Published in final edited form as:

Pediatr Blood Cancer. 2022 March ; 69(3): e29531. doi:10.1002/pbc.29531.

Neurocognitive functioning in preschool children with sickle cell disease

Andrew M. Heitzer[1],

Diana L. Cohen[1],

Victoria I. Okhomina[2],

Ana Trpchevska[1],

Brian Potter[1],

Jennifer Longoria[1],

Jerlym S. Porter[1],

Jeremie H. Estepp[3],

Allison King[4],

Misham Henley[3],

Guolian Kang[2],

Jane S. Hankins[3]

[1]Department of Psychology, St. Jude Children's Research Hospital, Memphis, TN

[2]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis, TN

[3]Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN

[4]Program in Occupational Therapy and Departments of Pediatrics and Medicine, Washington University, St. Louis, MO

Abstract

Background: Children with sickle cell disease (SCD) experience neurodevelopmental delays; however, there is limited research with preschool age children. This study examined neurocognitive risk and protective factors in preschoolers with SCD.

Procedure: Sixty-two patients with SCD (60% HbSS/HbSβ^0-thalassemia; 40% HbSC/HbSβ$^+$-thalassemia) between the ages of 3 and 6 years (Mean=4.77 years) received a neuropsychological evaluation as routine systematic surveillance. Patients were not selected for disease severity, prior central nervous system findings, or existing cognitive concerns. Thirty-four patients (82% HbSS/HbSβ^0-thalassemia) were prescribed hydroxyurea (HU) at the time of their neuropsychological evaluation. On average, these patients had been prescribed HU at 2.15 (Standard Deviation=1.45) years of age. The average dose was 28.8 mg/kg/day. Besides genotype, there were no group differences in medical or demographic factors based on HU treatment status.

Corresponding author: Andrew M. Heitzer; St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678; aheitzer@stjude.org; Phone: (901) 595-7650; Fax: (901) 595-4701.

Results: Patients with HbSS/HbSβ^0-thalassemia scored below normative expectations on measures of intelligence, verbal comprehension, and school readiness (false discovery rate adjusted p-value [pFDR]<0.05). Age, sickle genotype, and HU treatment exposure were not associated with measured neurocognitive outcomes (pFDR>0.05). Greater social vulnerability at the community level was associated with poorer performance on measures of intellectual functioning, verbal comprehension, visuomotor control, and school readiness, as well as parent report of executive dysfunction (pFDR<0.05). Greater household socioeconomic status was positively associated with academic readiness.

Conclusions: Preschoolers with severe SCD (HbSS/HbSβ^0-thalassemia) perform below age expectations on measures of intelligence and academic readiness. Sociodemographic factors were stronger drivers of neurocognitive performance than disease severity or disease-modifying treatment. Neurodevelopmental interventions targeting the home and broader community environment are needed.

Keywords

sickle cell disease; neurocognition; neurodevelopment; hydroxyurea; preschool; social determinants; socioeconomic status

Introduction

Sickle cell disease (SCD) is a group of genetic blood disorders that results in abnormal hemoglobin within red blood cells.[1] SCD affects approximately 100 000 individuals in the United States, and African American/Black individuals are disproportionally affected.[2] The most common and severe form of SCD is sickle cell anemia (HbSS/HbSβ^0-thalassemia).[3]

SCD is characterized by early and progressive neurocognitive deterioration.[1, 4] Slowed development is thought to result from a combination of social determinants[5] and biological factors.[6, 7] Community characteristics (e.g., poverty rates) and parental characteristics (e.g., level of education) have been found to be independent predictors of cognitive development in young children with SCD.[8, 9] The role of the socioeconomic environment is particularly salient in the United States where there are high levels of income inequality and a lack of universal healthcare. Chronic neurological insults include accumulated micro-infarcts, hypoxemia, and repeated tissue ischemia.[10] Silent infarcts occur in 25-35% of children with SCD.[11] Following the advent transcranial doppler screening for stroke risk and chronic transfusion therapy for those identified at risk, the prevalence of overt stroke is now approximately 2%.[12] Both silent infarcts and stroke are strongly associated with neurocognitive performance in SCD.[13]

There is limited research examining neurocognitive performance in early childhood and preschool patients with SCD, however. From birth to three years of age, studies have documented delays in cognitive, language, and motor functioning. Thompson and colleagues[14] followed 89 children with SCD from 6 to 36 months of age. They observed a significant decline in cognitive development from 12 to 24 months of age. Across other early childhood studies, researchers have documented developmental delays unrelated to lab values or sickle genotype in SCD.[15–19] Yet, a recent study documented increased risk for

developmental delays among 2- and 4-year-olds with a more severe SCD genotype using a parent screening questionnaire.[20] Environmental predictors of developmental delays include reduced parent education,[15, 19] family income,[15] and neighborhood resources.[17]

Three studies with small samples (n<30) have assessed neurocognitive performance in preschool-aged patients with SCD.[21–23] Findings documented deficits in language, visuospatial, and motor domains with medium to large effect sizes compared to normative expectations.[23] Consistent with early childhood studies, neurocognitive performance was associated with socioeconomic status but not lab values or genotype.[23] None of the preschool-aged studies examined school readiness skills, which are the strongest predictors of academic success in later elementary[24, 25] and high-school[26] in the general population. Steen and colleagues[27] examined cognitive and academic skills among students with SCD in kindergarten compared to demographically matched controls. They observed that students with SCD displayed lower scores on a measure of auditory discrimination and there was a trend towards lower language skills.

Treatments targeted at the symptom burden of SCD, including hydroxyurea (HU), have shown potential neuroprotective effects. Cross-sectional findings from a large SCD cohort (n=364) of patients from school age to young adulthood at our institution demonstrated that HU use was associated with higher scores on measures of overall intellectual functioning.[9] Further, we found that earlier use of HU was positively associated with most neurocognitive domains. The only study to examine neurocognitive outcomes following HU treatment in young children (9-18 months), found no difference in cognitive or adaptive development in children treated with HU vs. placebo over two years.[28] The mechanism behind these potential neuroprotective effects is unknown. HU reduces cerebral metabolic stress and improves oxygen delivery to the brain,[29, 30] potentially preserving neurocognitive skills.

Our understanding of neurocognitive performance and risk factors in preschool children with SCD is limited. In the present study, the first objective was to examine neurocognitive performance across a wide range of outcomes compared to normative expectations. The second objective was to determine if disease severity, HU treatment, or socioeconomic status were associated with outcomes. We hypothesized that preschoolers with SCD would perform below normative expectations across outcomes and that improved neurocognitive performance would be associated with HU treatment and increased socioeconomic status but not sickle genotype.

Methods

Participants

Preschool participants of the Sickle Cell Clinical Research Intervention Program (SCCRIP) study, ages 3 to 6 years with a cognitive assessment, were eligible for this study. The design of SCCRIP has been described previously.[31] Briefly, SCCRIP is a longitudinal lifetime cohort study that collects retrospective and prospective data on clinical, neurocognitive, psychosocial, geospatial, and health outcomes of children, adolescents, and adults with SCD. SCCRIP was approved by the St. Jude Internal Review Board, and all participants provided written informed consent prior to participation. These assessments are not clinical

referrals, but a systematic surveillance, as patients were not selected for disease severity, prior central nervous system findings, or existing cognitive concerns. All data were collected between 2012 – 2018.

Demographic, medical, and treatment variables

Social vulnerability on the community level was calculated using The Social Vulnerability Index (SVI).[32, 33] The SVI estimates the relative vulnerability of participants based on variables such as education, poverty, and housing data (renting vs. home ownership),[32] where a higher percentile score (range=0-100) means higher social vulnerability. The Barratt Simplified Measure of Social Status (BSMSS)[34] was used to measure household socioeconomic status based on a composite of maternal and paternal education as well as occupation status. The BSMSS yields a single comprehensive score ranging from 8 to 66 by adding the education and occupation scores, with a lower score equating to lower household socioeconomic status.

HU was administered to participants with HbSS/HbSβ^0-thalassemia according to NHLBI guidelines.[35] For participants with HbSC/HbSβ^+-thalassemia, HU administration was based on the frequency of acute disease complications.[36] Hematologic indices including total hemoglobin (Hb), fetal hemoglobin (HbF), white blood cell (WBC) count, and platelet count (PLT) were performed at steady state on the same day of neurocognitive testing or were the average value of measurements within three months prior to testing. Daytime Hb oxygen saturation was measured on the same day of the neurocognitive testing. Lab values were chosen as measures of disease severity as they reflect the underpinnings of the disease leading to clinical symptoms. Hb and HbF are well validated markers of disease severity in SCD. WBC and PLT count are markers of inflammation and are associated with worse clinical outcomes in SCD. Finally, daytime Hb oxygen saturation was used as a proxy for cerebral oxygen saturation.

Neurocognitive measures

Participants completed a battery of neurocognitive tests. The administration of all measures was completed by a licensed psychologist or a psychometrist supervised by a licensed psychologist. Testing was administered in a private room in the psychology clinic at St. Jude Children's Research Hospital. A structured interview was completed with all parents while their child completed testing. This interview assessed a wide range of topics such as developmental history, intervention services, and parent education/occupation.

The Wechsler Preschool & Primary Scale of Intelligence, Fourth Edition (WPPSI-IV)[37] was used to measure intelligence (FSIQ). For children below 4 years of age, the FSIQ contains the following subtests: Receptive Vocabulary (identifying spoken words), Information (verbal knowledge), Block Design (visuospatial reasoning), Object Assembly (visuospatial and abstract reasoning), and Picture Memory (visual working memory). The FSIQ for children above 4 years of age is composed of the following subtests: Information (verbal knowledge), Similarities (verbal abstract reasoning), Block Design (visuospatial reasoning), Matrix Reasoning (fluid/abstract reasoning), Picture Memory (visual working memory), and Bug Search (processing speed). The WPPSI-IV also provides a Verbal Comprehension

Index, measuring broad verbal skills. For children younger than 4, the index is composed of Receptive Vocabulary and Information subtests whereas children 4 and older complete the Information and Similarities subtests.

The Wide Range Assessment of Visual Motor Abilities (WRAVMA)[38] – Drawing subtest, measured visuomotor control. The Drawing subtest requires children to draw shapes of increasing complexity, and scoring is based on the accuracy of these drawings. School Readiness was assessed using the Bracken Basic Concept Scale: Receptive – Third Edition, School Readiness Composite (BBCS-3:R).[39] The BBCS-3:R measures knowledge of school readiness concepts such as shapes, colors, numbers, letters, and sizes. The Behavior Rating Inventory of Executive Function – Preschool (BRIEF-P) [40] was used to assess executive functioning in day-to-day activities based on parent report. Specifically, we report the Global Executive Composite (GEC) scale, which is a composite of all clinical scales, representing overall executive functioning. Most participants completed the entire battery of measures, and there was minimal missing data (WPPSI-IV = 1, WRAVMA = 2, BBCS-3:R = 2, BRIEF-P = 0).

All included measures demonstrate adequate reliability and validity for clinical use. Normative data for all included neuropsychological measures approximates the demographic distribution of the United States based on U.S. census data. African Americans accounted for approximately 12-18% of participants in the normative samples.

Statistical Analyses

Two-sample t-test or Wilcoxon rank sum test and Fisher's exact test were used to evaluate two group differences on demographic and medical/treatment variables. The Shapiro–Wilk test was used to test for normality of the data.

For our first objective, one-sample-t test or Wilcoxon signed rank test was used to compare neurocognitive performance across a wide range of outcomes to their normative expectations. Cohen's d was calculated as an effect size measure.[41] For the secondary objective, univariate correlation analyses were first conducted between neurocognitive outcomes with demographic, medical, and treatment factors using Pearson or Spearman correlation test for continuous variables and point-biserial correlation for the variable of currently on HU. Then univariate and multivariate linear regression models were used to assess the associations of neurocognitive performance with each of the factors including sickle genotype, HU treatment, or socioeconomic status along with common covariates of age at evaluation and sex. Before multivariate analysis, we checked all the covariates for multicollinearity (a variance inflation factor <2). All p-values were two-sided. False discovery rate (FDR) adjusted p values (pFDR or q-value) were used to account for multiple comparisons and pFDR < 0.05 was considered statistically significant. Because of small sample sizes, we were underpowered to conduct analyses separately for the secondary objective by sickle genotype. Analyses were performed in Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Demographic and clinical characteristics by HU use

Neurocognitive testing was administered to a total of 62 patients that on average were 4.77 (Standard Deviation [SD]=0.60) years of age at the time of testing (Table 1). Out of the entire sample, 34 (55%) patients received disease-modifying therapy in the form of HU. Those taking HU, started the medication at 2.15 (SD=1.45) years of age and were prescribed the medication for 2.62 (SD=1.07) years on average at the average dose of 29 mg/kg/day. Four patients received HU treatment for less than a year. Approximately 18% of patients had parent-reported developmental concerns and 16% received early intervention services. A large majority (88%) attended either daycare, preschool, or pre-kindergarten. As expected, patients with HbSS/HbSβ^0-thalassaemia were more likely to be prescribed HU than patients with HbSC/HbSβ^+-thalassaemia (pFDR=0.001). Patients prescribed HU displayed higher levels of HbF than those who were not prescribed HU (pFDR=0.05). No other medical or sociodemographic factors differed between the HU-treated and untreated groups (all pFDR>0.05).

The 62 patients with neurocognitive testing were similar to those without testing based on demographic characteristics (Supplemental Table 1). Univariate associations between neurocognitive outcomes with demographic, medical, and treatment factors are provided in Supplemental Table 2.

Sickle genotype and neurocognitive performance

As displayed in Table 2, patients with HbSS/HbSβ^0-thalassaemia performed below normative expectations on measures of intelligence (pFDR<0.01), school readiness (pFDR=0.01), and verbal comprehension (pFDR<0.01). In contrast, patients with HbSC/HbSβ^+-thalassaemia did not perform below normative expectations on any outcome (all pFDR>0.05). In univariate analyses, patients with HbSS/HbSβ^0-thalassaemia obtained lower intelligence scores than those with HbSC/HbSβ^+-thalassaemia (p=0.04), yet this group difference did not persist after correction for multiple comparisons (pFDR=0.18). In multivariate analyses, adjusted for household (BSMSS) and community (SVI) socioeconomic status, sex, and current HU use, there were no differences in neurocognitive performance between those with HbSS/HbSβ^0-thalassaemia and HbSC/HbSβ^+-thalassaemia.

Current use of HU and neurocognitive performance

Table 3 displays neurocognitive outcomes by HU treatment status. HU treatment was not associated with neurocognitive performance on any outcome measure in univariate analyses (all pFDR>0.05). Consistently, there was no effect of HU treatment on neurocognitive performance after adjusting for household (BSMSS) and community (SVI) socioeconomic status, age, genotype, and sex (all pFDR>0.05).

Lab values and neurocognitive performance

In multivariate analyses adjusting for household (BSMSS) and community (SVI) socioeconomic status, age, genotype, sex, and HU treatment there was no association

between HbF, Hb, WBC, or Hb oxygen saturation and any neurocognitive outcome (all pFDR>0.05). However, there was a positive association between PLT and intelligence (Estimate=0.04, SE=0.01, pFDR=0.02) and verbal comprehension (Estimate=0.04, SE=0.01, pFDR=0.01).

Socioeconomic status and neurocognitive performance

In univariate analyses (see Table 4), decreased household socioeconomic status (BSMSS) was associated with lower scores on a measure of School Readiness (pFDR=0.005). This association did persist in multivariate analysis, after adjusting for age, sex, sickle genotype, and HU treatment (pFDR=0.01). When community socioeconomic status (SVI) was added as a covariate, household socioeconomic status (BSMSS) did not maintain significance after adjustment for multiple comparisons (pFDR=0.06). Intelligence, visuomotor control, parent ratings of executive functioning, and verbal comprehension were not associated with household socioeconomic status (BSMSS) in univariate or multivariate analyses (all pFDR>0.05).

Table 4 displays associations between community socioeconomic status (SVI) and neurocognitive performance. Multivariate analyses adjusted for age, sex, genotype, and HU treatment, but not household socioeconomic status, demonstrated that increased social vulnerability was associated with lower scores on measures of intelligence, visuomotor control, academic readiness, and verbal comprehension as well as greater parent ratings of executive dysfunction (all pFDR<0.05). After adding household socioeconomic status (BSMSS) as a covariate, only the association between the SVI and visuomotor control remained (p=0.02), but this relationship did not persist after adjusting for the false discovery rate (pFDR=0.06).

Discussion

In the largest study of preschool children with SCD, poor neurocognitive performance was associated with reduced familial socioeconomic status and increased social vulnerability at the community level. Across most measures, HU treatment status and disease severity were not associated with neurocognition. Measures of overall intelligence and school readiness were below normative expectations for patients with HbSS/HbSβ^0-thalassaemia but not among those with HbSC/HbSβ^+-thalassaemia.

Consistent with several other studies,[17, 19, 23] sociodemographic factors were the primary contributor to neurocognitive outcomes amongst our sample of preschoolers with SCD. Unlike prior studies, we assessed both familial and community level metrics of socioeconomic status. Our analyses suggest that both metrics of socioeconomic status (e.g., poverty, housing data) contribute to early neurocognitive performance. Many patients diagnosed with SCD live in communities with limited resources and experience social, political, and economic marginalization.[42–44] These social determinants have a profound impact on nearly every facet of health.[45–47] As demonstrated in our analyses, community and familial socioeconomic status are highly associated and overlapping constructs. Prior work among young children with SCD has shown that parenting styles[14] and quality of the household environment[17] predict neurodevelopmental outcomes. These findings highlight

the importance of bolstering household and community-level resources for families of children with SCD and suggest targets for neurodevelopmental interventions. Medical providers may support these families by providing information on child development (e.g. importance of reading to child) and local community resources providing early intervention or high-quality preschool programs. Future research is needed to determine what specific aspects of community-level social vulnerability contribute to early neurocognitive development.

In contrast to studies of school-age and adolescent patients with SCD,[9, 48–50] HU treatment was not significantly associated with neurocognitive performance on any outcome measure. The most obvious explanation for this discrepancy is the limited duration of treatment exposure among our sample. On average, patients were treated with HU for 2.55 years at the time of their neurocognitive evaluation, compared to 3.04 years in our prior analyses of patients ranging from 8-24 years of age.[9] Duration of treatment is known to moderate the effects of HU treatment on neurocognitive performance.[9, 48] Furthermore, measures of disease severity did not appear to significantly contribute to neurocognitive outcomes in young patients with SCD in previous studies,[14, 19] therefore any neuroprotective effect of HU treatment at this young age is likely to be small relative to that of other children with longer treatment exposure. Lastly, the current sample of patients is much smaller than our previous analyses of older children,[9, 48] limiting the power to detect treatment effects. To determine the long-term effects of HU treatment, we will serially monitor these patients to determine the trajectory of neurocognitive functioning for those with and without HU treatment.

Preschool children with HbSS/HbSβ^0-thalassemia obtained scores below normative expectations on measures of overall intelligence and school readiness. Specifically, overall intelligence fell 3/4th of a standard deviation below expectations and school readiness fell a half standard deviation below normative values. In contrast, those with HbSC/HbSβ^+-thalassaemia performed within normative expectations across measures. Although group differences based on sickle genotype did not reach significance, it appears that patients with HbSS/HbSβ^0-thalassemia display neurocognitive weaknesses that are not present or detectable in HbSC/HbSβ^+-thalassaemia at this early age, consistent with neurocognitive differences based on genotype observed in adulthood[51] and select early childhood studies.[20] Reduced neurocognitive performance among patients with HbSS/HbSβ^0-thalassemia is potentially due to increased disease severity and higher risk of neurological complications. Visuomotor and executive functioning skills are known to be reduced in older patients with SCD,[52, 53] but these deficits were not yet apparent in our sample. Notably, we relied on parent-report of executive functioning skills, which may not be sensitive to some of the early executive deficits observed in other studies.[21] Weaknesses in school readiness skills were strongly associated with parent education and occupation (r=.42). Because school readiness is highly predictive of later academic performance and a variety of health outcomes, it is essential to increase access to evidence-based school readiness interventions and quality preschool programs for families with SCD. A large majority of our sample were in preschool or daycare, where they should be exposed to pre-academic skills. Therefore, poor performance on the school readiness measure may be reflective of the quality of teaching services.

Most lab markers of disease severity were not associated with neurocognitive performance. Several studies have observed that greater total hemoglobin and/or hematocrit levels are positively associated with neurocognitive outcomes,[54–56] yet others observed no significant differences.[23, 48, 57] Similarly, there are inconsistent findings for measures of HbF, PLT, and oxygen saturation.[9, 58, 59] In the only other preschool-age study of neurocognition to assess the association of lab values and neurocognitive performance, no significant associations were observed.[23] We found that total PLT was positively associated with a measure of intelligence following adjustment for covariates and multiple comparisons. Bernaudin and colleagues previously observed that thrombocytosis was associated with intelligence scores.[54] Additionally, a single study observed that the mean platelet volume is correlated with white matter volume in patients with SCD.[60] The association between PLT and neurocognition is unclear and requires further examination, as results are not consistent and the underlying mechanism whereby platelets may be contributing to brain function are not yet understood.

This study has several strengths including detailed medical, sociodemographic, and treatment history for all participants. The study utilized a wide range of neurocognitive outcomes and assessed multiple facets of socioeconomic status. However, notable limitations do exist. Only patients with clinical indications received neuroimaging, therefore we lacked information on history of silent infarcts or vessel stenoses that may contribute to neurocognitive performance. We were unable to randomize patients to HU, due to treatment being standard of care, and examiners were not blinded to treatment history. Four of the HU-treated patients had received treatment for less than a year, further limiting the neuroprotective effects of the medication. Due to a limited sample size, we were underpowered to examine the effects of HU treatment duration on neurocognitive functioning or interactions between SES and other variables of interest. We did not utilize a demographically matched or sibling-control group. Further, the demographic characteristics of the normative group differs from our sample limiting our interpretation of the results.

In conclusion, our findings suggest that preschool patients with HbSS/HbSβ^0-thalassaemia display deficits in intellectual functioning and academic readiness skills. These early deficits are predominately driven by a combination of familial- and community-level socioeconomic factors rather than disease severity. Yet, other relevant disease factors (e.g., neuroimaging findings and frequency of hospitalizations) were not assessed. Neuroprotective effects of HU treatment were not detected in our sample of preschoolers with SCD, potentially due to limited exposure. Longitudinal studies are needed to determine the neurocognitive trajectory of patients based on HU treatment status. Development of tailored behavioral interventions to address neurocognitive weaknesses early in life are essential for pre-school children with SCD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

A.M.H, D.L.C., J.S.H, and G.K. designed the study, interpreted data, and prepared the manuscript; G. K. and V. O. analyzed the data; J.L., B.P., and J.E. collected data and wrote the manuscript; A.T., A.A.K., J.S.P., and M.H. wrote the manuscript; and all authors critically reviewed and approved the final version of the manuscript.

J.S.H received funding from U01HL133996 during the conduct of this study. A.A.K received funding from R01HL129241, K24HL148305, K12HL137942, U01HL143477, and 5U01HL133994 during the time of his study. J.S.P was supported by K01HL125495 at the time of this project. This research was supported by the American Lebanese Syrian Associated Charities (ALSAC).

The authors would like to thank Jason Hodges, PhD, Pei-Lin Chen, MPH, Courtney Mays, Erin MacArthur, MS, Madelene Wilson, Tiana Thomas, Ruth Johnson, and Michelle Brignac, for support with data collection and regulatory matters.

Conflicts of Interest

Jane S. Hankins, Jeremie H. Estepp, and Allison King receive research funding from Global Blood Therapeutics. Jeremie H. Estepp receives consultancy fees from Global Blood Therapeutics, Forma Therapeutics and bluebird bio. Jane S. Hankins receives consultancy fees from Global Blood Therapeutics, Vindico Medical Education, UpToDate and bluebird bio. There are no other conflicts of interest to report.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations Key

SCD	Sickle Cell Disease
HU	Hydroxyurea
SCCRIP	Sickle Cell Clinical Research Intervention Program
SVI	Social Vulnerability Index
BSMSS	Barratt Simplified Measure of Social Status
Hb	Total Hemoglobin
HbF	Fetal Hemoglobin
WBC	White Blood Cell Count
PLT	Platelet Count
WPPSI-IV	Wechsler Preschool & Primary Scale of Intelligence, Fourth Edition
WRAVMA	Wide Range Assessment of Visual Motor Abilities
BBCS-3:R	Bracken Basic Concept Scale: Receptive – Third Edition
BRIEF-P	Behavior Rating Inventory of Executive Function – Preschool
pFDR	False Discovery Rate Adjusted p value
FSIQ	Full Scale IQ

References

1. Schatz J, McClellan CB. Sickle cell disease as a neurodevelopmental disorder. Mental retardation and developmental disabilities research reviews. 2006;12(3):200–207. [PubMed: 17061284]
2. Piel FB, Steinberg MH, Rees DC. Sickle cell disease. N Engl J Med. 2017;376(16):1561–1573. [PubMed: 28423290]
3. Steinberg MH, Rosenstock W, Coleman MB, et al. Effects of thalassemia and microcytosis on the hematologic and vasoocclusive severity of sickle cell anemia. Blood. Jun 1984;63(6):1353–60. [PubMed: 6722353]
4. Wang W, Enos L, Gallagher D, et al. Neuropsychologic performance in school-aged children with sickle cell disease: a report from the Cooperative Study of Sickle Cell Disease. The Journal of pediatrics. 2001;139(3):391–397. [PubMed: 11562619]
5. Bills SE, Schatz J, Hardy SJ, Reinman L. Social-environmental factors and cognitive and behavioral functioning in pediatric sickle cell disease. Child Neuropsychol. 2020;26(1):83–99. doi:10.1080/09297049.2019.1577371 [PubMed: 30789071]
6. DeBaun MR, Armstrong FD, McKinstry RC, Ware RE, Vichinsky E, Kirkham FJ. Silent cerebral infarcts: a review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. Blood. 2012;119(20):4587–4596. [PubMed: 22354000]
7. Steen RG, Miles MA, Helton KJ, et al. Cognitive impairment in children with hemoglobin SS sickle cell disease: relationship to MR imaging findings and hematocrit. American Journal of Neuroradiology. 2003;24(3):382–389. [PubMed: 12637286]
8. Aygun B, Parker J, Freeman MB, et al. Neurocognitive screening with the Brigance preschool screen-II in 3-year-old children with sickle cell disease. Pediatr Blood Cancer. Apr 2011;56(4):620–4. doi:10.1002/pbc.22833 [PubMed: 21298749]
9. Heitzer AM, Longoria J, Okhomina V, et al. Hydroxyurea treatment and neurocognitive functioning in sickle cell disease from school age to young adulthood. Br J Haematol. 2021;doi:10.1111/bjh.17687
10. Brown RT, Armstrong FD, Eckman JR. Neurocognitive aspects of pediatric sickle cell disease. J Learn Disabil. 1993;26(1):33–45. [PubMed: 8418188]
11. Houwing ME, Grohssteiner RL, Dremmen MHG, et al. Silent cerebral infarcts in patients with sickle cell disease: a systematic review and meta-analysis. BMC Med. 2020;18(1)doi:10.1186/s12916-020-01864-8
12. DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med. 2014;371(8):699–710. [PubMed: 25140956]
13. Prussien KV, Jordan LC, DeBaun MR, Compas BE. Cognitive function in sickle cell disease across domains, cerebral infarct status, and the lifespan: a meta-analysis. J Pediatr Psychol. 2019;44(8):948–958. [PubMed: 31050352]
14. Thompson RJ Jr, Gustafson KE, Bonner MJ, Ware RE. Neurocognitive development of young children with sickle cell disease through three years of age. J Pediatr Psychol. 2002;27(3):235–244. [PubMed: 11909931]
15. Armstrong FD, Elkin TD, Brown RC, et al. Developmental function in toddlers with sickle cell anemia. Pediatrics. 2013;131(2):e406–e414. [PubMed: 23296434]
16. Glass P, Brennan T, Wang J, et al. Neurodevelopmental Deficits Among Infants and Toddlers with Sickle Cell Disease. J Dev Behav Pediatr. 2013;34(6):399–405. doi:10.1097/dbp.0b013e31829c3c48 [PubMed: 23838585]
17. Drazen CH, Abel R, Gabir M, Farmer G, King AA. Prevalence of developmental delay and contributing factors among children with sickle cell disease. Pediatr Blood Cancer. 2016;63(3):504–510. [PubMed: 26575319]
18. Wang WC, Grover R, Gallagher D, Espeland M, Fandal A. Developmental screening in young children with sickle cell disease. Results of a cooperative study. The American journal of pediatric hematology/oncology. 1993;15(1):87–91. [PubMed: 7680549]
19. Aygun B, Parker J, Freeman MB, et al. Neurocognitive screening with the Brigance Preschool screen-II in 3-year-old children with sickle cell disease. Pediatr Blood Cancer. 2011;56(4):620–624. [PubMed: 21298749]

20. Schatz J, Reinman L, Bills SE, Johnston JD. Sociodemographic and Biomedical Correlates of Developmental Delay in 2-and 4-Year-Olds with Sickle Cell Disease. Journal of Developmental and Behavioral Pediatrics: JDBP. 2021;
21. Downes M, Kirkham FJ, Telfer PT, De Haan M. Assessment of executive functions in preschool children with sickle cell anemia. J Int Neuropsychol Soc. 2018;24(9):949–954. [PubMed: 29843828]
22. Downes M, Kirkham FJ, Telfer PT, De Haan M. Altered neurophysiological processing of auditory attention in preschool children with sickle cell disease. J Pediatr Psychol. 2018;43(8):856–869. [PubMed: 29048550]
23. Tarazi RA, Grant ML, Ely E, Barakat LP. Neuropsychological functioning in preschool-age children with sickle cell disease: the role of illness-related and psychosocial factors. Child Neuropsychol. 2007;13(2):155–172. [PubMed: 17364572]
24. Pagani LS, Fitzpatrick C. Children's School Readiness. Health Educ Behav. 2014;41(1):25–33. doi:10.1177/1090198113478818 [PubMed: 23445605]
25. Romano E, Babchishin L, Pagani LS, Kohen D. School readiness and later achievement: replication and extension using a nationwide Canadian survey. Dev Psychol. 2010;46(5):995. [PubMed: 20822218]
26. Fitzpatrick C, Boers E, Pagani LS. Kindergarten Readiness, Later Health, and Social Costs. Pediatrics. 2020;146(6):e20200978. doi:10.1542/peds.2020-0978 [PubMed: 33139455]
27. Grant Steen R, Hu XJ, Elliott VE, Miles MA, Jones S, Wang WC. Kindergarten readiness skills in children with sickle cell disease: evidence of early neurocognitive damage? J Child Neurol. 2002;17(2):111–116. [PubMed: 11952070]
28. Wang WC, Ware RE, Miller ST, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). The Lancet. 2011;377(9778):1663–1672. doi:10.1016/s0140-6736(11)60355-3
29. Fields ME, Guilliams KP, Ragan D, et al. Hydroxyurea reduces cerebral metabolic stress in patients with sickle cell anemia. Blood. 2019;133(22):2436–2444. doi:10.1182/blood-2018-09-876318 [PubMed: 30858231]
30. Estepp JH, Cong Z, Agodoa I, et al. What drives transcranial Doppler velocity improvement in paediatric sickle cell anaemia: analysis from the Sickle Cell Clinical Research and Intervention Program (SCCRIP) longitudinal cohort study. Br J Haematol. 2021;194(2):463–468. doi:10.1111/bjh.17620 [PubMed: 34131902]
31. Hankins JS, Estepp JH, Hodges JR, et al. Sickle Cell Clinical Research and Intervention Program (SCCRIP): A lifespan cohort study for sickle cell disease progression from the pediatric stage into adulthood. Pediatr Blood Cancer. Sep 2018;65(9):e27228. doi:10.1002/pbc.27228 [PubMed: 29797644]
32. Cutter SL, Boruff BJ, Shirley WL. Social vulnerability to environmental hazards. Social science quarterly. 2003;84(2):242–261.
33. Flanagan BE, Hallisey EJ, Adams E, Lavery A. Measuring Community Vulnerability to Natural and Anthropogenic Hazards: The Centers for Disease Control and Prevention's Social Vulnerability Index. J Environ Health. Jun 2018;80(10):34–36.
34. Barratt W The Barratt simplified measure of social status (BSMSS). Indiana State University Terre Haute, IN; 2006.
35. Yawn BP, Buchanan GR, Afenyi-Annan AN, et al. Management of sickle cell disease: summary of the 2014 evidence-based report by expert panel members. Jama. Sep 10 2014;312(10):1033–48. doi:10.1001/jama.2014.10517 [PubMed: 25203083]
36. Luchtman-Jones L, Pressel S, Hilliard L, et al. Effects of hydroxyurea treatment for patients with hemoglobin SC disease. American Journal of Hematology. 2016;91(2):238–242. doi:10.1002/ajh.24255 [PubMed: 26615793]
37. Wechsler D Wechsler Preschool and Primary Scale of Intelligence–Fourth Edition. Wppsi-Iv. January 2012 2012;
38. Adams W, Sheslow D. Wide Range Assessment of Visual Motor Abilities. Wide Range Wilmington, DE; 1995.

39. Bracken BA. Bracken Basic Concept Scale-third edition: Receptive. Harcourt Assessment San Antonio, TX; 2006.
40. Gioia GA, Espy KA, Isquith PK. Behavior Rating Inventory of Executive Function - Preschool Version. Psychological Assessment Resources Odessa FL; 2003.
41. Cohen J A power primer. Psychol Bull. July 1992 2016/09/01/1992;112(1):155. doi:10.1037/0033-2909.112.1.155 [PubMed: 19565683]
42. Nelson SC, Hackman HW. Race matters: perceptions of race and racism in a sickle cell center. Pediatr Blood Cancer. 2013;60(3):451–454. [PubMed: 23023789]
43. Power-Hays A, McGann PT. When actions speak louder than words—racism and sickle cell disease. N Engl J Med. 2020;383(20):1902–1903. [PubMed: 32871062]
44. Farber MD, Koshy M, Kinney TR, Cooperative Study of Sickle Cell D. Cooperative study of sickle cell disease: demographic and socioeconomic characteristics of patients and families with sickle cell disease. J Chronic Dis. 1985;38(6):495–505. [PubMed: 4008590]
45. Berghs M, Ola B, Cronin De Chavez A, Ebenso B. Time to apply a social determinants of health lens to addressing sickle cell disorders in sub-Saharan Africa. BMJ Global Health. 2020;5(7):e002601. doi:10.1136/bmjgh-2020-002601
46. Marmot M Social determinants of health inequalities. The Lancet. 2005;365(9464):1099–1104. doi:10.1016/s0140-6736(05)71146-6
47. Power-Hays A, Li S, Mensah A, Sobota A. Universal screening for social determinants of health in pediatric sickle cell disease: A quality-improvement initiative. Pediatr Blood Cancer. 2020;67(1)doi:10.1002/pbc.28006
48. Partanen M, Kang G, Wang WC, et al. Association between hydroxycarbamide exposure and neurocognitive function in adolescents with sickle cell disease. Br J Haematol. 2020;189(6):1192–1203. doi:10.1111/bjh.16519 [PubMed: 32103506]
49. Puffer E, Schatz J, Roberts CW. The Association of Oral Hydroxyurea Therapy with Improved Cognitive Functioning in Sickle Cell Disease. Child Neuropsychol. 2007;13(2):142–154. doi:10.1080/09297040600584626 [PubMed: 17364571]
50. Tarazi RA, Patrick KE, Iampietro M, Apollonsky N. Hydroxyurea Use Associated with Nonverbal and Executive Skills in Sickle Cell Anemia. J Pediatr Psychol. 2021;doi:10.1093/jpepsy/jsab015
51. Jorgensen DR, Metti A, Butters MA, Mettenburg JM, Rosano C, Novelli EM. Disease severity and slower psychomotor speed in adults with sickle cell disease. Blood Advances. 2017;1(21):1790–1795. doi:10.1182/bloodadvances.2017008219 [PubMed: 29296825]
52. Burkhardt L, Lobitz S, Koustenis E, Rueckriegel SM, Driever PH. Cognitive and fine motor deficits in a pediatric sickle cell disease cohort of mixed ethnic origin. Ann Hematol. 2017;96(2):199–213. [PubMed: 27796476]
53. Smith KE, Schatz J. Working memory in children with neurocognitive effects from sickle cell disease: contributions of the central executive and processing speed. Dev Neuropsychol. 2016;41(4):231–244. [PubMed: 27759435]
54. Bernaudin F, Verlhac S, Freard F, et al. Multicenter prospective study of children with sickle cell disease: radiographic and psychometric correlation. J Child Neurol. 2000;15(5):333–343. [PubMed: 10830200]
55. Ruffieux N, Njamnshi AK, Wonkam A, et al. Association between biological markers of sickle cell disease and cognitive functioning amongst Cameroonian children. Child Neuropsychol. 2013;19(2):143–160. [PubMed: 22176123]
56. Schatz J, Finke R, Roberts CW. Interactions of biomedical and environmental risk factors for cognitive development: a preliminary study of sickle cell disease. J Dev Behav Pediatr. 2004;25(5):303–310. [PubMed: 15502546]
57. Knight S, Singhal A, Thomas P, Serjeant G. Factors associated with lowered intelligence in homozygous sickle cell disease. Arch Dis Child. 1995;73(4):316–320. [PubMed: 7492195]
58. King AA, Strouse JJ, Rodeghier MJ, et al. Parent education and biologic factors influence on cognition in sickle cell anemia. Am J Hematol. 2014;89(2):162–167. [PubMed: 24123128]
59. Vichinsky EP, Neumayr LD, Gold JI, et al. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. JAMA. 2010;303(18):1823–1831. [PubMed: 20460621]

60. Choi S, Bush AM, Borzage MT, et al. Hemoglobin and mean platelet volume predicts diffuse T1-MRI white matter volume decrease in sickle cell disease patients. NeuroImage: Clinical. 2017;15:239–246. doi:10.1016/j.nicl.2017.04.023 [PubMed: 28540180]

Table 1.

Participant characteristics overall and by current HU use

	Overall N = 62	Currently on HU n=33	Not Currently on HU n=29	pFDR
	Frequency (%)	Frequency (%)	Frequency (%)	
Sex				
Female	33 (53.23%)	18 (54.55%)	15 (51.72%)	0.93
Male	29 (46.77%)	15 (45.45%)	14 (48.28%)	
Race				
Black	60 (96.77%)	31 (93.94%)	29 (100.00%)	0.81
White	2 (3.23%)	2 (6.06%)	0 (0.00%)	
Sickle Cell Disease Genotype				
Hb SS/HbSβ^0-thalassemia	37 (59.68%)	27 (81.82%)	10 (34.48%)	**0.001**
Hb SC /HbSβ+-thalassemia / Other	25 (40.32%)	6 (18.18%)	19 (65.52%)	
TCD[a]				
Abnormal	0 (0%)	0 (0%)	0 (0%)	
Conditional	5 (15.15%)	3 (13.04%)	2 (20.00%)	0.81
Normal	28 (84.85%)	20 (86.96%)	8 (80.00%)	
Overall vulnerability summary ranking[b], Mean (SD)	63.68 (30.10)	61.45 (29.89)	66.22 (30.67)	0.81
Very Low (0-15.99)	7 (11.29%)	3 (9.09%)	4 (13.79%)	
Low (16-26.99)	4 (6.45%)	3 (9.09%)	1 (3.45%)	
Moderate (27-37.99)	5 (8.06%)	4 (12.12%)	1 (3.45%)	0.81
High (38-48.99)	3 (4.84%)	2 (6.06%)	1 (3.45%)	
Very High (49-100)	43 (69.35%)	21 (63.64%)	22 (75.86%)	
Born premature	9 (15.52%)	3 (9.68%)	6 (22.22%)	0.79
Concerns about achieving developmental milestones	10 (17.54%)	4 (12.90%)	6 (23.08%)	0.81
Early intervention services	9 (15.79%)	5 (16.13%)	4 (15.38%)	1.00

	Overall N = 62	Currently on HU n=33	Not Currently on HU n=29	pFDR
	Frequency (%)	**Frequency (%)**	**Frequency (%)**	
Daycare/pre-school/pre-K attendance	51 (87.93%)	28 (90.32%)	23 (85.19%)	0.86
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**pFDR**
Age at evaluation (years)	4.77 (0.60)	4.82 (0.63)	4.73 (0.57)	0.81
Age Started HU (years)	2.15 (1.45)	2.15 (1.45)	--	--
Duration on HU (years)	2.62 (1.07)	2.62 (1.07)	--	--
BSMSS	31 (13)	31 (13)	33 (13)	0.81
Number of adults (>18) living in home	2 (1)	2 (1)	2 (0)	0.93
Number of children living in home	2 (1)	2 (2)	2 (1)	0.55
Hemoglobin (g/dL)	9.9 (1.6)	9.6 (1.5)	10.3 (1.7)	0.30
WBC (x10e3/mm3)	9.7 (3.8)	8.9 (3.5)	10.7 (4.0)	0.29
HbF (g/dL)	20.3 (10.7)	22.2 (10.0)	10.1 (9.3)	0.05
Platelet Count (mm3)	344 (150)	347 (177)	341 (107)	0.93
Oxygen Saturation (%)	99 (1)	99 (1)	99 (1)	1.00

M, mean; SD, standard deviation; n, sample size; %, percent; FDR, false discovery rate; HU, hydroxyurea; TCD, transcranial doppler; WBC, white blood cell count; HbF, fetal haemoglobin; BSMSS, Barratt Simplified Measure of Social Status. Values presented as mean (standard deviation) or frequency(group%) unless otherwise noted; Census tract characteristics are reported as percentage.

FDR adjusted p<0.05 were considered significant. Hematologic indices were the average value of measurements collected within 3 months of or the one closest to neurocognitive assessment.

[a] Transcranial doppler mean flow velocity values for each artery: normal (< 170 cm per second), conditional (170- 199 cm per second), and abnormal (> 200 cm per second).

[b] Classifies individuals based on social vulnerabilities at the neighborhood level (e.g. poverty, education, housing data); a higher percentile score indicates higher social vulnerability.

Table 2.

Comparison of participant neurocognitive performance to population norms by genotype

		HbSS/HbSβ0-thalassemia			HbSC/HbSβ+-thalassemia			Effect of Genotype			Adjusted Effect of Genotype		
Measure	**Score**	**Mean (SD)**	**Cohen's D**	**pFDR**	**Mean (SD)**	**Cohen's D**	**pFDR**	**Estimate[a]**	**SE**	**pFDR**	**Estimate[b]**	**SE**	**pFDR**
WPPSI-IV	Full Scale IQ	88 (16)	−0.76	**<.001**	97 (15)	−0.20	0.72	−8.81	4.11	0.18	−5.83	5.15	0.85
WPPSI-IV	Verbal Comprehension	90(14)	−0.71	**<.001**	95 (15)	−0.32	0.62	−5.55	3.76	0.28	−4.38	4.55	0.85
WRAVMA	Drawing	96 (18)	−0.24	0.23	102 (19)	0.10	0.98	−5.60	4.76	0.31	1.07	6.13	0.99
BBCS-3:R	School Readiness Composite	91 (19)	−0.54	**0.01**	97 (17)	−0.17	0.72	−6.66	4.78	0.28	−0.24	5.74	0.99
BRIEF-P Parent	Global Executive Composite	52 (14)	0.19	0.63	51 (13)	0.07	0.98	1.46	3.50	0.68	−0.09	4.59	0.99

SD, standard deviation; SE, standard error; FDR, false discovery rate; WPPSI-IV, The Wechsler Preschool & Primary Scale of Intelligence, Fourth Edition; WRAVMA, The Wide Range Assessment of Visual Motor Abilities; BBCS-3:R, Bracken Basic Concept Scale: Receptive – Third Edition, BRIEF-P, The Behavior Rating Inventory of Executive Function – Preschool

[a]: Model is Neurocognitive measure = B0 + B×genotype where estimate above is Bgenotype and represents the change in score for a SS/SB theta patients compared to SC/SB+/other patients.

[b]: Effect of genotype on neurocognitive score after adjusting for BSMSS, social vulnerability index, sex, and current HU treatment status

Table 3.

Comparison of participant neurocognitive performance to population norms by hydroxyurea treatment status at evaluation

		Current Hydroxyurea			No Current Hydroxyurea			Effect of Current Hydroxyurea Use			Adjusted Effect of Current Hydroxyurea Use		
Measure	**Score**	**Mean (SD)**	**Cohen's D**	**pFDR**	**Mean (SD)**	**Cohen's D**	**pFDR**	**Estimate[a]**	**SE**	**pFDR**	**Estimate[b]**	**SE**	**pFDR**
WPPSI-IV	Full Scale IQ	90 (17)	−0.60	**0.02**	93 (15)	−0.45	0.05	−2.96	4.16	0.98	−0.56	4.90	0.91
WPPSI-IV	Verbal Comprehension	93 (15)	−0.50	**0.02**	91 (14)	−0.59	**0.02**	1.19	3.76	0.98	3.42	4.42	0.91
WRAVMA	Drawing	98 (19)	−0.14	0.59	99 (18)	−0.06	0.48	−1.40	4.74	0.98	−3.61	5.99	0.91
BBCS-3:R	School Readiness Composite	94 (19)	−0.38	0.10	93 (18)	−0.39	0.11	0.14	4.80	0.98	−2.38	5.65	0.91
BRIEF-P Parent	Global Executive Composite	52 (14)	0.15	0.73	52 (13)	0.14	0.94	0.23	3.45	0.98	0.90	4.48	0.91

ISD, standard deviation; SE, standard error; FDR, false discovery rate; WPPSI-IV, The Wechsler Preschool & Primary Scale of Intelligence, Fourth Edition; WRAVMA, The Wide Range Assessment of Visual Motor Abilities; BBCS-3:R, Bracken Basic Concept Scale: Receptive – Third Edition, BRIEF-P, The Behavior Rating Inventory of Executive Function – Preschool

[a]: Estimated change in score for current HU user compared to patient currently not using HU.

[b]: Estimate for effect of current HU use on score after adjusting for BSMSS, social vulnerability index, age at assessment, genotype, sex, and current HU treatment status

Table 4.

Socioeconomic status and neurocognitive performance

		Univariate BSMSS Effect				Multivariate BSMSS Effect			Univariate SVI Effect				Multivariate SVI Effect (No BSMSS)			Multivariate SVI Effect		
Measure	**Score**	**Estimate** [a]	**SE**	**Standardized β** [b]	**pFDR**	**Estimate** [c]	**SE**	**pFDR**	**Estimate** [d]	**SE**	**Standardized β** [e]	**pFDR**	**Estimate** [f]	**SE**	**pFDR**	**Estimate** [g]	**SE**	**pFDR**
WPPSI-IV	Full Scale IQ	0.23	0.15	0.20	0.18	0.07	0.18	0.86	−0.15	0.07	−0.29	**0.02**	−0.16	0.07	**0.04**	−0.13	0.08	0.16
WPPSI-IV	Verbal Comprehension	0.31	0.15	0.29	0.09	0.25	0.16	0.30	−0.18	0.06	−0.37	**0.01**	−0.18	0.06	**0.01**	−0.11	0.08	0.20
WRAVMA	Drawing	0.19	0.20	0.13	0.34	0.04	0.21	0.86	−0.24	0.07	−0.40	**0.004**	−0.27	0.08	**0.007**	−0.26	0.10	0.06
BBCS-3:R	School Readiness Composite	0.62	0.18	0.45	**0.005**	0.52	0.20	0.06	−0.25	0.07	−0.42	**0.003**	−0.24	0.08	**0.008**	−0.16	0.09	0.16
BRIEF-P Parent	Global Executive Composite	−0.25	0.14	−0.24	0.13	−0.21	0.16	0.33	0.14	0.05	0.32	**0.01**	0.12	0.06	**0.04**	0.08	0.08	0.27

SD, standard deviation; SE, standard error; FDR, false discovery rate; WPPSI-IV, The Wechsler Preschool & Primary Scale of Intelligence, Fourth Edition; WRAVMA, The Wide Range Assessment of Visual Motor Abilities; BBCS-3:R, Bracken Basic Concept Scale: Receptive – Third Edition, BRIEF-P, The Behavior Rating Inventory of Executive Function – Preschool; BSMSS, Barratt Simplified Measure of Social Status; SVI, Social Vulnerability Index

[a]: Model is Neurocognitive measure = $B_0 + B_{BSMSS} \times$ BSMSS where estimate above is B_{BSMSS} and represents the change in score for a 1 point increase in BSMSS score.

[b]: Model is Neurocognitive measure = $B_0 + B_{BSMSS} \times$ BSMSS where standardized estimate of the change in score for 1 standard deviation of change in BSMSS score.

[c]: Estimate for effect of 1 point increase in BSMSS score on score after adjusting for SVI, age at evaluation, genotype, sex, and current HU treatment status

[d]: Estimate for effect of SVI on score

[e]: Standardized estimate for effect of SVI on score

[f]: Estimate for effect of SVI on score after adjusting for age at assessment, genotype, sex, and current hydroxyurea (HU) treatment status

[g]: Estimate for effect of SVI on score after adjusting for BSMSS, age at assessment, genotype, sex, and current hydroxyurea (HU) treatment status