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The association between sleep disturbances and neurocognitive function in pediatric sickle cell disease

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ABSTRACT

Background and objective: Youth with sickle cell disease (SCD) without neurological complications continue to be at increased risk of neurocognitive difficulties. Nocturnal hypoxemia is associated with neurocognitive outcomes and has been identified as a chronic complication in youth with SCD. The objective of this study was to assess the relationship between sleep disturbances and neurocognitive functioning in youth with SCD, while taking into account demographic and socioeconomic factors.

Methods: Youth with SCD were identified through retrospective chart review who underwent a standardized polysomnography (PSG) and completed a neuropsychological testing battery to assess cognitive skills, including verbal comprehension, working memory, processing speed, and cognitive flexibility. Questionnaires were also collected to assess parent-reported concerns with their youth's executive and adaptive skills.

Results: Twenty-seven youth with SCD, ages 6–17, were identified who completed both a PSG and neuropsychological testing. Results demonstrated that verbal comprehension decreased by 2.37 standard points for every unit decrease in mean nocturnal oxygen saturation (SpO2) ($p = 0.031$). Working memory was also found to decrease by 1.46 standard points for each 1% increase in time spent under 90% oxygen saturation (pTST SpO2 < 90%) ($p = 0.030$). Sleep parameters did not significantly predict other cognitive scores or parent-reported executive or behavioral ratings.

Conclusion: Our study found that sleep disturbance, mean nocturnal SpO2 and pTST SpO2 < 90%, significantly affected verbal comprehension and working memory performance, respectively. Overall, these findings have the potential to identify sleep needs in youth with SCD to promote sleep-targeted interventions as a modifiable factor to reduce neurocognitive deficits.

1. Introduction

Sickle cell disease (SCD) is a hereditary red blood cell disorder that affects approximately 100,000 Americans [1]. SCD is caused by a single gene deletion in the beta-globin gene, producing hemoglobin S (HbS) [2]. The polymerization of HbS in deoxygenated states causes the red blood cell to change shape (i.e., sickling) [2]. Sickled red blood cells lead to a surge of adverse effects such as early hemolysis, vaso-occlusion, chronic anemia, silent cerebral infarcts, and overt strokes; several of which can cause long-term effects and have a significant impact on quality of life (QoL) [2–5]. However, advancement in newborn screening and early treatment, including antibiotic prophylaxis, transfusions, hydroxyurea, stem cell transplantation and gene therapy, has increased the life expectancy for children and adolescents [6]. Given that the mortality rate for youth with SCD continues to steadily decline [7], there is a need for research assessing how to improve overall QoL as well as functional status.

Moreover, frequent complications associated with SCD, such as vaso-occlusion, chronic anemia, silent cerebral infarcts, and overt

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Abbreviations

ADI	Area deprivation index
AEA	Adult education attainment
AHI	Apnea hypopnea index
BASC-3	Behavior assessment system for children, third edition
BRIEF-2	Behavior rating inventory of executive function, second edition
COI	Child opportunity index
DDK	Diversity data kids
DKEFS	Delis-kaplan executive function system
EOI	Education opportunity index
ETCO2	Capnography
FSIQ	Full scale intelligence quotient
HbS	Hemoglobin S
PS	Processing speed
PSG	Polysomnography
PTST SPO2 <90%	The total percentage of time spent below 90% oxygen saturation
QOL	Quality of life
SCD	Sickle cell disease
SES	Socioeconomic status
SPO2	mean nocturnal oxygen saturation
VC	Verbal comprehension
WISC	Wechsler intelligence scale for children
WM	Working memory

strokes, have a notable impact on brain physiology, thus influencing neurocognitive development [8,9]. Significant deficits across all neurocognitive domains are also present in youth with SCD without the above complications, most commonly attributed to social and environmental disadvantages [9,10]. Neurocognitive dysfunction in youth with SCD has been repeatedly documented, including deficits in intellectual functioning, attention, memory, executive function, and processing speed [11–15]. According to a meta-analysis conducted by Prussien et al. [9], full-scale intellectual quotient (FSIQ), verbal reasoning, perceptual reasoning, processing speed, and executive function deficits increased from preschool (medium effect size) to school-aged (large effect size) children with SCD, with significant deficits in executive function and processing speed remaining in adulthood [9]. Similar patterns of deficits across youth with SCD are seen throughout multiple meta-analyses [8,10,16,17], indicating a decline in neurocognitive abilities in individuals with SCD as they age. Neurocognitive abilities are also highly associated with academic achievement, QoL, independent skills, self-care, and self-advocacy [18]. Despite these findings, modifiable health-related factors (e.g., sleep, diet, or exercise) that may potentially influence neurocognitive deficits are largely unknown.

One health-related factor, sleep, has been associated with neurocognitive outcomes in other childhood populations. During childhood to adolescence, sleep becomes especially important for the developing brain [19–21]. One study found better sleep quality to be linked to improved neurocognitive abilities in typically-developing children [20]. Literature of the association between sleep and neurocognition have found that sleep problems are associated with difficulties in various domains of neurocognition, including memory, attention, intelligence, and executive function [22–25]. In addition, a study found decreased inhibitory control and attention under deoxygenated conditions [22]. Deficits in executive functioning can also lead to negative downstream effects on other neurocognitive domains (e.g., processing speed, attention, and memory) [26,27]. Despite emerging evidence of sleep difficulties and resulting neurocognitive outcomes [28–30], limited research has been done on the physiological pathway of sleep difficulties and its link to neurocognitive abilities, especially within SCD. Sleep is a diverse construct that can be assessed in various ways. Specifically, sleep disturbance such as sleep disordered breathing and sleep fragmentation due to arousals, are both prominent factors identified as affecting optimal sleep [31,32]. Sleep disturbance has been documented as reoccurring in individuals with SCD, and has been linked to increasing the risk of pain crises, acute chest syndrome, and polymerization of sickle hemoglobin [33–37]. Typically throughout the stages of sleep, especially during REM sleep, the respiratory rate is reduced, resulting in decreased nocturnal oxygen saturation compared to wakefulness [38]. Sleep disordered breathing specifically is classified by upper airway dysfunction during sleep resulting in strained respiratory exchange and snoring, and can be associated with intermittent hypoxemia [39]. A possible mechanism of sleep disordered breathing is obstructive sleep apnea, characterized by a significant decrease of airflow from partial or complete upper airway obstruction during sleep [40]. Obstructive sleep apnea is commonly caused by adenotonsillar hypertrophy [41]. Considering SCD complications such as functional asplenia, it is theorized that youth with SCD may be prone to the development of adenoidal and tonsillar hypertrophy as a compensatory response [42–44]. In addition, sickled red blood cells carry less oxygen and move through the vascular system with more difficulty, producing a two fold deoxygenated state during sleep. These findings raise important questions about the potential effects of chronic sleep disturbance on neurocognitive function in youth with SCD.

Additionally, certain social and environmental factors, such as socioeconomic status (SES), may also play a role in sleep disturbance. In typically-developing children, those with socioeconomic disadvantages, including lower household income, lower education quality, and adverse environmental factors, have a greater risk of sleep problems when compared to higher SES peers [45]. Healthy children of lower SES are also at greater risk of increased sleep disruptions, reduced total nighttime sleep, and increased daytime sleepiness [46]. A few conceptualizations of SES and its role on sleep include education status, economic situation, and neighborhood deprivation. Parents with higher levels of education are more likely to have knowledge on the importance of sleep and model healthy sleep behaviors [47]; economic status has been linked to family stress and parenting which has been found to increase sleep problems [48–50]; and lastly neighborhood deprivation including air pollution is shown to have a significant impact on sleep [45,51,52]. SES is also a consistent contributor to health disparities in underserved populations [53]. Among health burdens, SCD affects majority Black Americans, who are also at increased risk of living in deprived areas and having lower income [54,55]. Studies have demonstrated that sociodemographic factors such as race and sex represent greater risk of sleep problems. Specifically, black adolescents sleep less and experience more fragmented sleep, while female adolescents experience worse sleep quality and more daytime sleepiness [56]. In contrast, a study found that living in a disadvantaged neighborhood was the greatest risk factor for obstructive sleep apnea above ethnicity and other health characteristics. Despite these findings, a couple of studies found that SCD is the significant indicator of sleep disordered breathing above and beyond race, sex, and socioeconomic status [57,58]. SES has been

shown to independently influence cognitive impairments and be correlated with lower QoL in underserved populations [50,59]. Individual SES variables, including maternal education and household income, have been identified as key predictors of FSIQ and reliable indicators for targeted interventions to improve cognition [17]. As such, youth with SCD are at increased risk of neurocognitive deficits and insufficient sleep, classified as respiratory abnormalities that can affect oxygenation to the brain tissue, as well as economic disadvantages that present additional stressors that potentially confound cognitive abilities and sleep. Thus, the aim of the current study is to determine the influence of sleep disturbance on neurocognitive functioning, while taking into account demographic and socioeconomic factors in youth with SCD.

2. Methods

2.1. Data collection

Participants were identified by a retrospective review of sleep study evaluations conducted through the Division of Pediatric Pulmonary and Sleep Medicine at Children's of Alabama Hospital. Retrospective sleep study data were cross-referenced with neurocognitive data for patients with SCD, collected through the Division of Hematology/Oncology. Participants were included in the current study if the neurocognitive testing was within 90 days before their sleep study or within five years post-sleep study (time between studies M = 14.48 months, Range 3–55). Due to the retrospective nature of this study and considering the neurodevelopmental window between childhood and adolescence, neuropsychological evaluation given within 5 years or less were considered valid for inclusion in this study. Objective neurocognitive data focused specifically within the neurocognitive domains of executive function, including measures of cognitive flexibility, attention, processing speed, and working memory. Additionally, parent-report measures of executive function and emotional and adaptive functioning were also collected.

2.2. Participants

This study was comprised from a cohort of 859 youth with sickle cell disease. The current study included 27 children and adolescents with SCD seen at the Children's of Alabama Center for Childhood Cancer and Blood Disorders Sickle Cell Clinic between 2011 and 2021. To be included in the current study, participants had to a) be between 6 and 18 years of age, b) have SCD, c) primarily English speaking, and d) have completed both neurocognitive testing and a polysomnography (PSG). Participants were excluded from the current study if they a) had a history of neurological disorders (overt stroke, seizures, or moyamoya disease), b) were on prescribed psychotropic medication, or c) were diagnosed with an intellectual disability, autism spectrum disorder, or a pervasive developmental disorder. Attention-Deficit-Hyperactivity Disorder (ADHD) and ADHD medication was not explicitly included in the exclusion criteria; however, review of the 27 participants indicated that none were on ADHD medication (stimulant or non-stimulant medication) at the time of their neurocognitive testing. The most recent medical chart record before each participant's neurocognitive test was reviewed by trained clinical researchers. This study collected participant date of birth, SCD complications, medications, SCD genotype, hospitalization(s), home address, and contact information, abstracted from medical records. Participants for this study are shown in Fig. 1.

The study was approved by the University of Alabama at Birmingham Institutional Review Board.

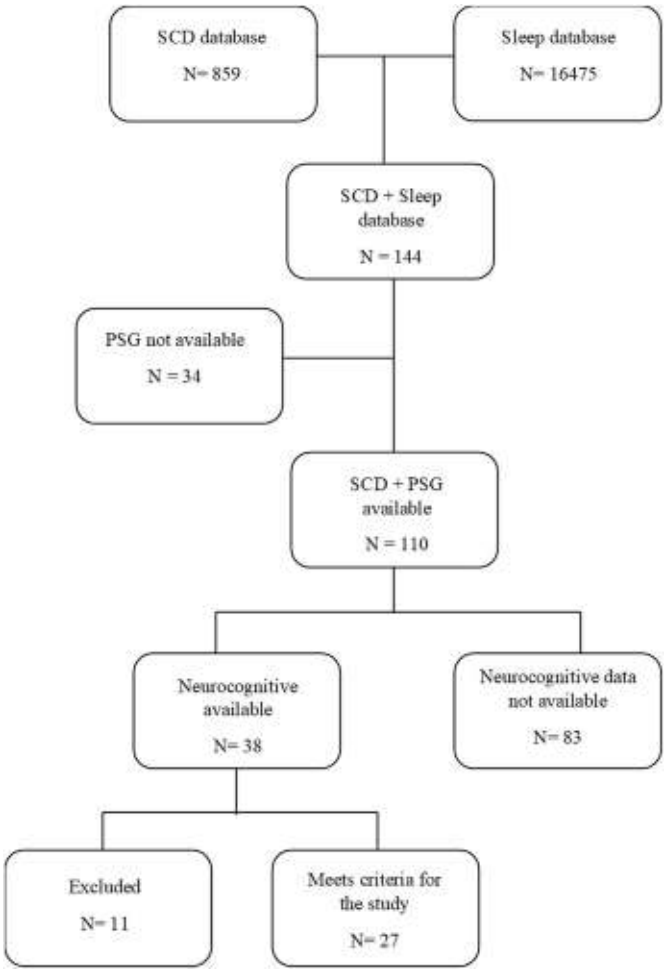

Fig. 1. The flow chart of the study population
Abbreviations: SCD: sickle cell disease; PSG: polysomnography.

2.3. Measures

Neurocognitive Measures: Due to the retrospective nature of the data collection, a variety of neurocognitive measures were used as part of routine clinical care by a licensed neuropsychologist. As such, efforts were made to combine similar measures based on the construct area. Based on the present study's objective to assess executive function skills, the following measures were selected: Wechsler Scales of Intelligence (WISC) to investigate verbal comprehension [VC], working memory [WM], and processing speed [PS] [60–63]; Delis-Kaplan Executive Function System (DKEFS), Trail Making Test, Number-Letter Sequencing to assess cognitive flexibility [64]; Behavior Rating Inventory of Executive Function (BRIEF-2) [65] parent-report questionnaire to assess executive function outcomes; and Behavior Assessment for Children (BASC-3) [66] to assess parent-report of emotional and behavioral function. The working memory and processing speed indices are sub-composites of the full-scale intelligence quotient on the WISC; therefore, the verbal comprehension sub-composite score was utilized to account for intellectual functioning in further analyses.

Sleep Study: Sleep disturbance was assessed by quantifying sleep disordered breathing and sleep fragmentation. A standard PSG was obtained for each participant. Each PSG was performed in an uninterrupted controlled environment; included monitoring electroencephalography, thoracic and abdominal respiratory effort, airflow, snore sensor, capnography (EtCO2), and continuous pulse

oximetry. Standard protocols from the American Academy of Sleep Medicine guidelines were utilized to collect and score PSG data [67]. Sleep fragmentation was defined by the total combined number of spontaneous and respiratory arousals during a night; and sleep disordered breathing was represented by three parameters (apnea hypopnea index [AHI], mean nocturnal oxygen saturation [SpO2] and the percent of total sleep time spent below 90% O2 [pTST SpO2 <90%]). For patients with multiple sleep studies, the initial sleep study data was used for analysis on every participant to capture sleep parameters earlier into brain development and to control for treatment effects that can be seen on follow-up sleep study data.

Socioeconomic Status: All the following variables obtained were measured based on participants' neighborhood-level SES. Participants' home addresses were obtained through medical record abstraction and used to identify individual neighborhood deprivation measured by the Area Deprivation Index (ADI). The ADI combines 17 measures in the domains of education, employment, housing quality, and poverty drawn from the US American Community Survey and aggregated to Census block groups, proxies for neighborhoods [68,69]. This study used the state-level ADI scores (1-10) for Alabama Census block groups, with higher scores indicating worse disadvantage. The ADI was reverse coded (1 = most disadvantaged, 10 = least disadvantage) to correspond to the direction of the other SES variables. Participants' addresses were also used to obtain Child Opportunity Index (COI) scores from the Diversity Data Kids (DDK) database [70]. The COI is a composite index that captures opportunity based on 29 indicators, such as access to safe housing, good schools, healthy foods, green spaces, clean air, and living-wage jobs, aggregated at the Census tract level. COI scores are calculated on a 1–5 Likert scale, with higher scores indicating better opportunity. Previous literature has identified education quality, parental education, and household income as predictors of neurocognitive outcomes and academic achievement [17,71,72]. Thus, we included them as separate measures to explore their independent contributions. Specifically, we abstracted separately the Education Opportunity index (EOI), a COI sub-measure that includes 11 indicators of education attainment, quality, and resources, and the Adult Education Attainment (AEA), which measures the percent of adults aged 25 and over with a college degree. We also obtained the neighborhood median annual household income. The COI and EOI were coded into five categories (1 = very low opportunity, 2 = low, 3 = moderate, 4 = high, 5 = very high opportunity).

2.4. Statistical analyses

Sleep disturbance was correlated with neurocognitive measures to determine the association between the two variables. Stepwise linear regression analysis was used to determine explained variance and the most powerful predictors of neurocognitive outcomes using sleep disturbance parameters while controlling for SES, age, and time between sleep study and neurocognitive assessment. Pearson's partial correlation coefficients were conducted to determine the degree of the linear relationship between sleep disturbance and SES after controlling for the effects of age and gender. Two-tailed zero-order Pearson correlations were performed between SES variables to determine the association and ultimately determine the variable to use as a covariate. Assumptions of multiple regression were met including normality, independence, linearity, and homoscedasticity. We accounted for clustering of individuals within Census tracts by using robust standard errors [73]. All statistical analyses were conducted using IBM SPSS version 27 (IBM Corporation, Armonk, New York), with an alpha level set to 0.05.

3. Results

3.1. Sample characteristics

Participants were 27 children and adolescents with SCD ages 6–17 years at the time of their neurocognitive testing (mean ± SD, 10.6 ± 3.5), and ages during their sleep study ranged from 5 to 15 years (9.4 ± 3.2). All participants were African American, predominantly HbSS genotype (89% HbSS, 7% HbSB+, 4% HbSC), and 48% were female. The average time between participants' sleep study and neurocognitive assessment was 14.5 months. Descriptive statistics for sleep parameters include AHI (1.2 ± 1.9), mean SpO2 (96.9% ± 1.6%), pTST SpO2<90% (1.3% ± 3.7%), and the arousal index (5.1 ± 3.9); 2 of the 27 participants underwent a tonsillectomy or adenoidectomy before their sleep study. Descriptive statistics for SES variables were as follows: mean household income was $39,286 (standard error ± 2526), and the percent of adults over 25 years of age with at least a college degree was 18.9% ± 1.8%. The ADI scale was dichotomized into most disadvantaged [1–5] and least disadvantaged [6-10] (56% and 44%, respectively; mean ± standard error (SEM), 4.85, ± .50). Frequencies were also obtained for the COI rating (33% very low, 41% low, 19% moderate, and 7% very high; SEM ± 0.21), and the EOI rating (48% very low, 18% low, 22% moderate, and 4% very high; SEM ± 0.26), Table 1. Correlations between the socioeconomic variables were strong. The correlation between the ADI and COI was 0.70; between ADI and EOI, 0.61; between ADI and AEA, 0.70; and between ADI and mean household income, 0.62. All correlations were statistically significant ($p < 0.001$). Multicollinearity was assessed using collinearity diagnostics for all SES variables. Given the moderate collinearity amongst SES variables, the variable with the most variance, ADI, was selected as the primary SES covariate to use in further analyses.

The mean overall intellectual ability (mean, 84.15, 95% CI [80.52, 87.78]) and the mean verbal comprehension (85.41, [81.65, 89.17]) in this study's sample were both 15 standard points below or more from the population average (1 SD), representing neurocognitive abilities in this sample to be clinically meaningfully below the age-normative group mean of 100 and standard deviation of 15, Fig. 2.

3.2. Correlations with sleep parameters

Based on the four proposed sleep disturbance parameters during PSG, (AHI, mean SpO2, pTST SpO2 < 90%, and the arousal index), partial correlations were conducted to explore associations with neurocognitive outcomes. No significant correlations were found. Partial correlations between sleep measures and SES variables adjusting for age, sex, and time between studies were also conducted, and no significant correlations were found.

3.3. Sleep and verbal comprehension

The covariates (time between participant's sleep study and neurocognitive assessment, age, and ADI) and the four sleep disturbance parameters (AHI, mean SpO2, pTST SpO2 < 90% and the arousal index) were entered in stepwise linear regression analysis to predict verbal comprehension scores. The results of the regression indicated that the explained variance for the covariates alone was 16% (R = 0.40), which increased to 31% (R = 0.56) with the

Table 1
Sample characteristics.

Characteristic (N = 27)		Range
Age at Sleep Study y, M (SD)	9.4 (3.2)	5–15
Age at Neuropsych Testing y, M (SD)	10.6 (3.5)	6–17
Female sex, n (%)	13 (48)	
Race, n (%)		
African American	27 (100)	
Sickle Cell Disease Phenotype, n (%):		
HbSS	24 (88.9)	
HbSB^{+}	2 (7.4)	
HbSC	1 (3.7)	
History of Asthma, n (%)	18 (66.7)	
History of Acute Chest Syndrome, n (%)	18 (66.7)	
Hydroxyurea Treatment, n (%)	24 (88.9)	
Transfusion Treatment, n (%)	18 (66.7)	
Obstructive Sleep Apnea, n (%)	9 (33.3)	
Time Between Sleep Study and Neurocognitive Testing, mo, M (SD)	14.5 (17.0)	3–55
Mean O_2, M (SD)	96.9% (1.6%)	93.1%–99.2%
pTST SpO_2 < 90%, M (SD)	1.3% (3.7%)	0%–17%
Apnea hypopnea index, M (SD)	1.2 (1.9)	0–7.5
Arousal index, M (SD)	5.1 (3.9)	0–17
Socioeconomic Status:		
Median Household Income, M (SD)	39,286.3 (1,3126.0)	17, 083–82, 969
Adult Educational Attainment, M (SD)	18.9 (9.3)	9–44
Area Deprivation Index, n (%):		
Most Disadvantaged (1–5)	15 (56%)	
Least Disadvantage (6-10)	12 (44%)	
Child Opportunity Index, n (%):		
Very Low	9 (33%)	
Low	11 (41%)	
Moderate	5 (19%)	
Very High	2 (7%)	
Education Index, n (%):		
Very low	13 (48%)	
Low	5 (18%)	
Moderate	2 (22%)	
Very High	1 (4%)	

M: mean; SD: standard deviation; mo: months; y: year.

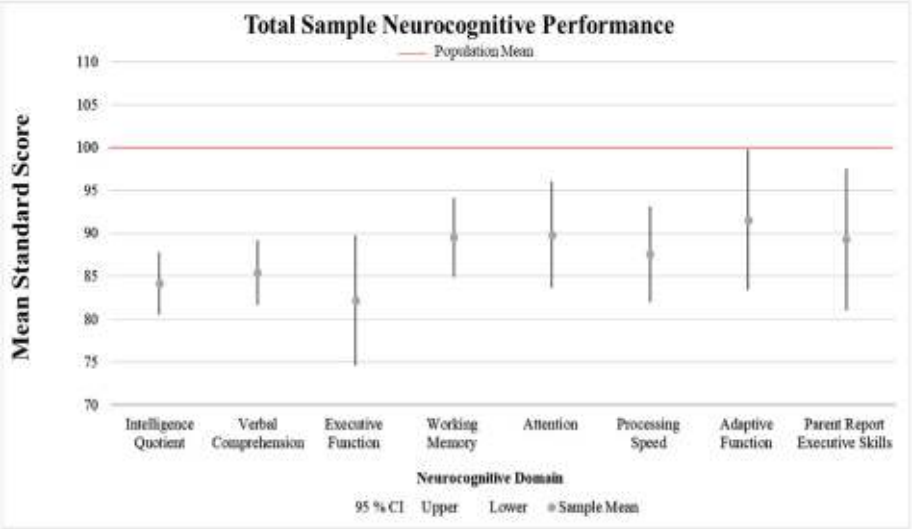

Fig. 2. Total sample mean for each cognitive domain based on age equivalents Bar graph of neuropsychological performance across domains. Scores are represented as standard scores (red line represents mean 100, standard deviation 15), including 95% minimum (bottom line) and maximum (top line) confidence intervals (CI). . (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

addition of mean SpO2, $F(2,24) = 5.36$, $p = 0.012$. The mean nocturnal SpO2 significantly predicted verbal comprehension above and beyond demographic and SES factors. Specifically, verbal comprehension decreased by 2.37 standard points for every unit decrease on average in mean SpO2 (Table 2). The three remaining sleep parameters, the AHI, arousal index, and pTST SpO2 <90% were excluded from the model as they did not significantly add more to the prediction of verbal comprehension.

Table 2
Stepwise linear regression resultsStepwise
linear regression models for different neurocognitive measures.

Dependent Variable	Explained Variance %		Variables Included in the Model	Unstandardized Coefficients		Standardized Coefficients	
	R [2]	Adj R^2		B	Standard Error	β	*p*
Verbal Comprehension Index (n = 27)	0.56	0.31	Constant	−148.27	100.35		0.153
			Time Between Sleep Study and Neuropsych Testing	0.28	0.10	0.49	0.010
			Mean O2	2.37	1.03	0.40	0.031
Working Memory Index (n = 27)	0.38	0.32	Constant	83.91	2.46		<0.001
			Time Between Sleep Study and Neuropsych Testing	0.52	0.14	0.76	0.001
			pTST SpO2 <90%	−1.46	0.63	−0.46	0.030

Mean O2: mean oxygen saturation; pTST SpO2<90%: percent of total time spent under 90% oxygen saturation; Neuropsych: neuropsychological.

3.4. Sleep and working memory

Using stepwise linear regression model to predict working memory scores from the four sleep disturbance parameters (AHI, mean SpO2, pTST SpO2 < 90% and the arousal index) while accounting for the following covariates, time between participant's sleep study and neurocognitive assessment, age, and ADI; the strongest predictor was pTST SpO2 < 90%. Explained variance for the covariates alone was 24% (R = 0.49), the variance increased to 38% (R = 0.61) after adding pTST SpO2 < 90%, $F(2, 24) = 7.23$, $p < 0.01$ Therefore, pTST SpO2 < 90% significantly predicted working memory scores above and beyond demographic and SES factors. Specifically, working memory decreased by 1.47 standard points for every 1% increase in time spent under 90% oxygen saturation (pTST SpO2 <90%) (Table 2). The three remaining sleep parameters, the AHI, arousal index and mean SpO2 were excluded from the model as they did not significantly add more to the prediction of working memory. Additionally, AHI, SpO2, pTST SpO2 < 90%, and the arousal index did not significantly predict the other executive function skills (cognitive flexibility, processing speed, attention), or parent reported executive functioning, emotional, or behavioral functioning. To account for pulmonary treatment effects, these regressions were run again without the two participants who received a tonsillectomy and adenoidectomy between their PSG and neurocognitive tests. Results remained consistent for both verbal comprehension (p = 0.037) and working memory (p = 0.022).

4. Discussion

To our knowledge, this study is the first to examine the relationship between sleep and neurocognition using objective measures of sleep disturbance, including PSG in a controlled environment, and standardized neurocognitive assessments to determine neurocognitive outcomes while accounting for SES in youth with SCD. The current study found that sleep disturbance significantly affects verbal comprehension and working memory abilities in youth with SCD. Specifically, mean nocturnal SpO2 and pTST SpO2 < 90%, which are fairly accurate readings of deoxygenation measured by a PSG in a controlled environment, significantly predicted performance on measures of verbal comprehension and working memory, respectively. In addition, consistent with other studies, we found lower neurocognitive outcomes in youth with SCD compared to normative samples. These results are consistent with previous studies [22,74] and provide evidence that nocturnal oxygen desaturation is a risk factor for neurocognitive deficits.

Findings of sleep and verbal abilities are variable across studies. While some studies did not find sleep disordered breathing to be significantly related to verbal abilities in young children [75,76], other studies found verbal abilities to be significantly linked to nocturnal sleep disturbance ranging from snoring to obstructive sleep apnea, with increased deficits seen in children with high severity and morbidity [77–79]. Reduced phonological processing has also been found to be associated with sleep disordered breathing, which is a critical skill in learning to read and ultimately developing verbal abilities [80]. Likewise, verbal comprehension measures utilized in the current study are cognitive processes involving logical thinking, generalization thinking, and abstract thinking that typically reflect left frontal brain function. Thus, the pathophysiological mechanism underlying the decline seen in verbal comprehension may be associated with decreased activation in the prefrontal cortex, which is known to be affected by nocturnal oxygen desaturation the most [28–30,81–85].

In addition, this study found decreased working memory ability related to nocturnal oxygen desaturation. Working memory is a form of executive functioning also associated with prefrontal activation, specifically in the dorsolateral prefrontal cortex which also relies heavily on metabolic resources during sleep [86]. As youth with SCD reach adolescence and young adulthood, a time when executive skills are in high demand, treatment noncompliance and mortality rates increase [87–89]. Executive function is a fundamental skill that is important for cultivating skills of independence, self-determination, and decision making [90]. Difficulties in these neurocognitive skills may compromise medical adherence, QoL, and mortality rates for youth with SCD. Thus, this study's findings and other studies reporting lower performances in cognitive functioning, including verbal intelligence, executive function, attention, working memory, and processing speed, correlated with sleep disturbance severity [22,25] are consistent with previous literature on the implications of reduced metabolic resources in the prefrontal cortex.

When considering the associations found between sleep disturbance, verbal comprehension and working memory, it is important to discuss the similarities and differences of these tasks. Specifically, for the two cognitive domains found to be significant in this study, verbal comprehension utilizes abstract verbal reasoning and working memory relies on the ability to hold and manipulation information in mind. Verbal comprehension and working memory are two constructs that require greater cognitive processes and the coordination of multiple brain regions. Interestingly, executive function skills (cognitive flexibility, processing speed, attention) were not found to be significant with sleep disturbance in this study. Processing speed, attention, and cognitive flexibility tasks are all tasks that are environmentally specific. It may be that in the controlled testing environment (i.e., quiet, distraction free setting) in which tasks are short and discrete, sleep disturbance does not affect these skills. It is plausible that it is only when individuals must marshal these skills in a busier environment with multiple demands on attention and processing (e.g., home, school, work) that the effects of sleep disturbances are then observed. However, it

may also be that given our small sample size we were unable to identify other areas of executive function that could be related to sleep disturbances. Our results found that cognitive flexibility and processing speed approached significance with a p value of 0.06 and 0.10, respectively; with a larger sample size it is possible cognitive flexibility and processing speed domains are also affected by sleep disturbances. Lastly, research has demonstrated that the parent report of executive functioning does not sufficiently predict performance based executive function ability [91,92]. One explanation for this lack of correlation between subjective and objective measures of executive function, is that the BRIEF parent report measure taps into aspects outside of executive function such as the behavioral components and environmental influences while the objective measures of executive functioning assess the cognitive component.

Moreover, 9 (33%) of the participants in this study were diagnosed with obstructive sleep apnea (OSA), classified by an AHI $\geq$ 1; however, 2 (7%) of participants fell in the moderate OSA range. The prevalence rate of cormorbid OSA in youth with SCD is 41%. OSA is associated with increased risk of sleep disorded breathing and increased SCD complications including pain frequency and neurologial impairments [41,93]. Thus, this study's findings of neurocognitive impairment with a sample of low grade OSA demonstrate an important implication for children with more severe respiratory complications. Additionally, reduced SpO2 in SCD individuals increases the risk of pain crises, acute chest syndrome, and stroke [33–37]. More specifically, decreased SpO2 induces polymerization or sickling of the hemoglobin molecule (HbS) [43]. Sickling of the hemoglobin molecule (HbS) results in vaso-occlusion, blocking organ blood supply, and decreasing oxygen to organ tissues throughout the body [2,3]. Consequently, the cycle of recurrent deoxygenation suggests an increased risk of low levels of oxygen delivered to the developing brain of youth with SCD. Extending on a small but growing area of literature, the results demonstrate that youth with SCD are at risk of medical complications, neurocognitive deficits, as well as a decreased QoL, which can be affected by sleep disturbances. As low oxygenation is the primary trigger of red blood cells sickling, SCD children are at an even higher risk of neurocognitive deficits related to sleep disturbances.

SCD is most prevalent in African Americans, and they are at increased risk of living in deprived areas [54]. The neurocognitive deficits seen in youth with SCD are commonly linked to SES, given that SES is a consistent contributor to health disparities and decreased QoL in underserved populations [53,94]. Conversely, previous literature also shows that despite economic disadvantage, children show similar cognitive performance with optimal sleep quality. The SES in this study skewed mostly towards high disadvantage and was not significantly associated with the neurocognitive domains explored. Although SES plays a role in sleep quality, sleep disturbance measured by deoxygenation may be differently associated with SES and needs to be explored separately. Thus, future research should consider other socioeconomic factors that affect sleep, such as noise and air pollution.

This study provides a preliminary basis for describing the relationship between neurocognition and sleep disturbance parameters in youth with SCD. Yet, this research has a few limitations. First, the central limitation is the small sample size which limits the generalizations that can be made from the results. Nevertheless, our sample demonstrated significant neurocognitive deficits across neurocognitive domains and highlighted the pervasive SES disadvantages of patients living with SCD. Also, we controlled for comorbid conditions that affect neurocognition, including silent infarcts and stroke. Lastly, while our sample size was smaller, we used objective PSG data in a clinical setting, which has much higher sensitivity and accuracy than both in home measures and patient-reported sleep questionnaires. Additionally, this study included mainly youth who have sickle cell anemia (SCA, HbSS) genotype, which according to several meta-analysis studies, demonstrates a sample of participants at higher risk of more profound neurocognitive deficits due to increased risk of medical complications [8,10,17]. Therefore, this study represents likely outcomes for future larger studies. Second, due to the retrospective nature of this study, the range of duration between participant's PSG and neurocognitive is wide. Future studies should collect prospective data on neurocognition in conjunction with PSG during a narrower age range when youth experience the most prominent brain growth and development. Lastly, it is important to note this study used neighborhood SES metrics, which have less variation than patient- or household-level SES measures. Future studies should collect patient and household SES measures to assess the influence of socioeconomic and environmental factors on sleep disturbance and neurocognitive outcomes.

5. Conclusion

Our results support nocturnal hypoxemia is a possible contributory factor for verbal comprehension and working memory difficulties in youth with SCD. Given the vital role of normal oxygenation in brain development, the use of standardized hospital-based PSG in this study suggests nocturnal hypoxemia as a plausible biological risk factor. These findings along with findings of medical complications associated with low oxygen saturation, support future prospective research of supplemental oxygen during sleep for patients with SCD and nighttime hypoxemia. Overall, these findings identify the need for optimal nocturnal oxygen in youth with SCD, and sleep as a potential modifiable factor to be targeted by behavioral and pharmacological interventions to reduce neurocognitive deficits.

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CRediT authorship contribution statement

Tiffany Tucker: study design, initiation of the project, data collection, Formal analysis, and management of the project, verified data, data interpretations, writing the manuscript. **Ammar Saadoon Alishlash:** Conceptualization, oversight, literature search, Methodology, data extraction, writing of the manuscript. **Jeffrey D. Lebensburger:** Conceptualization, and study design, oversight, Writing – original draft. **Olivio J. Clay:** Formal analysis, data interpretations, study design, oversight, Writing – original draft. **Gabriela R. Oates:** Methodology, oversight, data interpretations, writing of the manuscript. **Anis Nourani:** data extraction, Conceptualization, Methodology. **Smita Bhatia:** Supervision, and oversight, writing of the manuscript. **Donna L. Murdaugh:** Conceptualization, and design, Supervision, and oversight, literature search, data interpretations, data extraction, Methodology, writing of the manuscript.

Declaration of competing interest

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

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