's but a significant positive effect of haemoglobin on PSI was observed after removing sex and SCI from the model (p= 0.001). Additionally, there was a significant positive effect of haemoglobin on PRI (p = 0.05) (Figure 5B) and a trend level positive effect on WMI (p = 0.05) (Table 5).

Discussion

The current study sought to examine cognitive profiles using cross sectional trajectories in Tanzanian children with SCA and their non-SCA siblings and explored potential risk factors for difficulties. Children with SCA showed lower performance when compared with non-SCA sibling controls on tests of PSI, PRI, and WMI. Performance on the Raven's as well as the WISC-IV subtests including Block Design, Picture Concept, Coding, Symbol Search, and Cancellation were assessed cross-sectionally with raw scores to investigate the effect of age.

Previous studies have consistently shown that deficits in cognitive function in children with SCA increase with age.[8,30, 38] We found that, as expected scores for older children were better than younger children, but rates of improvement were slower in patients with SCA for the Coding and Cancellation subtests compared to non-SCA sibling controls. Our findings on the effect of age on cognition differ from the reports of previous studies where they observed a decline in cognitive functioning with increasing age.[8,]. We cannot ascertain here if this represents a slower rate of improvement on the task or a premature plateauing of the trajectory, but future longitudinal studies would allow this to be addressed. Both disease progression and systematically withheld social and environmental resources may affect cognitive development in patients with SCA.[8,17,21,40]

Overall, as in prior studies,[8,10,19,23] the findings indicate poorer cognitive performance in children with SCA compared to controls. The observed pattern, with patients particularly at risk for difficulties with processing speed, is also consistent with that of previous studies.[41,38] However, most often these studies do not compare cognition to siblings and even more rarely are these analyses conducted in patients with SCA from African countries, a region with the largest SCA burden. Previous studies conducted in Tanzania[23], Nigeria[38] and Cameroon[42] have reported no differences in working memory between patients with SCA and non-SCA siblings.

Silent cerebral infarctions, one of the most common neurological complications in children with SCA, have been linked to cognitive impairment in various studies in the USA and Europe.[10,19,20,43,44,45] In our study, there were no significant differences in cognition between patients with and without SCI or vasculopathy, but scores were lower in patients with these pathologies on some subtests. Our observations are contrary to studies which have reported that

children with evidence of SCI on MRI have lower IQ scores than children without evidence of SCI.[8,17]A meta-analysis by Kawadler et al[17] on the effect of SCI on full-scale IQ (FSIQ) found that children with SCA and SCI scored significantly lower than children with SCA without SCI, although both groups scored significantly lower than the normative mean and sibling controls.[17,40] The current study did not look at FSIQ, but a previous study in Tanzanian children with SCA showed similar findings when comparing IQ between patients with SCA and non-SCA sibling controls, although they did not have MRI data.[23] Adult studies have reported no difference between patients with SCA and brain abnormalities, including lacunar/white matter hyperintensities/SCI and patients with normal brain on MRI across domains.[46] Further longitudinal studies are justified

There have been no studies on the effect on vasculopathy detected on MRA on cognition in patients with SCA, although it is well known that vasculopathy is associated with overt stroke[24,25] and SCI.[27,28,47] In our study, there were no significant differences in cognitive performance between patients with and without vasculopathy. Moreover, children with SCA with no vasculopathy had lower PS than children with vasculopathy and healthy siblings controls, indicating that vasculopathy may not represent a major risk factor for reduced cognitive performance in this patient group. However, this could in part also be due to the lower prevalence of vasculopathy in our study, where the overall prevalence was 14.5%, and only 4 and 5 patients had mild (grade 1) and moderate (grade 2) vasculopathy respectively. Severe vasculopathy (vessel occlusion) which can be associated with severe restriction of blood flow leading to cerebral hypoperfusion and potentially causing cognitive impairment[48] was not observed in the current study.

In our study, patients with SCA had a significantly lower mean haemoglobin (7.5; SD 1.51) g/dL as compared to non-SCA sibling controls (12.09, SD, 1.05 g/dL). Interestingly, we observed a significant positive effect of haemoglobin on PSI in both SCA and non-SCA individuals. A significant positive effect of Hb on PSI and PRI was also observed in a subset comprised of SCA patients only. Lower haemoglobin or lower haematocrit has been associated with hypoxaemia which might lead to diffuse cerebral microstructural injury[19,49]and impaired cognition.[41]

Limitations

Although nonverbal tests were used for cognitive assessment, some cultural factors may have contributed to the results observed. This is one of the larger studies to include controls as well as patients with SCA, but we may have been underpowered to detect effects of the MRI variables in the multivariable analyses, particularly for vasculopathy. As there are relatively few data on cognition in SCA from Africa, we included some children who had not had an MRI; there were no demographic or cognitive differences between those with and without MRI but more neuroimaging data would be needed to determine the relative importance of lesions detectable by MRI on cognition. The cognitive profiles were examined using cross sectional raw score data rather than scaled data as we were interested in the developmental trajectory. In addition, there are few normative data from countries outside Europe and the USA and scaling may not be appropriate outside the setting in which the data were acquired. Another limitation is that we did not include educational background or attainment in this study. This was a cross sectional study; longitudinal studies are needed to establish any causal association relationship between developmental trajectories and other factors while multicentre studies will needed for generalisation of findings to African countries.

Strengths

The current study design included comparison of children with SCA with their siblings acting as a control group. This comparison may potentially reduce cofounding effects such as exposure to different schooling, parenting styles, diet and SES status of a family which it may be difficult to eliminate or control for.

Conclusions

The current study supports findings from previous studies showing that children with SCA have cognitive difficulties compared with controls. As with data collected in the USA and UK, the domain of processing speed appears to be particularly vulnerable in Tanzanian children with SCA despite different cultural contexts. Although cross-sectional data indicates that cognitive performance improves with age through childhood and adolescence, the rate of improvement

appears to be slower in patients with SCA compared to non-SCA sibling controls, particularly in the processing speed domain. SCI and vasculopathy were not associated with cognitive deficits in this study. Haemoglobin was significantly positively associated with cognitive function. Further work is required to explore the causes of cognitive profiles in this patient group. Studies examining microstructural brain integrity and cognitive functioning alongside access to socioeconomic- and environmental- resources in African children would be informative.

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Table 1. Demographic, MRI/ MRA characteristics of the study participants

	All controls (n=71)	**All patients with Sickle Cell Anaemia (n=73)**	**Control with MRI (n=39)**	**SCI- (n=48)**	**SCI+ (n=21)**
Age in years Mean (SD)	11.1 (2.9,)	11.9 (2.9)	11.1 (2.9)	12.0 (2.8)	12.4 (2.7)
Sex	42M, 29F	41M, 32F	22M, 17F	26M, 22F	12M, 9F
Haemoglobin g/dL),mean (SD)	12.1 (1.0)[a***]	7.5 (1.3)[b***]	12.0 (1.1)[c***]	7.5 (1.4)[d***]	7.6 (1.3)[e***]
			Control with MRA (n=39)	**VASC- (n=60)**	**VASC+ (n=9)**
Age in years Mean (SD)			11.1 (2.9)	12.0 (2.7)	12.5 (3.0)
Sex			22M, 17F	34M, 26F	4M, 5F
Haemoglobin g/dL, mean (SD)			12.0 (1.1)[f***]	7.6 (1.3)[g***]	7.1 (1.3)[h***]

SCI- (no silent cerebral infarction), SCI+: presence of SCI, VASC-: no vasculopathy, VASC+: presence of vasculopathy grade 1 or 2, [a]n=58, [b]n=73

[c]n=38 controls; [d]n=48 SCI-, [e]n=21 SCI+, [f]n=38 controls, [g]n= 60 VASC-, [h]n= 9 VASC+

***, p <0.001

Table 2. Cognitive functioning among patients with sickle cell anaemia (n=73) and healthy controls (n = 71)

	Mean difference	95% confidence intervals	t	P	Effect size
Raven's	0.482	-1.951 to 2.915	.392	.696	.067
Processing Speed Index	7.352	2.673 to 12.031	3.106	.002	.517
Perceptual Reasoning Index	2.957	-0.650 to 6.563	1.620	.142	.271
Working memory index	4.149	-0.640 to 8.938	1.713	.089	.285

Table 3 Cognitive function differences in controls and SCI +/-

Mean (SD)	Mean difference from controls		ANOVA F	*P*	*Post-hoc (Dunnett's)*
	SCI- (n=48)	SCI+ (n=21)			
Raven's	0.388	-1.211	0.344	.710	
PSI	**-4.303**	**-9.303**	**3.690**	**.028**	**SCI+<Control**
PRI	**-1.77**	**-5.677**	**2.175**	**.118**	
WMI	**-1.819**	**-7.420**	**2.235**	**.111**	

PSI Processing Speed Index, PRI Perceptual Reasoning Index, WMI Working memory index.

The Patient group was compared to controls with MRI data (n=39)

Table 4. Cognitive function differences in controls and VASC+/-

Mean (SD)	Mean difference from controls		ANOVA F	*P*	*Post-hoc (Dunnett's)*
	VASC- (n=60)	VASC+ (n=9)			
Raven's	0.273	-2.292	0.517	.597	
PSI	-8.352	-0.752	5.696	.004	VASC- <Control
PRI	-2.712	-4.415	1.345	.264	
WMI	-3.554	-3.344	1.071	.346	

PSI Processing Speed Index PRI Perceptual Reasoning Index WMI Working memory index

The patient group was compared to controls with MRA data (n=39)

.

Table 5: Regression Results for effect of Haemoglobin on cognitive function in patients and non_SCA_siblings

	Standardized Coefficients B-values	95% CI		p
Ravens (n=144)				
Age	.490	-2.407	-.737	<.001
Male sex	.149	-7.228	2.093	.277
Haemoglobin at time of MRI (g/L)	.103	-.840	1.925	.438
SCI	-.103	-6.597	2.889	.440
Processing speed (PSI) (n=144)				
Age	-.340	-2.407	-.737	<.001
Male sex	-.098	-7.228	2.093	.277
Haemoglobin at time of MRI (g/L)	.103	-.840	1.925	.438
SCI	-.103	-6.597	2.889	.440
After exluding Male sex and SCI				
Age	-.309	-2.368	-.761	<.001
Haemoglobin at time of MRI (g/L)	.274	.660	2.471	.001
Perceptual reasoning (PRI) (n=144)				
Age	.107	-1.547	-.069	.032
Male sex	.199	.292	8.540	.036
Haemoglobin at time of MRI (g/L)	.107	-.746	1.700	.441
SCI	-.020	-4.498	3.894	.887
Working memory (WM) (n=144)				
Age	-.036	-1.157	.799	.717
Male sex	-.010	-5.754	5.162	.915
Haemoglobin at time of MRI (g/L)	.106	-1.017	2.220	.463
SCI	-.089	-7.273	3.834	.540

Figures

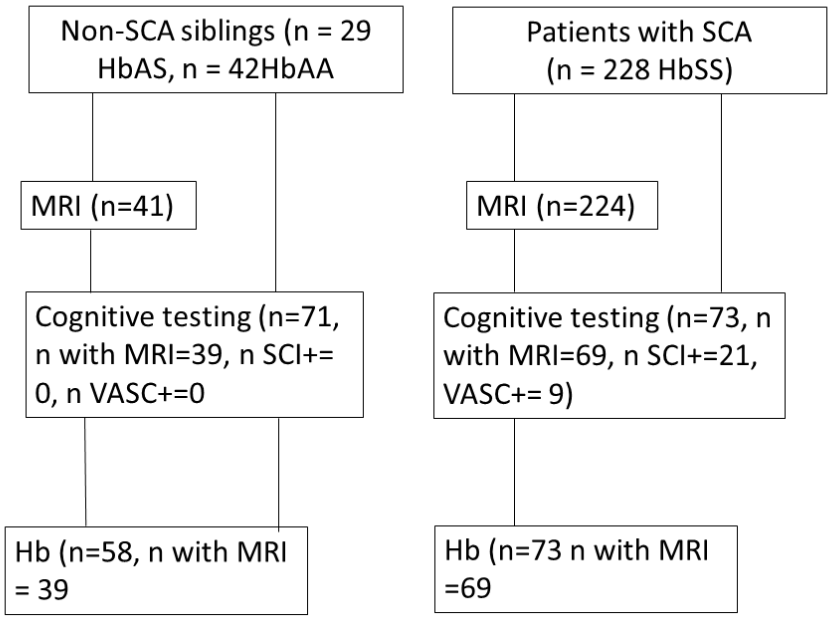

Figure 1. Study Flow Diagram

Study flow diagram showing total number of recruited SCA patients and Non-SCA siblings who underwent cognitive assessment and MRI/MRA investigation.

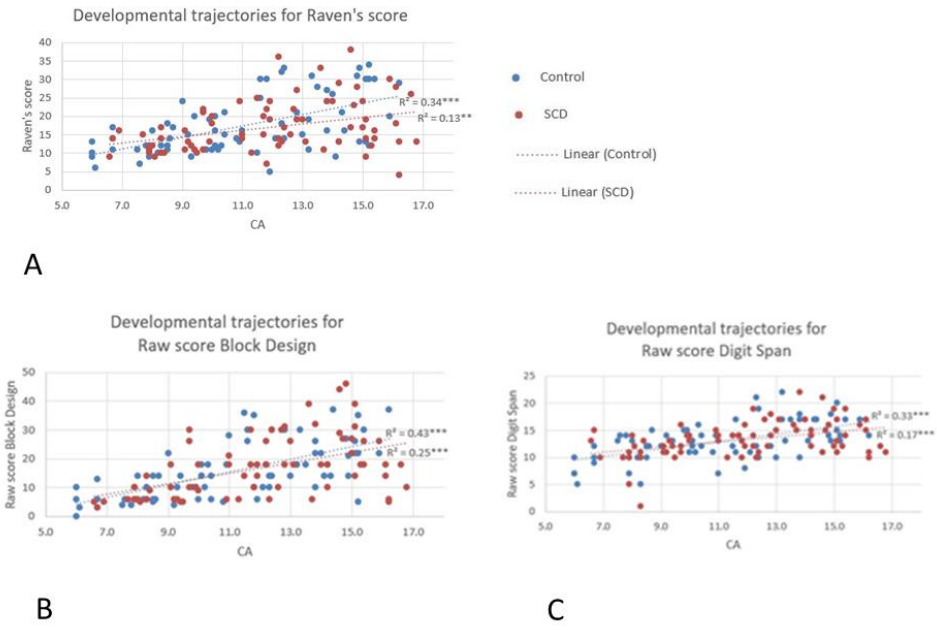

Figure 2. Developmental trajectories for performance on cognitive tasks in SCA and non-SCA groups. Significant positive effect of age was observed on A; Raven's, B; block design, C; Digit span.

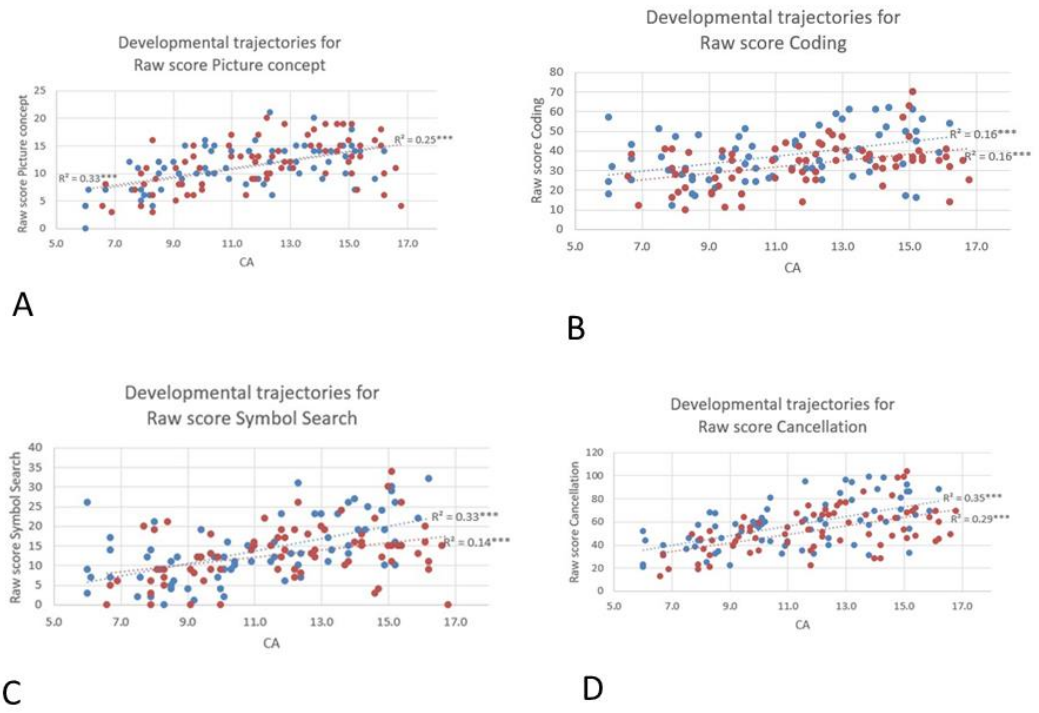

Figure 3. Developmental trajectories for performance on cognitive tasks in SCA and non_SCA groups. Significant positive effect of age was observed on A; picture concept, B; coding, C; symbol search, D; cancellation

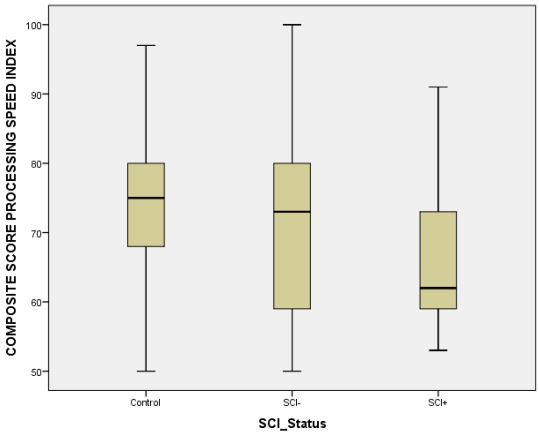

Figure 4. Boxplot showing processing speed index (PSI) across controls and patients with (SCI+) and without (SCI-) silent cerebral infarction.

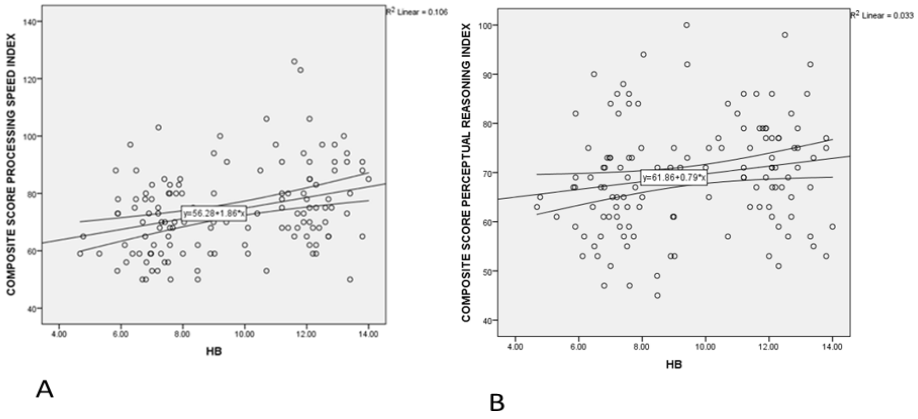

Figure 5. Relationship between Haemoglobin, processing speed index (PSI) and Perceptual Reasoning Index (PRI). A scatter diagram with the regression line and 95% confidence intervals showing a positive effect of Haemoglobin on PSI (A) and PRI (B)