

ORIGINAL PAPER

A case-control and seven-year longitudinal neurocognitive study of adults with sickle cell disease in Ghana

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Funding information

National Heart, Lung, and Blood Institute, Grant/Award Number: K23 HL135396; National Institute of Mental Health; Patient-Centered Outcomes Research Institute

Summary

Ageing in sickle cell disease (SCD) is associated with a myriad of end-organ complications, including cerebrovascular damage and cognitive impairment (CI). Although CI is very common in SCD, little is known about cognitive functioning and how it changes with age. This study examines cognitive patterns of 63 adults with SCD and 60 non-SCD, age- and education-matched controls in Ghana. Of those adults with SCD, 34 completed the neuropsychological battery at baseline and again seven years later. In cross-sectional data, adults with SCD performed worse than controls in all cognitive test domains ($p < 0.01$ for all). The seven-year follow-up data showed that the group exhibited a significant decline in visuospatial abilities (ranging from Cohen's $d = 1.40$ to 2.38), and to a lesser extent, in processing speed and executive functioning. Exploratory analyses showed a significant time-by-education interaction, indicating that education may be protective from decline in cognitive performance. These findings have implications for clinical practice. Early neuropsychological surveillance coupled with early assessment and remedial programmes will provide avenues for enhancing the quality of life of adults living with SCD in Ghana.

KEYWORDS

cognitive functioning, longitudinal studies, neurocognitive test, psychology, psychosocial, sickle cell disease

INTRODUCTION

Sickle cell disease (SCD), an inherited blood disorder that is the most common genetic disorder worldwide, primarily affects

people of African descent.^{1–3} The SCD genetic polymorphism produces mutant haemoglobin molecules that polymerize within the erythrocyte during deoxygenation, resulting in sustained haemolytic anaemia and painful vaso-occlusive

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events.⁴ As individuals with SCD begin to live into adulthood, the chronic impact of sustained haemolytic anaemia and episodic vaso-occlusive events takes its toll, not only contributing to chronic pain but also accelerating the ageing process and risk for damage to organs,⁵ including the brain.

Declining brain health and cognitive impairment are major complications of sickle cell disease

Due to tissue hypoxia⁶ and rapidly progressive vasculopathy,^{7,8} ageing adults with SCD are likely to exhibit declining brain health, especially accelerated brain atrophy⁹ and cerebral microvascular disease.^{10,11} The most visible and disruptive manifestation of deteriorating brain health is cognitive impairment (CI).¹² Studies have demonstrated a high prevalence of CI among individuals with SCD as compared to their healthy counterparts,¹³ and it is well recognized that CI can occur in asymptomatic SCD patients with no history of stroke or other overt haematological complications.^{14,15} Some data suggest that even children will experience an increase in cognitive deficits with age.¹⁶ It is critically important to understand and address neuropsychological functioning in the ageing SCD population, because cognitive difficulties among individuals with SCD¹⁷ can interfere with medication management, communication, comprehension, capacity to live independently and ability to remain gainfully employed.¹⁸

Despite the recognition that people with SCD are now more likely to live into adulthood — a benefit of improved screening for risk factors, routine clinical care and evidence-based therapies^{7,19,20} — there are still limited data examining cognitive functioning among adults with SCD and progression of impairment over time. Most of the existing data in the United States, Europe and African countries are limited to children. The existing data suggest that SCD is associated with global cognitive dysfunction leading to deficits in several cognitive domains including executive functioning,¹³ while some studies suggest deficits may be limited to processing speed.^{17,21} Further, it is not clear what factors are predictive of poor neurocognitive functioning and decline in SCD. Although current data would suggest that low haemoglobin level and disease severity may be risk factors for poor neurocognitive outcomes,^{13,22} because these data are cross-sectional, it remains unclear whether disease severity actually has an impact on progression of CI, or whether it indirectly impacts cognitive function via early-life factors such as disrupted educational attainment.

A majority of SCD-related cognitive studies are conducted in the United States although a majority of people with SCD do not live there. We need more studies exploring neurocognitive functioning in African countries, where most people affected by SCD live. Ghana is the country with the second-highest prevalence of SCD in West Africa. Nearly 2% of all Ghanaian children born every year have SCD and about 25%–30% of the population have the sickle cell

trait.²³ Currently, the Adult Sickle Cell Clinic located at the Korle-Bu Teaching Hospital, Accra, Ghana (KBTH), has a SCD population estimated to be 26 000, including both children and adults (Adult Sickle Cell Clinic, Korle-Bu Records, 2017). Adults with SCD in Ghana do not have ready access to evidence-based disease-modifying interventions such as hydroxyurea (hydroxycarbamide) and exchange transfusions; thus, this population may be at particularly high risk for poor brain outcomes and other disease complications.

The objective of the current study was to understand patterns of neurocognitive functioning among adults with SCD in Ghana. First, in cross-sectional data, we compared the cognitive function of adults with SCD to non-SCD age- and sex-matched controls. This baseline control group is particularly important given the lack of studies validating the use of neurocognitive tests in West Africa or scaled norms for this population. Second, in the SCD group only, we repeated neurocognitive testing seven years later to assess changes in cognitive functioning. We also investigated the relationship between cognitive functioning in SCD and known demographic and clinical risk factors, that is, haemoglobin level,^{13,17} SCD genotype,²² and education.²⁴

METHODS

Participants

Adults 18 years of age and older with SCD (homozygous sickle cell anaemia [HbSS] or sickle haemoglobin C disease [HbSC]) and at least five years of education or more, were recruited from a national adult sickle cell clinic at a teaching hospital in Ghana. The non-SCD control group participants were recruited from the Korle-Bu Polyclinic and the Sickle Cell Clinic at KBTH. They were significant others or caregivers of sickle cell patients who accompanied patients to the clinic or people who visited or worked in KBTH and had HbAA genotype or heterozygosity for haemoglobin S (HbAS) or haemoglobin C (HbAC). Attempts were made to identify age- and sex-matched non-SCD participants of equivalent education.

Procedure

This study was conducted from May–June 2011 until December 2018–March 2019 and was approved by the the Ethical and Protocol Review Committee of the College of Health Sciences, Korle-Bu Campus (EPRC), Ethics Committee for Humanities (ECH) University of Ghana, Legon (ECH 143/17–18) and the Protocol and Ethical Review Committee of KBTH (KBTH-IRB/00075/2018). The protocol was explained to interested and eligible patients. Enrolled participants provided informed consent and demographic data including gender, age, education, employment status and SCD-related complications. In addition to demographic data, for the SCD group we documented medical complications that may relate to

cognitive outcomes, including history of stroke (overt and silent) and transient ischaemic attack (TIA), and any other medical complications associated with SCD. This was followed by the administration of the neurocognitive test battery described below and in Table S1. The SCD group was retested with the same battery of cognitive tests about seven years later.

The set of tests was selected in order to both assess a wide range of cognitive domains and to compare data to other studies, while also limiting the length of time and difficulty of administration. The following tests were administered in English by a masters-level clinical psychologist and two trained undergraduate psychology students (Table S1): measures of global cognitive functioning [Revised Quick Cognitive Screening Test (RQCST)],²⁵ processing speed and executive functioning tests (Trails A and B),^{26–28} the Modified Card-Sorting Test (MCST),^{29–31} the Digit Symbol Substitution Test (DSST),^{32,33} motor skills (Grooved Pegboard),^{34,35} memory [Recognition Memory Test (RMT)],^{36,37} visuospatial skills [Rey–Osterrieth Complex Figure Test (ROCF)],^{38,39} the Wide Range Achievement Test (WRAT-4),^{40–42} and the Cognitive Failures Questionnaire (CFQ).⁴³ Participants were given periodic breaks to reduce fatigue.

Data analysis

Cross-sectional differences by group

Independent *t*-tests were used to compare demographic characteristics between adult SCD patients and adult non-SCD controls. We then used ANCOVA to test group differences on cognitive test scores at baseline. All models included sex, age and education as covariates and group scores are reported as estimated marginal means adjusted for covariates. We used the Bonferroni procedure to correct for multiple comparisons.^{44,45}

Longitudinal changes in functioning

Independent *t*-tests were used to compare demographic and clinical characteristics between those who were retested at seven years and those who were lost to follow-up. Repeated-measures ANCOVA tested within-subject changes in the cognitive test scores over the seven-year follow-up period. In exploratory analyses, for each cognitive outcome we tested, in separate models, the main effect and interaction with time for haemoglobin level, SCD genotype and education. No corrections for multiple tests were applied for the exploratory analyses. For this study, a meaningful cognitive deficit or change in performance for a given subtest is considered as a 0.5 standard deviation or greater change or difference between groups.⁴⁶

Principal components analysis (PCA) with oblique rotation was utilized to confirm the neurocognitive measures

examining each construct or domain for the present study. IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA) was used for all data analysis.

RESULTS

Participants

A total of 123 adults participated in the study, 63 adults with SCD (mean age = 29.4, range = 18–50 years) and 60 non-SCD adults (mean age = 33.5, range = 18–57 years). The sickle cell patients included 47 with HbSS and 16 with HbSC genotype. Among the non-SCD group, 12 had sickle cell trait (HbAS), one had HbAC and 47 had the normal HbAA genotype. Table 1 presents the demographic characteristics of both groups. There were no age or gender differences between the two groups; however, the non-SCD control group had a slightly higher education level and were more likely to be current students than the SCD group.

Cognitive test scores for SCD patients versus controls

The baseline cognitive test scores for the adults with SCD and the non-SCD comparison group are presented in Tables 2 and 3 for raw and scaled scores respectively. When controlling for age, gender and education, the SCD group scored worse, with lower raw and scaled scores and Card-Sorting categories, more perseverations on the Card-Sorting, and longer times for the Trail-Making and Grooved Pegboard tests (psychomotor speed) than the non-SCD comparison group on all cognitive tests except for the Recognition Memory for Faces (RMF). Despite the consistently lower scores on neurocognitive tests, compared to the non-SCD counterparts, the SCD patient group did not report a higher daily rate of cognitive failures on the CFQ self-report measure ($p = 0.28$).

Seven-year follow-up drop-out

All SCD patients were re-approached seven years later to complete the same battery of neuropsychological tests as was completed at baseline. Of the 63 eligible participants, 34 adults with SCD completed follow-up testing (Table 1). A total of 26 participants were lost to follow-up due to death (24%, $n = 7$), migration to other countries (7%, $n = 2$), unavailability due to tight work schedules or other obligations (14%, $n = 4$) and inactive phone numbers (50%, $n = 13$) (Table 1). Three additional participants did not complete sufficient testing at follow-up to be included. Independent-sample *t*-tests and chi-square analyses to investigate differences in level or changes in socio-demographic and illness-related variables of

TABLE 1 Demographic and clinical characteristics for $n = 63$ adults with sickle cell disease (SCD) and $n = 60$ adult controls without SCD from Ghana

	Controls in cross-sectional study			SCD patients in cross-sectional study			Longitudinal SCD study			
							Participants $n = 34$		Non-participants $n = 29$	
	HbAA $n = 47$	HbAS or HbAC $n = 13$	All controls $n = 60$	HbSS $n = 47$	HbSC $n = 16$	All SCD patients ($n = 63$)	HbSS $n = 24$	HbSC $n = 10$	HbSS $n = 23$	HbSC $n = 6$
Age (years) M (SD)	23.9 (5.6)	24.9 (4.9)	24.1 (5.5)	27.7 (6.6)*	33.6 (10.5)*	29.2 (8.2)	29.4 (7.5)	33.3 (7.2)	26.0 (5.2)*	34.0 (15.7)
Education (years) M (SD)	12.5 (2.4)	12.8 (2.4)	12.6 (2.4)	12.4 (2.4)	11.4 (3.5)	12.1 (2.8)	12.2 (2.5)	11.2 (4.1)	12.5 (2.4)	11.7 (2.6)
Age of registration y M (SD)				8.5 (8.9)	21.8 (12.3)	13.2 (11.2)	11.5 (9.2)	22.9 (9.5)	10.7 (12.2)	24.0 (16.5)
Years follow-up M (SD)				19.2 (9.5)	10.6 (7.9)	15.4 (9.8)	17.9 (11.6)	10.4 (8.5)	19.1 (7.6)	12.0 (8.7)
Gender										
Males n (%)	27 (57)	7 (54)	34 (57)	24 (51)	5 (31)	29 (46)	12 (50)	4 (40)	12 (52)	1 (17)
Females n (%)	20 (43)	6 (46)	26 (43)	23 (49)	11 (69)	34 (54)	12 (50)	6 (60)	11 (48)	5 (83)
Handedness										
Right n (%)	40 (85)	13 (100)	53 (88)	35 (74)	13 (81)	48 (76)	15 (63)	7 (70)	20 (87)	6 (100)
Left n (%)	7 (15)	0	7 (12)	8 (17)	2 (13)	10 (16)	6 (25)	2 (20)	2 (9)	0 (0)
Ambidextrous n (%)	0	0	0 (0)	4 (9)	1 (6)	5 (8)	3 (12)	1 (10)	1 (4)	0 (0)
Occupation										
Ever employed	37 (80)	9 (69)	46 (78)	35 (78)	16 (89)	51 (81)	19 (79)	10 (100)	17 (74)	5 (83)
Never employed	9 (20)	4 (31)	13 (22)	10 (22)	2 (11)	12 (19)	5 (21)	0 (0)	7 (26)	1 (17)
Currently employed	17 (37)	5 (38)	22 (37)	29 (62)	14 (88)	43 (68)	16 (67)	9 (90)	13 (57)	5 (83)
Currently unemployed	29 (63)	8 (62)	37 (63)	18 (38)	2 (12)	20 (32)	8 (33)	1 (10)	10 (43)	1 (17)
Haemoglobin										
Average of last two haemoglobin levels (g/l)				76 (15)	95 (14)		78 (14)	98 (19)	68 (15)*	121 (00)
Crisis frequency at baseline										
Never	46 (100)	13 (100)	59 (100)	2 (4)	4 (25)	6 (9)	2 (8)	2 (20)	0 (0)	2 (33.3)
Rarely	0	0	0	10 (21)	5 (31)	15 (24)	4 (17)	3 (30)	6 (26)	2 (33.3)
Sometimes	0	0	0	35 (75)	7 (44)	42 (67)	18 (75)	5 (50)	17 (74)	2 (33.3)
Crisis type										
None	46 (100)	13 (100)	59 (100)	0 (0)	0 (0)	0 (0)	0	0	0	0
Sequestration	0	0	0	0 (0)	3 (19)	3 (5)	1 (4)	0	3 (13)	1
Aplastic	0	0	0	2 (4.5)	1 (6)	3 (5)	1 (4)	0	1	0
Vascular	0	0	0	2 (4.5)	0 (0)	2 (3)	0 (0)	1 (10)	2	2
Haemolytic	0	0	0	3 (6)	0 (0)	3 (5)	3 (13)	0	0	0
Vascular + haemolytic	0	0	0	38 (85)	12 (75)	50 (82)	19 (79)	9 (90)	24	3

TABLE 1 (Continued)

	Controls in cross-sectional study			SCD patients in cross-sectional study			Longitudinal SCD study				
	HbAA <i>n</i> = 47	HbAS or HbAC <i>n</i> = 13	All controls <i>n</i> = 60	HbSS <i>n</i> = 47	All SCD patients (<i>n</i> = 63)		Participants <i>n</i> = 34		Non-participants <i>n</i> = 29		
					HbSC <i>n</i> = 16		HbSS <i>n</i> = 24	HbSC <i>n</i> = 10	HbSS <i>n</i> = 23	HbSC <i>n</i> = 6	
Died										7	0
Number of chronic organ SCD complications											
None	46	13	59	9	8	17	10	7	2	1	
One	0	0	0	26	5	31	8	3	8	3	
Two	0	0	0	10	5	15	4	0	19	2	
≥3	0	0	0	0	0	0	2	0	0	0	
Neurological complications											
Overt stroke	0	0	0	2	0	2	3	0	0	0	
Seizures	0	0	0	3	1	4	4	2	2	0	
Headache	28	7	35	21	14	35	31	21	18	5	
Visual loss	2	0	2	7	3	10	11	5	4	2	
Hearing loss	2	0	2	5	0	5	6	0	4	0	
Other organ complications											
Leg ulcers	0	0	0	10	0	10	12	0	4	0	
Priapism	0	0	0	6	2	8	6	2	3	0	
Leg ulcer + priapism	0	0	0	10	5	15	11	5	11	4	
Bone necrosis	0	0	0	6	2	8	8	3	5	1	
Spleen problem	0	0	0	2	0	2	2	0	1	0	
Eye problem	0	0	0	1	1	2	4	3	0	0	
Stomach ulcer	0	0	0	1	0	1	1	0	0	0	

**p* < 0.05 for difference between patients and controls.†0.05 < *p* < 0.1 for difference between those followed and those lost to follow-up.‡*p* < 0.05 for difference between those followed and those lost to follow-up.

TABLE 2 Baseline differences in neuropsychological test (raw) between adults with sickle cell disease (SCD, $n = 63$) and a non-SCD adult control group ($n = 60$)

Test	SCD (raw)		Non-SCD (raw)		Normative sample	Test values (raw scores)		
	Mean (SE)	95% CI	Mean (SE)	95% CI	Mean (SD)	F-test	Cohen's d	p value
RQCST								
Verbal	26.13 (0.81)	24.52, 27.74	32.71 (0.84)	31.04, 34.37	35.51 (5.78) ¹	31.48	0.21	<0.0001
Non-verbal	24.94 (0.47)	24.01, 25.87	26.71 (0.49)	25.75, 27.68	28.88 (4.03) ¹	6.88	0.05	0.010
Global scores	62.56 (1.08)	60.43, 64.69	70.89 (1.11)	68.69, 73.09	72.78 (8.63) ¹	28.97	0.20	<0.0001
Trail-making test								
TMTa	73.78 (4.16)	65.54, 82.02	56.54 (4.27)	48.09, 64.99	24.40 (8.71) ²	8.34	0.07	0.005
TMTb	176.79 (10.57)	155.86, 197.71	111.02 (10.84)	89.56, 132.48	50.68 (12.36) ²	18.81	0.14	<0.0001
TMT(b-a)	102.79 (9.58)	83.82, 121.76	54.43 (9.82)	34.97, 73.89		12.37	0.10	0.001
Modified Card-Sorting								
Category score	3.63 (0.25)	3.13, 4.12	4.45 (0.24)	3.98, 4.93	4.9 (1.7) ³	5.65	0.05	0.019
Percentage perseverative errors	30.24 (3.01)	24.28, 36.21	18.52 (2.93)	12.71, 24.32	26.5 (12.2) ³	7.71	0.07	0.006
WAIS-R-NI								
Digit symbol substitution	32.10 (1.51)	29.11, 35.10	50.10 (1.56)	47.00, 53.20	41.7 (12.1) ⁴	68.16	0.37	<0.0001
Picture completion	6.49 (0.52)	5.46, 7.53	10.90 (0.54)	9.83, 11.96	10.0 (3.0)	34.20	0.23	<0.0001
Digital symbol delayed	11.51 (1.02)	9.50, 13.52	19.03 (1.05)	16.95, 21.12	10.0 (3.0)	26.32	0.19	<0.0001
Spatial span	9.84 (0.49)	8.87, 10.81	13.17 (0.51)	12.16, 14.18	10.0 (3.0)	22.12	0.16	<0.0001
Block design	10.84 (1.07)	8.72, 12.96	21.41 (1.13)	19.17, 23.64	10.0 (3.0)	45.99	0.28	<0.0001
Similarities	9.42 (0.54)	8.35, 10.50	13.51 (0.57)	12.38, 14.63	10.0 (3.0)	26.65	0.19	<0.0001
Digital span	11.97 (0.56)	10.86, 13.08	15.15 (0.58)	14.00, 16.31	10.0 (3.0)	15.49	0.12	<0.0001
NART								
NARTfig	99.93 (1.05)	97.85, 102.00	110.25 (1.07)	108.14, 112.37	100.0 (15.0)	47.69	0.30	<0.0001
NARTviq	97.96 (1.15)	95.68, 100.25	109.50 (1.19)	107.16, 111.85	100.0 (15.0)	48.53	0.30	<0.0001
NARTpiq	101.73 (0.82)	100.10, 103.36	109.75 (0.84)	108.08, 111.42	100.0 (15.0)	46.35	0.29	<0.0001
Rey-Osterrieth complex figure task								
Rey copy	33.04 (0.52)	32.02, 34.06	35.08 (0.53)	34.03, 36.14	31.30 (3.78) ⁵	7.61	0.06	0.007
Rey immediate recall	19.72 (0.95)	17.85, 21.59	25.00 (0.99)	23.05, 26.96	15.75 (5.76) ⁵	14.81	0.12	<0.0001
Rey delayed recall	19.48 (0.96)	17.58, 21.39	25.78 (0.99)	23.82, 27.74	15.25 (5.83) ⁵	20.85	0.16	<0.0001
Grooved Pegboard								
Dominant hand	66.35 (1.59)	63.20, 69.50	62.76 (1.87)	59.04, 66.47	62.5 (9.6) ⁶	2.15	0.02	0.146
Non-dominant hand	88.78 (3.32)	82.19, 95.38	77.78 (3.85)	70.14, 85.42	67.9 (11.0) ⁶	4.69	0.05	0.033
Recognition memory								
Words	32.18 (1.34)	29.53, 34.82	40.90 (1.38)	38.16, 43.63	38.43 (4.19) ⁷	20.59	0.15	<0.0001
Faces	26.63 (0.74)	25.16, 28.10	26.97 (0.77)	25.44, 28.50	47.77 (2.49) ⁷	0.10	0.00	0.752
WRAT-IV								
Reading	45.91 (1.53)	42.88, 48.95	57.53 (1.55)	54.47, 60.59	59.45 (7.46) ⁸	28.42	0.20	<0.0001
Numerical/Arithmetic	27.37 (1.11)	25.17, 29.56	40.25 (1.16)	37.94, 42.55	39.83 (5.53) ⁹	64.36	0.35	<0.0001

Abbreviations: CI, confidence interval; NART, National Adult Reading Test; RQCST, Revised Quick Cognitive Screening Test; TMT, trail-making test; WAIS-R-NI, Wechsler Adult Intelligence Scale-Revised as a Neuropsychological Instrument; WRAT-IV, Wide Range Achievement Test.

TABLE 3 Baseline differences in neuropsychological test (scaled) between adults with sickle cell disease (SCD, $n = 63$) and a non-SCD adult control group ($n = 60$)

Test	SCD (Z-scored or scaled)		Non-SCD (Z-scored or scaled)		Normative sample	Test values (scaled scores)		
	Mean (SE)	95% CI	Mean (SE)	95% CI	Mean (SD)	F-test	Cohen's d	p value
RQCST (Z-scored)								
Verbal	-1.64 (0.14)	-1.92, -1.36	-0.49 (0.15)	-0.78, -0.20	35.51 (5.78) ¹	31.48	0.21	<0.0001
Non-verbal	-0.98 (0.12)	-1.21, -0.75	-0.54 (0.12)	-0.78, -0.30	28.88 (4.03) ¹	6.88	0.05	0.010
Global scores	-1.18 (0.13)	-1.43, -0.94	-0.22 (0.13)	-0.47, -0.04	72.78 (8.63) ¹	28.97	0.20	<0.0001
Trail-making test								
TMTa	5.67 (0.48)	4.72, 6.62	3.69 (0.49)	2.72, 4.66	24.40 (8.71) ²	8.34	0.07	0.005
TMTb	10.20 (0.86)	8.51, 11.90	4.88 (0.88)	3.15, 6.62	50.68 (12.36) ²	18.81	0.14	<0.0001
TMT(b-a)	4.53 (0.78)	2.99, 6.08	1.19 (0.80)	-0.40, 2.78		8.88	0.07	0.004
Modified Card-Sorting								
Category score	-0.75 (0.15)	-1.04, -0.46	-0.26 (0.14)	-0.54, 0.02	4.9 (1.7) ³	5.65	0.05	0.019
Percentage perseverative errors	0.31 (0.25)	-0.18, 0.80	-0.65 (0.24)	-1.13, -0.18	26.5 (12.2) ³	7.71	0.07	0.006
WAIS-R-NI (scaled)								
Digit symbol substitution	5.20 (0.27)	4.65, 5.74	8.72 (0.28)	8.16, 9.28	10.0 (3.0)	80.19	0.41	<0.0001
Picture completion	4.57 (0.30)	3.98, 5.17	9.05 (0.30)	8.45, 9.64	10.0 (3.0)	111.45	0.51	<0.0001
Digital symbol delayed	11.50 (1.01)	9.49, 13.51	19.22 (1.05)	17.15, 21.30	10.0 (3.0)	27.95	0.20	<0.0001
Spatial span	10.45 (0.46)	9.54, 11.36	13.42 (0.46)	12.50, 14.34	10.0 (3.0)	20.77	0.16	<0.0001
Block design	5.33 (0.28)	4.78, 5.89	8.23 (0.29)	7.66, 8.79	10.0 (3.0)	52.61	0.31	<0.0001
Similarities	5.73 (0.26)	5.22, 6.25	8.25 (0.27)	7.72, 8.77	10.0 (3.0)	45.25	0.29	<0.0001
Digital span	8.13 (0.31)	7.51, 8.75	10.90 (0.32)	10.26, 11.54	10.0 (3.0)	38.08	0.25	<0.0001
Rey-Osterrieth complex figure task								
Rey copy	0.46 (0.14)	0.19, 0.73	1.00 (0.14)	0.72, 1.28	31.30 (3.78) ⁵	7.61	0.06	0.007
Rey immediate recall	0.69 (0.16)	0.36, 1.01	1.61 (0.17)	1.27, 1.95	15.75 (5.76) ⁵	14.81	0.12	<0.0001
Rey delayed recall	0.73 (0.17)	0.40, 1.05	1.81 (0.17)	1.47, 2.14	15.25 (5.83) ⁵	20.85	0.16	<0.0001
Grooved Pegboard								
Dominant hand	0.40 (0.17)	0.07, 0.73	0.03 (0.20)	-0.36, 0.41	62.5 (9.6) ⁶	2.15	0.02	0.146
Non-dominant hand	1.90 (0.30)	1.30, 2.50	0.90 (0.35)	0.20, 1.59	67.9 (11.0) ⁶	4.69	0.05	0.033
Recognition memory								
Words	-1.53 (0.44)	-9.17, 2.52	0.63 (0.16)	-2.97, 2.52	38.43 (4.19) ⁷	20.59	0.15	<0.0001
Faces	-2.82 (0.18)	-3.17, -2.47	-2.74 (0.18)	-3.10, -2.37	47.77 (2.49) ⁷	0.10	0.00	0.752
WRAT-IV								
Reading	-1.82 (0.21)	-2.22, -1.41	-0.26 (0.21)	-0.67, 0.15	59.45 (7.46) ⁸	28.42	0.20	<0.0001
Numerical/arithmetic	-2.25 (0.20)	-2.65, -1.86	0.08 (0.21)	-0.34, 0.49	39.83 (5.53) ⁹	64.36	0.35	<0.0001

Abbreviations: CI, confidence interval; RQCST, Revised Quick Cognitive Screening Test; TMT, trail-making test; WAIS-R-NI, Wechsler Adult Intelligence Scale-Revised as a Neuropsychological Instrument; WRAT-IV, Wide Range Achievement Test.

participating ($n = 34$) and non-participating ($n = 29$) participants at baseline showed no significant differences on socio-demographic variables (i.e. age, gender, education, age of registration, years of being treated and managed at the clinic) and clinical variables (i.e. genotype, number of SCD complications, haemoglobin levels and white blood count levels; all $p > 0.05$) (Table 1).

Seven-year follow-up outcomes

Overall cognitive functioning as measured by the RQCST showed a significant decline over the seven-year follow-up period on verbal, non-verbal and global subtest scores (all $p < 0.01$) (Tables 4 and 5 for raw and scaled scores respectively). For specific domain tests, significant declines were

TABLE 4 Baseline and seven-year follow-up differences in neurocognitive test raw scores among adults with sickle cell disease (SCD, $n=34$) in Ghana

Test	Baseline raw Mean (SE)	Follow-up raw Mean (SE)	F-test	Cohen's <i>d</i>	<i>p</i> value	CI for baseline raw	CI for follow-up raw	Mean difference (decline) Mean (SE)
RQCST								
Verbal	24.22 (1.08)	22.50 (0.88)	5.74	0.16	0.023	22.02, 26.42	20.70, 24.30	-1.72 (0.72)
Non-verbal	24.06 (0.69)	17.63 (0.74)	63.85	0.67	<0.0001	22.66, 25.47	16.12, 19.13	-6.44 (0.81)
Global scores	59.78 (1.33)	51.09 (1.25)	64.89	0.68	<0.0001	57.06, 62.51	48.54, 53.65	-8.69 (1.08)
Trail-making test								
TMTa	81.03 (8.54)	67.55 (5.84)	1.92	0.06	0.176	63.62, 98.44	55.63, 79.46	-13.49 (9.74)
TMTb	197.42 (15.81)	173.21 (15.38)	1.80	0.06	0.190	165.18, 229.67	141.85, 204.57	-24.21 (18.01)
TMT(b-a)	118.22 (15.73)	109.63 (14.52)	0.16	0.01	0.697	86.10, 150.34	79.98, 139.27	-8.59 (21.84)
Modified card-sorting								
Task category	3.79 (0.34)	3.04 (0.36)	5.97	0.18	0.021	3.08, 4.49	2.29, 3.78	-0.75 (0.31)
Percentage perseverative errors	28.69 (3.82)	39.28 (5.30)	3.65	0.12	0.067	20.85, 36.54	28.40, 50.16	10.59 (5.54)
WAIS-R-NI								
Digit symbol substitution	30.72 (1.67)	29.13 (1.67)	1.70	0.05	0.203	27.31, 34.13	25.71, 32.54	-1.59 (1.23)
Digit symbol substitution delayed	11.22 (1.52)	6.75 (1.10)	10.89	0.27	0.002	8.13, 14.31	4.51, 8.99	-4.47 (1.35)
Block design	10.97 (1.40)	21.85 (1.71)	43.16	0.58	<0.0001	8.13, 13.82	18.35, 25.34	10.88 (1.66)
Digital span	12.53 (0.47)	11.75 (0.57)	2.27	0.07	0.143	11.57, 13.49	10.59, 12.91	-0.78 (0.52)
Spatial span	10.76 (0.50)	10.07 (0.41)	2.00	0.07	0.169	9.73, 11.78	9.22, 10.92	-0.69 (0.49)
Rey-Osterrieth complex figure task								
Rey copy	33.16 (0.81)	20.69 (0.94)	182.22	0.86	<0.0001	31.51, 34.80	18.76, 22.61	-12.47 (0.92)
Rey immediate recall	19.77 (1.18)	11.02 (0.73)	56.46	0.65	<0.0001	17.36, 22.17	9.52, 12.51	-8.75 (1.16)
Rey delayed recall	18.60 (1.52)	10.85 (0.69)	36.66	0.56	<0.0001	15.50, 21.70	9.44, 12.26	-7.75 (1.28)
Grooved Pegboard								
Dominant hand	64.69 (1.84)	68.97 (2.20)	4.01	0.12	0.054	60.94, 68.43	64.49, 73.45	4.28 (2.14)
Non-dominant hand	87.97 (4.97)	91.36 (4.19)	0.45	0.02	0.507	77.82, 98.12	82.80, 99.91	3.39 (5.04)
WRAT-IV								
WRAT-IV reading	43.09 (2.02)	42.47 (1.92)	0.57	0.02	0.456	38.97, 47.22	38.54, 46.39	-0.63 (0.83)
WRAT-IV numerical	28.66 (1.41)	30.81 (0.87)	2.36	0.07	0.135	25.79, 31.53	29.05, 32.58	2.16 (1.40)
CFQ total	32.63 (3.85)	31.11 (3.46)	0.23	0.01	0.637	24.73, 40.52	24.01 (38.21)	-1.52 (3.18)

Abbreviations: CFQ, Cognitive Failures Questionnaire; CI, confidence interval; RQCST, Revised Quick Cognitive Screening Test; TMT, trail-making test; WAIS-R-NI, Wechsler Adult Intelligence Scale-Revised as a Neuropsychological Instrument; WRAT-IV, Wide Range Achievement Test.

TABLE 5 Baseline and seven-year follow-up differences in neurocognitive test scaled scores among adults with sickle cell disease (SCD, $n=34$) in Ghana

Test	Baseline scaled	Baseline Z-scores Mean (SE)	Follow-up scaled	Follow-up Z-scores Mean (SE)	F-Test	Cohen's <i>d</i>	<i>p</i> -value	CI for baseline raw	CI for follow-up raw	Decline Mean (SE)
RQCST										
Verbal		-1.90 (0.19)		-2.27 (0.15)	8.80	0.23	0.006	-2.29, -1.52	-2.59, -1.96	-0.37 (0.13)
Non-verbal		-1.20 (0.17)		-2.79 (0.18)	62.84	0.68	<0.0001	-1.54, -0.86	-3.17, -2.42	-1.60 (0.20)
Global scores		-1.51 (0.16)		-6.39 (0.09)	972.29	0.97	<0.0001	-1.82, -1.19	-6.56, -6.22	-4.89 (0.16)
Trail-making test										
TMTa		6.50 (0.98)		4.95 (0.67)	1.92	0.06	0.176	4.50, 8.50	3.59, 6.32	-1.55 (1.11)
TMTb		11.87 (1.28)		9.91 (1.24)	1.80	0.06	0.190	9.26, 14.48	7.38, 12.45	-1.96 (1.46)
TMT(b-a)		5.37 (1.34)		4.96 (1.26)	0.04	0.00	0.838	2.65, 8.09	2.39, 7.53	-0.41 (2.00)
Modified card-sorting										
Task category		-0.66 (0.20)		-1.10 (0.21)	5.97	0.18	0.021	-1.07, -0.24	-1.53, -0.66	-0.44 (0.18)
Percentage perseverative errors		7.00 (1.03)		9.86 (1.43)	3.64	0.12	0.067	4.88, 9.12	6.92, 12.80	2.86 (1.50)
WAIS-R-NI										
Digit symbol substitution	5.00 (0.22)		4.56 (0.26)		3.45	0.10	0.073	4.55, 5.46	4.07, 5.05	-0.44 (0.23)
Digit symbol substitution delayed	11.22 (1.52)		4.56 (0.33)		21.49	0.42	<0.0001	8.13, 14.31	3.89, 5.23	-6.66 (1.44)
Block design	5.18 (0.41)		7.61 (0.49)		26.98	0.46	<0.0001	4.35, 6.02	6.61, 8.60	2.42 (0.47)
Digital span	8.06 (0.35)		7.34 (0.38)		2.85	0.09	0.102	7.34, 8.79	6.56, 8.12	-0.72 (0.43)
Spatial span	10.76 (0.50)		10.07 (0.41)		2.00	0.07	0.167	9.73, 11.78	9.22, 10.92	-0.69 (0.49)
Rey-Osterrieth complex figure task										
Rey copy		0.49 (0.21)		-2.81 (0.25)	182.22	0.86	<0.0001	0.06, 0.93	-3.32, -2.30	-3.30 (0.24)
Rey immediate recall		0.70 (0.21)		-0.82 (0.13)	56.46	0.65	<0.0001	0.28, 1.12	-1.08, -0.56	-1.52 (0.20)
Rey delayed recall		0.58 (0.26)		-0.76 (0.12)	36.66	0.56	<0.0001	0.04, 1.11	-1.00, -0.51	-1.33 (0.22)
Grooved Pegboard										
Dominant hand		0.23 (0.19)		0.67 (0.23)	4.01	0.12	0.054	-0.16, 0.62	0.21, 1.14	0.45 (0.22)
Non-dominant hand		1.82 (0.45)		2.13 (0.38)	0.45	0.02	0.507	0.90, 2.75	1.36, 2.91	0.31 (0.46)
WRAT-IV										
WRAT-IV reading		-2.19 (0.27)		-2.28 (0.26)	0.57	0.02	0.456	-2.75, -1.64	-2.80, -1.75	-0.08 (0.11)
WRAT-IV numerical		-2.02 (0.25)		-1.63 (0.11)	2.32	0.07	0.139	-2.52, -1.52	-1.86, -1.40	0.39 (0.26)

Abbreviations: CI, confidence interval; RQCST, Revised Quick Cognitive Screening Test; TMT, trail-making test; WAIS-R-NI, Wechsler Adult Intelligence Scale-Revised as a Neuropsychological Instrument; WRAT-IV, Wide Range Achievement Test.

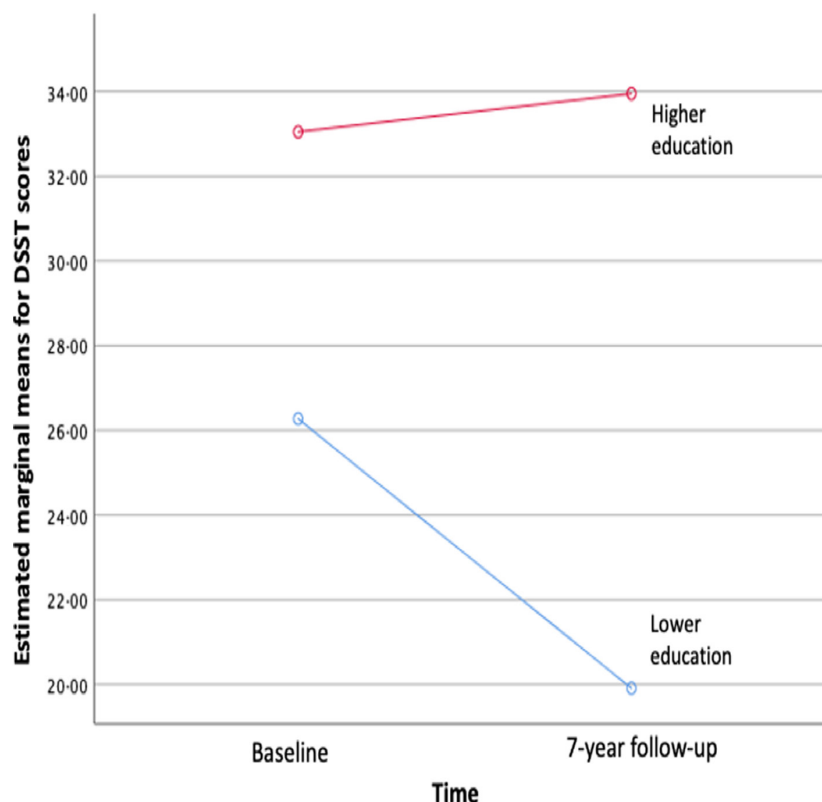


FIGURE 1 Time-by-education interaction for Digit Symbol Substitution Test (DSST)

observed for the Modified Card-Sorting task category score ($p < 0.01$), a measure of executive functioning; all components of the ROCF (all $p < 0.01$), indicating a decline in visuospatial processing and memory; and lower digit symbol substitution scores ($p = 0.01$), suggesting slower processing speed at seven-year follow-up as compared to baseline. No declines were observed for the Trail-Making Tests (TMT), which also measure executive functioning and processing speed.

Education, haemoglobin and genotype as possible moderators

We were also interested in possible factors that would explain any declines in cognitive functioning over time. Specifically, we tested the main effect and interaction with time for haemoglobin level, SCD genotype and education. In these exploratory analyses, the time-by-education interaction was marginally significant for TMT A ($p = 0.05$), Rey's immediate recall ($p = 0.03$) and DSST ($p = 0.01$; [Figure 1](#)). All three interaction effects showed that patients with higher education had limited or no significant decrease in performance over the seven-year period when compared to patients with lower education, who demonstrated a significant decrease in performance over time on tests of processing speed and visuospatial memory. Baseline haemoglobin level and SCD genotype did not have a direct effect nor were they significant moderators of change in cognitive functioning over time ([Tables 6 and 7](#) for raw and scaled scores respectively).

Principal components analysis

The Kaiser–Meyer–Oklin measure of sampling adequacy was 0.73 and Bartlett's test of sphericity was significant, (190) = 1085.74, $p < 0.0001$, indicating the appropriateness of the measures for PCA. Preliminary analysis performed produced six components with Eigen values above Kaiser's criterion of 1. The scree plot inflexions allowed retaining all six components ([Table 8](#)).

DISCUSSION

This two-part, case-control comparison and seven-year follow-up cohort study based in West Africa is the first of its kind in SCD. To our knowledge, no other SCD studies have evaluated cognitive function among adults with sickle cell disease in Africa, and no other SCD studies have assessed cognitive changes among adults or children over more than three years. Given the global nature of SCD, and the fact that more patients are living into adulthood, understanding patterns of cognitive functioning and age-related changes will be important for improving long-term SCD care.

Consistent with prior studies conducted in the United States,^{17,47–49} the current study found, in a Ghanaian population, that compared to those without SCD, adults with SCD had poorer performance on all cognitive domains. For many domains, adults with SCD performed a standard deviation, or more, worse than their non-SCD counterparts.

TABLE 6 Multivariable regression models of the association between haemoglobin level and measures of neuropsychological tests (raw scores)

Test	Haemoglobin		
	Coefficient (SE)	p-value	Confidence interval
RQ CST			
Verbal	-1.06 (0.85)	0.22	-2.79, 0.67
Non-verbal	-0.60 (0.41)	0.16	-1.45, 0.24
Global scores	-1.80 (1.03)	0.09	-3.91, 0.31
Trail-making test			
TMTa	4.59 (5.57)	0.42	-6.79, 15.97
TMTb	11.07 (11.23)	0.33	-11.86, 33.99
TMT(b-a)	6.48 (9.73)	0.51	-13.41, 26.36
Modified card-sorting			
Category score	0.03 (0.20)	0.89	-0.38, 0.44
Percentage perseverative errors	-0.80 (2.40)	0.74	-5.72, 4.12
WAIS-R-NI			
Digit symbol substitution	-0.41 (1.04)	0.70	-2.53, 1.71
Picture completion total	0.19 (0.45)	0.67	-0.73, 1.12
Digital symbol delayed	-0.04 (0.95)	0.97	-1.98, 1.90
Spatial span	-0.11 (0.31)	0.72	-0.74, 0.52
Block design	0.38 (0.79)	0.64	-1.24, 1.99
Similarities	-0.33 (0.42)	0.44	-1.18, 0.52
Digital span	-0.66 (0.32)	0.05	-1.31, -0.01
Rey-Osterrieth complex figure task			
Rey copy	-0.72 (0.54)	0.19	-1.82, 0.38
Rey immediate recall	-0.31 (0.77)	0.69	-1.89, 1.27
Rey delayed recall	-1.56 (1.06)	0.15	-3.73, 0.61
Grooved Pegboard			
Dominant hand	1.13 (1.09)	0.31	-1.11, 3.36
Non-dominant hand	0.28 (2.92)	0.92	-5.68, 6.24
Recognition memory			
Faces	0.29 (0.59)	0.62	-0.91, 1.49
Words	-0.63 (1.53)	0.69	-3.76, 2.51
WRAT-IV			
WRAT-IV reading	-1.97 (1.76)	0.27	-5.58, 1.64
WRAT-IV numerical/arithmetic	0.08 (0.79)	0.92	-1.53, 1.68

Abbreviations: RQ CST, Revised Quick Cognitive Screening Test; TMT, Trail-Making Test; WAIS-R-NI, Wechsler Adult Intelligence Scale-Revised as a Neuropsychological Instrument; WRAT-IV, Wide Range Achievement Test.

At the seven-year follow-up, SCD patients exhibited a slight decline in cognitive performance on some domains: visuospatial ability, executive functioning and processing speed. The decline in processing speed and executive functioning was not consistent across tests,

with the DSST and MCST showing a decline but the TMT scores not differing at follow-up. Also, this decline appeared to be more pronounced for SCD patients with lower education. Across high and low education, however, patients did not self-report any changes in their cognitive functioning over the seven-year period on the CSQ, thus suggesting that any changes in functioning were not perceived by the individuals themselves. This may be due to lack of patient insight into cognitive changes, the changes being imperceptible to the individual given the declines are gradual over several years, or an imperfect overlap between measurement of self-report and objective cognitive performance.

Change in neurological functioning

Studies examining neurocognitive change in SCD have been mixed, with some studies in adults reporting a decline in cognitive performance over time^{50,51} while some studies do not find such a decline.⁵² Among children with SCD, Anderson *et al.*⁵³ reported no significant changes in neuropsychological functioning after a year in very young children, but another investigation did find changes over 1–2 years of assessment in young children with SCD.⁵⁴ However, Yarboi *et al.*⁵⁵ reported mixed findings, where significant decline was observed in cognitive measures such as letter-word identification, spelling, and visual scanning, with no changes in other cognitive measures.

Studies on visuospatial skills of SCD patients have generally found SCD adults and children to have mild deficits in this cognitive domain.^{48,53,56} This is the first study to our knowledge to demonstrate change in visuospatial abilities among adults with SCD. Some data suggest that structural brain changes may contribute to visuospatial deficits in SCD, specifically parietal lobe lesions.^{57,58} It is possible that the decline in visuospatial performance may have been directly due to structural brain changes, atrophy or lesions, caused by ischaemia, hypoxia or chronic anaemia. Determining the potential causes of cognitive decline in SCD will require studies that examine not only neurocognitive functioning but also structural and functional brain measures.

Mechanism contributing to poorer performance and decline over time

Although disease severity has been associated with poorer cognitive functioning in SCD, the exact mechanism is unknown.²¹ Several studies, in SCD and in older populations, have linked lower haemoglobin levels to poorer cognitive performance, and studies of ageing link anaemia to increased risk of dementia.^{49,56,59} In the current study, however, haemoglobin was not correlated with cognitive function among SCD adults in cross-sectional or longitudinal data. Genotype, which has previously been correlated

TABLE 7 Regression of measures of neuropsychological test (scaled scores) and haemoglobin level

Test	Haemoglobin level		
	Coefficient (SE)	p value	Confidence interval
RQCST			
Verbal	−0.19 (0.15)	0.22	−0.49, 0.12
Non-verbal	−0.15 (0.10)	0.16	−0.36, 0.06
Global scores	−0.21 (0.12)	0.09	−0.45, 0.04
Trail-making test			
TMTa	0.53 (0.64)	0.42	−0.78, 1.83
TMTb	0.90 (0.91)	0.33	−0.96, 2.75
TMT(b-a)	0.37 (0.81)	0.65	−1.29, 2.02
Modified card-sorting			
Category score	0.02 (0.12)	0.89	−0.23, 0.56
Percentage perseverative errors	−0.22 (0.65)	0.74	−1.55, 1.11
WAIS-R-NI			
Digit symbol substitution	0.04 (0.14)	0.77	−0.24, 0.33
Picture completion total	0.36 (0.21)	0.09	−0.06, 0.79
Digital symbol delayed	−0.04 (0.95)	0.97	−1.98, 1.90
Spatial span	−0.11 (0.31)	0.72	−0.74, 0.52
Block design	0.01 (0.23)	0.98	−0.46, 0.47
Similarities	−0.01 (0.15)	0.95	−0.32, 0.30
Digital span	−0.66 (0.24)	0.01	−1.14, −0.17
Rey–Osterrieth complex figure task			
Rey copy	−0.19 (0.14)	0.19	−0.48, 0.10
Rey immediate recall	−0.05 (0.13)	0.69	−0.33, 0.22
Rey delayed recall	−0.27 (0.18)	0.15	−0.64, 0.11
Grooved Pegboard			
Dominant hand	0.12 (0.11)	0.31	−0.12, 0.35
Non-dominant hand	0.03 (0.27)	0.92	−0.52, 0.57
Recognition memory			
Faces	0.07 (0.14)	0.62	−0.22, 0.36
WRAT-IV			
WRAT-IV reading	−0.26 (0.24)	0.27	−0.75, 0.22
WRAT-IV numerical/arithmetic	−0.20 (0.32)	0.54	−0.86, 0.46

Note: Bold value shows the association between haemoglobin levels of participants and the various neuropsychological measures.
Abbreviations: RQCST, Revised Quick Cognitive Screening Test; TMT, trail-making test; WAIS-R-NI, Wechsler Adult Intelligence Scale-Revised as a Neuropsychological Instrument; WRAT-IV, Wide Range Achievement Test.

with processing speed,²² was also not associated with outcomes in the current data. Other haematological factors that have been associated with improved cognitive measures, such as higher fetal haemoglobin and creatinine,²¹ were not available for the current cohort of patients.

Psychosocial factors throughout the life course

Education was a significant predictor of cognitive performance and a moderator of change in performance over time. Psychosocial factors directly related to education level have been associated with cognitive deficits in SCD. Lifestyle factors during early development such as school absenteeism, frequency of hospitalization, poor family functioning and low maternal education, can affect academic performance and cognitive performance in SCD.^{24,60,61} Indeed, early-life disadvantage has downstream effects leading to cognitive deficits that in turn compromise functioning later in life such as ability to engage in routine daily activities, academics and gainful employment.^{18,62,63} Therefore, there is a need to assess these cognitive changes early enough to improve on early diagnosis, prognosis, interventions and quality of life.

Validity of cognitive measures in West Africa

There are limited data from West Africa but the existing data suggest both children and adults with SCD experience deficits in memory, processing speed, executive functioning and visuospatial ability.^{14,15,64} One challenge, however, for the current and prior studies has been the lack of culturally validated neurocognitive measures. With the exception of the Wide Range Achievement Test (WRAT), the cognitive tests administered to participants in this study have not been adapted for use in Ghana. This may have a significant effect on the interpretation of these scores, particularly when comparing our findings to studies of neuropsychological testing in the United States. Indeed, the scores on the Trail-Making Test (TMT), Recognition Memory for Faces (RMF), Recognition Memory for Words (RMW), Boston Naming Test (BNT), digit symbol, block design, Controlled Oral Word Association Test (COWAT), Verbal Selective Reminding Test (VSRT) and category naming in this sample were lower than expected based on the normative data of individuals with similar ages and educational attainment or individuals who were older (Tables 2 and 3).^{28,37,65–68} Lack of prior exposure to similar types of tests may have made it challenging for participants to quickly understand testing instructions. For instance, study staff administering the testing noted that several participants did not understand the instructions for the Trail-Making Test, leading to abnormally long test-taking times ($n = 14$ participants >5 min to complete TMTb). Indeed, for the group that repeated the test seven years later, there were marginal improvements in scores, suggesting prior exposure to the test may have benefited performance.

Cultural factors and neuropsychological testing

Evidence suggests that cultural factors have a robust and complex influence on neuropsychological test performance.^{69,70} For instance, Manly *et al.* (2002) found that

TABLE 8 Summary of factor loadings of neurocognitive measures for cross-sectional data at baseline

Neurocognitive measures	Component					
	1	2	3	4	5	6
WRAT reading	0.814			−0.472	0.496	
Category naming test	0.800					
Verbal selective reminding test	0.758				0.317	
WAIS-R-NI digit symbol	0.749		−0.521	−0.431	0.483	0.396
WAIS-R-NI digit symbol delayed	0.517	−0.378	−0.392		0.448	0.302
WRAT numerical	0.486			−0.392	0.360	0.456
COWAT		0.874				
WAIS block design	0.381	0.620	−0.365		0.346	
Rey copy	0.417	−0.553	−0.411	−0.548	0.466	
Grooved Pegboard non-dominant hand			0.874		−0.343	
Grooved Pegboard dominant hand			0.797	0.331		
TMTa	−0.392		0.684		−0.344	
TMTb-a				0.975		
TMTb	−0.344		0.374	0.960	−0.381	
WAIS digital span	0.409			−0.364	0.782	
WAIS spatial span			−0.401	−0.328	0.774	
MCST category score	0.348				0.733	
MCST perseverative errors	0.342				0.711	
Rey immediate recall		−0.477	−0.547	−0.410	0.690	
Rey delayed recall		−0.518	−0.584	−0.394	0.669	
Recognition memory for faces		0.325				0.578

Note: Bold value shows the neurocognitive domains or components after Principal Component Analysis.

Abbreviations: COWAT, Controlled Oral Word Association Test; MCST, Modified Card-Sorting Test; TMT, Trail-Making Test; WAIS-R-NI, Wechsler Adult Intelligence Scale-Revised as a Neuropsychological Instrument; WRAT, Wide Range Achievement Test.

quality of education accounted for reduced neuropsychological test performance among African Americans when compared to non-Hispanic White adults. Other cultural factors that can influence cognitive performance include, but are not limited to, native language, cultural acculturation and geographic ancestry.^{71–73} In the current study, we can speculate that cultural factors may have influenced participant test-taking ability and resultant testing outcomes; however, because the current study included only individuals from Ghana these data are unable to clearly identify whether cultural factors and prior educational experiences may be contributing to the observed performance.

Given the numerous cultural factors that can influence test performance, tests not adapted for diverse groups may lack cross-cultural validity and be subject to bias such that performance on the tests does not reflect the underlying cognitive abilities they were designed to assess.⁷⁰ As a result, the lower scores observed on some of the neuropsychological assessments could partly indicate the presence of certain test characteristics that highlight cultural differences and related factors such as social development, rather than serving as a true assessment of cognitive abilities. Despite the limitations of using tests that have not been validated for this West African population, we can presume any effect cultural factors may have had on neurocognitive assessment scores is relatively

constant across both groups in this sample. Thus, although we cannot compare results from this study across populations, our data showing differences between adults with SCD vs non-SCD adults within the same population appear to be robust, consistent with *a priori* hypotheses, and can be interpreted with some confidence.

Limitations

Despite the interesting nature of the present data, this study has several limitations that should be taken into account. First, about 26 000 patients are treated at this clinic setting and no specific efforts were made for this study to capture a representative sample of this larger population. Thus, the baseline convenience sample may present some selection bias and there may also be bias in the follow-up study of those with sickle cell anaemia. Similarly, several participants in the control group were recruited into the study while they were accompanying an SCD patient visiting the clinic. Because people who are not employed will be more likely to have time to accompany a patient during a clinic visit, it is not surprising, therefore, that the control group presented with a higher rate of unemployment compared to the SCD group.

Over the course of the seven-year follow-up period, there was a significant loss of participants in the SCD group (42% attrition) with almost 15% of the baseline cohort dying during the follow-up period, and others potentially unavailable due to other medical or socioeconomic complications. The cohort at seven years, therefore, may have been biased for selection of the mostly healthy and socioeconomically stable participants and we did not include whether they were or had a carer. Despite the high attrition, the 41.27% attrition rate for the seven-year present study is reasonably lower compared to the 56.67% and 70.79% attrition rates over one and three years for the Yarboi *et al.*⁵⁵ and Thompson *et al.*⁵⁴ studies, respectively.

Prior studies have examined laboratory clinical factors as predictors of neurocognitive functioning. Collecting these data such as fetal haemoglobin, transfusion history and frequency of hospitalizations, can be challenging in low-resource settings. Although this study does present data on haemoglobin level and SCD genotype, there are several other clinical markers of disease severity and treatment that are potentially important for assessing neurocognitive functioning that were not accounted for in this study. One such factor, hydroxyurea use, may be associated with improved cognitive performance.⁷⁴ In the current setting, given the several socioeconomic factors affecting hydroxyurea availability, we were unable to accurately assess hydroxyurea prescribing and adherence to evaluate it as a clinical factor.

Finally, the lack of neuroimaging data in this study also leaves many unanswered questions regarding the types of structural and/or functional brain alterations that may be occurring among individuals with SCD and contributing to reduced cognitive performance. Although functional assessment allows diagnosis in patients with a history of overt stroke, this does not negate the possibility of other brain changes. The prevalence of silent cerebral infarcts in adult SCD patients varies^{75,76} but some data would suggest a prevalence as high as 43% in unselected adults with HbSS.⁷⁷ Use of magnetic resonance imaging (MRI) or other neuroimaging modalities could also have important implications for developing appropriate approaches to cognitive rehabilitation. Including these types of data is a goal for future studies.

CONCLUSION

The current study investigated the extent of neuropsychological deficits observed in adults with SCD receiving care at a teaching hospital in West Africa. Consistent with prior studies and our predictions, compared to controls, patients with SCD experienced poorer cognitive performance at baseline. Further, patients with SCD, particularly those with a lower educational level, appeared to experience worsening cognitive performance over time. Future studies should include neuroimaging evaluation in order to provide clarity regarding the neurobiological bases of the cognitive deficits observed among individuals with SCD. It would also be of

benefit for future studies to utilize neuropsychological tests that have been adapted or validated for use in West African populations. Detailed longitudinal studies that expand on the current investigation will help us understand and evaluate the progression of cognitive health in SCD and how age, education and disease severity impact cognitive outcomes.

ACKNOWLEDGEMENTS

We would like to thank Andrea Ball for providing medical writing and editorial support, as well as her other intellectual contributions to this manuscript. This work was (partially) supported through a Patient-Centered Outcomes Research Institute (PCORI) Award (CER-2018C2-13320) and the National Institute of Mental Health (NIMH) R34 MH125152. All statements in this report, including its findings and conclusions, are solely those of the authors and do not necessarily represent the views of PCORI, its Board of Governors or the Methodology Committee.

CONFLICT OF INTEREST

Charles Jonassaint is an equity holder and officer of Expressive Painimation Inc. There are no other author conflicts of interest to disclose that are relevant to this study or anything reported in the manuscript.

DATA AVAILABILITY STATEMENT

Raw data were generated at the University of Ghana. Derived data supporting the findings of this study are available from the corresponding author (Mary A. Ampomah) on request.

PATIENT CONSENT STATEMENT

Written informed consent has been obtained from all participants of this study.

PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

No excerpts from copyrighted works or any works owned by third parties were included in this manuscript.

CLINICAL TRIAL REGISTRATION

No clinical trial registration was required for this study.

NOVELTY STATEMENT

What is the NEW aspect of your work? This study presents data from the longest period of follow-up for any pre-post cognitive study in an adult sickle cell population to date.

What is the CENTRAL finding of your work? Adults with sickle cell disease presented with poorer cognitive functioning than non-SCD adults and exhibited significant cognitive decline over a seven-year period.

What is the SPECIFIC clinical relevance of your work? Early and regular assessment of cognitive functioning should be a standard part of routine SCD care for patients in West Africa.

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How to cite this article: Ampomah MA, Drake JA, Anum A, Amponsah B, Dei-Adomakoh Y, Anie K, et al. A case-control and seven-year longitudinal neurocognitive study of adults with sickle cell disease in Ghana. *Br J Haematol*. 2022;00:1–16. <https://doi.org/10.1111/bjh.18386>