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## Hydroxyurea treatment and neurocognitive functioning in sickle cell disease from school age to young adulthood

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### Summary

Neurocognitive impairment is common in sickle cell disease (SCD) and is associated with significant functional limitations. In a cross-sectional analysis, we examined the association between hydroxyurea (HU) treatment and neurocognitive functioning from school-age to young adulthood in individuals with SCD. A total of 215 patients with HbSS/HbS $\beta^0$ -thalassaemia (71% HU treated) and 149 patients with HbSC/HbS $\beta^+$ -thalassaemia (20% HU treated) completed neurocognitive measures at one of four developmental stages: school-age (age 8–9 years), early adolescence (age 12–13 years), late adolescence (age 16–17 years) and young adulthood (ages 19–24 years). For participants with multiple assessments, only the most recent evaluation was included. In multivariable analysis adjusted for social vulnerability, HU treatment and sex, older age was associated with a reduction in overall intelligence quotient (IQ) of 0.55 points per year of life [standard error (SE) = 0.18, false discovery rate adjusted *P* value (*PFDR*) = 0.01] for patients with HbSS/HbS $\beta^0$ -thalassaemia. Earlier initiation of HU (*n* = 152) in HbSS/HbS $\beta^0$ -thalassaemia was associated with higher scores on neurocognitive measures across most domains, including IQ [estimate (SE) 0.77 (0.25)/year, *PFDR* = 0.01], after adjusting for social vulnerability, sex and treatment duration. These results support the early use of HU to limit the detrimental neurocognitive effects of SCD, while highlighting the need for additional measures to further mitigate neurocognitive deterioration.

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Author contributions

Andrew M. Heitzer, Jane S. Hankins and Guolian Kang designed the study, interpreted data and prepared the manuscript. Guolian Kang and Victoria Okhominina analysed the data. Jennifer Longoria, Brian Potter, Darcy Raches, Jane E. Schreiber and Winfred C. Wang collected data and wrote the manuscript. Allison A. King wrote the manuscript, and all authors critically reviewed and approved the final version of the manuscript.

## Keywords

sickle cell disease; neurocognition; hydroxyurea; aging; fetal haemoglobin

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## Introduction

Patients with sickle cell disease (SCD) are at increased risk of numerous brain complications, including overt stroke, silent cerebral infarctions and chronic insufficiencies in oxygen and/or glucose delivery to the brain.<sup>1–3</sup> Neurocognitive deficits are observed early in life.<sup>4</sup> Over time, owing to accumulated micro-infarcts, chronic hypoxaemia and repeated tissue ischaemia,<sup>5</sup> individuals with SCD tend to display slowed acquisition of neurocognitive skills.<sup>6</sup>

Among patients with SCD, there is significant heterogeneity in neurocognitive outcomes. In children, greater deficits in cognitive functioning are associated with more severe anaemia, lower total haemoglobin (Hb), lower fetal Hb (HbF), lower oxygen saturation, silent cerebral infarcts and overt stroke.<sup>7–9</sup> While demographic factors, including reduced parent education and household income are also associated with poorer cognitive outcomes in childhood,<sup>7,8</sup> risk factors for neurocognitive deficits are not well characterised across all developmental stages.

A single study, utilising the Cooperative Study of Sickle Cell Disease (CSSCD) cohort, examined longitudinal outcomes in SCD.<sup>6</sup> Results indicated slowed cognitive growth compared to same age peers. However, that study did not examine a wide range of neurocognitive constructs such as memory or executive functioning, and the oldest participants were aged 17 years. Additionally, no participants in the CSSCD were treated with hydroxyurea (HU).<sup>7,10</sup>

Hydroxyurea increases HbF<sup>11</sup> and is associated with less frequent pain episodes,<sup>12</sup> reduced mortality<sup>12,13</sup> and improved health-related quality of life.<sup>14</sup> HU reduces overall transcranial Doppler ultrasonography velocities and stroke occurrence.<sup>15–17</sup> Preliminary evidence suggests that HU treatment is positively associated with neurocognitive functioning.<sup>18–20</sup> Prior work by our group demonstrated effects of HU use on measures of verbal reasoning, processing speed and working memory, yet most of these findings did not persist after adjustment for multiple comparisons.<sup>19</sup> Prior studies assessing the relationship between HU treatment and neurocognition are limited by small samples and narrow age ranges.<sup>18–20</sup> No studies have examined if age of HU initiation affects neurocognitive outcomes or mechanisms of action.

In the present study, we present a multi-age cross-sectional analysis to examine neurocognitive outcomes in individuals with SCD from school age through to young adulthood. The first objective was to examine the effect of age on neurocognitive functioning and to assess how age interacts with risk factors across the lifespan. We hypothesised that older age would be associated with worse performance, relative to same age peers. A secondary objective was to evaluate the association between HU use and neurocognitive outcomes. We hypothesised that current use of HU would be positively

associated with neurocognitive functioning and that among those treated with HU, earlier treatment initiation would be positively correlated with neurocognition.

## Methods

This research was approved by the Institutional Review Board (IRB) at St. Jude Children's Research Hospital (St. Jude, USA). Written informed consent was obtained from all participants (or their legal guardian if a minor) and adolescents gave assent according to the requirements of the IRB.

## Participants

All participants of the Sickle Cell Clinical Research Intervention Program (SCCRIP) study, aged 8–25 years, were eligible for this study. The design of SCCRIP has been described previously.<sup>21</sup> 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. Neurocognitive assessments are performed approximately every 4 years between the ages of 8 and 24 years and every 6 years thereafter. These screening 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. Testing broadly occurred at one of four developmental stages: school age (age 8–9 years), early adolescence (age 12–13 years), late adolescence (age 16–17 years) and young adulthood (age 19–24 years). Of the 625 eligible participants in SCCRIP, 368 received a neurocognitive assessment. We excluded five patients with a history of stroke, resulting in a total sample of 363. A total of 59 participants received multiple neurocognitive assessments as part of longitudinal monitoring, and the most recent assessment was used for analyses. All data were collected between 2012 and 2018.

## Demographic, medical and treatment variables

Demographic, medical and treatment variables were abstracted from the SCCRIP database. The Social Vulnerability Index (SVI)<sup>22,23</sup> was used to classify individuals based on social vulnerabilities at the neighbourhood level (e.g. poverty, education and housing data)<sup>22</sup>; a higher percentile score indicates higher social vulnerability. Participants with HbSS/HbS $\beta^0$ -thalassaemia received HU according to National Heart, Lung, and Blood Institute (NHLBI) guidelines.<sup>24</sup> For participants with HbSC/HbS $\beta^+$ -thalassaemia, HU initiation was guided by the frequency of acute disease complications.<sup>25</sup> HU dosing began at 20 mg/kg/day and increased in 5 mg/kg increments every 8–12 weeks to the maximum tolerated dose, defined by an absolute neutrophil count of  $2-4 \times 10^9/l$  or the presence of haematological toxicity.<sup>26,27</sup> All patients were kept at the maximum tolerated dose, as per our institution's standard practice. Haematological indices including Hb, HbF, white blood cell (WBC) count and platelet count were performed at steady state on the day of neurocognitive testing or were the average value of measurements within 3 months prior to testing. Daytime Hb oxygen saturation was obtained on the day of the neurocognitive testing and >2 months from a blood transfusion.

## Neurocognitive measures

Participants in SCCRIP completed a battery of neurocognitive tests. The administration of all measures was supervised by a licensed psychologist. The Wechsler Abbreviated Scale of Intelligence-Second Edition (WASI-II)<sup>28</sup> provided an estimated Full-Scale Intelligence Quotient (IQ) (4-subtest; FSIQ), Verbal Comprehension Index and Perceptual Reasoning Index. Depending on the participant's age, the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV)<sup>29</sup> or Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV)<sup>30</sup> Digit Span (working memory) and Coding (graphomotor processing speed) subtests were used. Delis–Kaplan Executive Function System<sup>31</sup> subtests included Trail Making, Number Sequencing and Number/Letter Switching (executive task switching) and Category/Letter Fluency (verbal fluency). The Wide Range Assessment of Memory and Learning (WRAML), Second Edition,<sup>32</sup> Story Memory subtest, measured verbal memory. Visuomotor integration was assessed using the Beery-Buktenica Visual Motor Integration (VMI) Test, Sixth Edition.<sup>33</sup> Fine motor dexterity and speed were measured with the Grooved Pegboard Test.<sup>34</sup> Academic achievement measures included Letter-Word Identification and Math Fluency from the Woodcock–Johnson Test of Achievement, Third Edition<sup>35</sup>.

## Statistical analyses

Two-sample *t*-test or analysis of variance (ANOVA), Wilcoxon rank sum test or Kruskal–Wallis rank-sum test and Fisher's exact test were used to evaluate two or more than 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 and second objectives, multivariate linear regression models were used to examine the effects of age and HU treatment on neurocognitive functioning after adjustment for SVI and sex. Due to differences in the pathophysiology of SCD based on genotype, we conducted all analyses separately for patients with HbSS/HbS $\beta^0$ -thalassaemia and HbSC/HbS $\beta^+$ -thalassaemia. We did not include laboratory values in our primary analyses, as they were considered potential treatment mechanisms that could mask the relationship between HU and neurocognitive functioning. To assess the effect of age at HU treatment initiation, duration of HU treatment was added to the model. Age was analysed both as a continuous and ordinal variable (i.e. 0 = school age, 1 = early adolescence, 2 = late adolescence and 3 = young adulthood).

Propensity score analyses were conducted to assess the HU effect on neurocognitive performance, controlling for covariates reflecting greater likelihood of receiving HU treatment.<sup>36,37</sup> We estimated the propensity score by fitting a logistic regression model with HU treatment as the outcome and age, sex and SVI as covariates in the model. We used propensity score matching with a 1:1 ratio, without replacement, and nearest distance matching for age, sex and SVI using 'matchit' R software (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria).<sup>38</sup>

As an exploratory objective, we assessed potential mechanisms of HU treatment on overall IQ. Laboratory measurements, including HbF, Hb, WBC count, platelet count and Hb oxygen saturation were examined individually with overall IQ in the linear regression

models with adjustment for covariates described above. Covariates with significant associations at  $P < 0.10$  were included in the multivariable analyses to obtain the final model using stepwise model selection. All the covariates were tested for multicollinearity before entering the model (a variance inflation factor  $< 2$ ). We then conducted mediation analyses to evaluate mediated effects of HU on IQ via laboratory measurements that were retained in the final model, after adjusting for potential confounding variables. Bootstrapping approach was further used to calculate the 95% confidence interval (CI) to confirm the mediation analyses results. The variation of IQ explained by individual covariates in the final model was calculated using the coefficient of multiple determination ( $R^2$ ).

For analyses involving multiple comparisons, false discovery rate (FDR) adjusted  $P$  values ( $PFDR$ )  $< 0.05$  were used to account for multiple comparisons. Analyses were performed in R, version 3.5.3 and Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

### Demographic and clinical characteristics

A total of 363 patients, aged 8–25 years, received neurocognitive testing and the mean (SD) age at evaluation was 14.1 (4.8) years. Those that received neurocognitive testing were statistically comparable to those who did not, except the latter were significantly younger (Table S1).

### Age and neurocognitive performance

Older age was associated with poorer neurocognitive performance across most domains for patients with HbSS/HbS $\beta^0$ -thalassaemia ( $PFDR < 0.05$ ) after adjusting for covariates. For each year of life, there was a mean (SE) reduction of 1.24 (0.22), 1.79 (0.22) and 1.05 (0.23) points in word reading, math fluency and visuomotor integration respectively (all  $PFDR < 0.001$ ). Overall IQ reduced by a mean (SE) of 0.55 (0.18) points/year of increased patient age ( $PFDR = 0.01$ ). Older age was associated with poorer performance on a measure of word reading [ $PFDR = 0.02$ ; mean (SE) estimate  $-1.05$  (0.31)] for patients with HbSC/HbS $\beta^+$ -thalassaemia. No other measures were associated with age ( $PFDR > 0.05$ ). Among patients with HbSS/HbS $\beta^0$ -thalassaemia, the proportion of participants with clinically significant ( $< 5$ th percentile) neurocognitive impairments increased across age time-points for most neurocognitive measures ( $PFDR < 0.05$ ; Fig 1) after adjusting for covariates. Rates of impairment ( $< 5$ th percentile) did not significantly increase across age time-points for any domain after adjustment for multiple comparisons ( $PFDR > 0.05$ ; data not shown) among patients with HbSC/HbS $\beta^+$ -thalassaemia.

### Hydroxyurea and neurocognitive performance

Group differences on demographic and biological variables by HU treatment status separated by genotype are listed in Table I. Patients with HbSS/HbS $\beta^0$ -thalassaemia currently treated with HU had higher levels of overall Hb ( $PFDR = 0.002$ ), higher HbF ( $PFDR < 0.001$ ) and a lower WBC count ( $PFDR < 0.001$ ) than those not treated with

HU. Patients with HbSC/HbS $\beta^+$ -thalassaemia treated with HU were younger than those not treated ( $\text{PFDR} = 0.007$ ).

Those treated with HU had higher scores on measures of verbal comprehension, perceptual reasoning and overall IQ for all genotypes (all  $P < 0.05$ ; Table II and Table S2). However, after corrections for multiple comparisons, these effects only remained for patients with HbSS/HbS $\beta^0$ -thalassaemia (all  $\text{PFDR} < 0.05$  except for perceptual reasoning,  $\text{PFDR} = 0.062$ ). Among patients with HbSS/HbS $\beta^0$ -thalassaemia, those taking HU had a mean (SE) 6.42 (1.96) point elevation in IQ compared to their untreated peers.

Using propensity score, we selected 62 HU-treated and 62 untreated patients with HbSS/HbS $\beta^0$ -thalassaemia matched by age, SVI and sex. These two matched groups were comparable in all clinical features and propensity score (Table S3), except that HU-treated patients had higher HbF, Hb, lower WBC and platelet counts. The propensity score analysis confirmed the HU treatment effect on overall IQ (estimate 6.2, 95% CI 1.6–11.0;  $P = 0.009$ ,  $\text{PFDR} = 0.14$ ). Similarly, 29 HU-treated and 29 untreated patients with HbSC/HbS $\beta^+$ -thalassaemia were matched by age, SVI and sex. The groups did not differ on any clinical or demographic feature. The analysis indicated an HU treatment effect on overall IQ (estimate 8.2, 95% CI 2.5–14;  $P = 0.007$ ,  $\text{PFDR} = 0.064$ ). However, due to limited power, none of the effects remained significant after adjusting for multiple comparisons ( $\text{PFDR} > 0.05$ ).

Among patients with HbSS/HbS $\beta^0$ -thalassaemia, longer duration of HU treatment was positively associated with neurocognitive performance on measures of perceptual reasoning and overall IQ, after adjusting for age at evaluation, SVI and sex, at  $\text{PFDR} < 0.05$  (Table III and Table S4). In the group treated with HU, older age at initial HU treatment was associated with worse neurocognitive performance across most domains after adjusting for duration of treatment, sex and SVI at  $\text{PFDR} < 0.05$  (Fig 2; Table III and Table S4). There was no effect of duration of HU treatment or age of treatment initiation on any neurocognitive outcome for patients with HbSC/HbS $\beta^+$ -thalassaemia ( $\text{PFDR} > 0.05$ ).

### Variance in IQ explained

Variables from the first and second objectives were included alongside laboratory values that reflect disease severity and/or HU effect. Among patients with HbSS/HbS $\beta^0$ -thalassaemia, four covariates: age, SVI, HbF and HU treatment status, remained in the final model ( $P < 0.05$ ). These four factors combined accounted for 15.72% (95% CI 8.86–26.19) of the variance in overall IQ (Fig 3, Panel A). Of these predictors, SVI accounted for the greatest amount of variance (5.90%, 95% CI 1.26–13.37;  $P = 0.0004$ ), followed by age at assessment (3.14%, 95% CI 0.19–9.33;  $P = 0.01$ ), HU treatment (2.55%, 95% CI 0.08–8.36;  $P = 0.02$ ) and HbF (2.51%, 95% CI 0.08–8.30;  $P = 0.02$ ). For patients with HbSC/HbS $\beta^+$ -thalassaemia, SVI accounted for the greatest amount of variance (7.41%, 95% CI 1.41–17.12;  $P = 0.001$ ) followed by HU treatment status (4.28%, 95% CI 0.25–12.65;  $P = 0.01$ ) (Fig 3, Panel B) in the final model.

### Hydroxyurea mediation analyses of IQ

Among patients with HbSS/HbS $\beta^0$ -thalassaemia, multivariate analyses revealed that HbF levels were positively associated with IQ ( $P = 0.02$ ) after adjustment for age, SVI and HU

treatment. In contrast, there was no effect of Hb, Hb oxygen saturation, WBC or platelet counts on IQ ( $P > 0.63$ ). Therefore, we explored the effect of HU on IQ mediated by HbF. HbF mediated the effect of HU treatment on IQ ( $P = 0.03$ ). There were also direct effects of HU on IQ ( $P = 0.03$ ), after accounting for HbF. In contrast, no haematological indices were associated with IQ among patients with HbSC/HbS $\beta^+$ -thalassaemia (all  $P > 0.35$ ).

## Discussion

In the present large cross-sectional analysis of patients with SCD, ranging from school age to young adulthood, worse neurocognitive performance was associated with increased social vulnerability and absence of HU treatment across genotypes. Patients with HbSS/HbS $\beta^0$ -thalassaemia demonstrated worse performance with increasing age compared to normative expectations. In our present data, areas of neurocognitive weakness became most apparent in adolescence as patients prepare to transition to adulthood. Among those individuals treated with HU, the neurocognitive effects were reduced, but not eliminated.

Consistent with prior research,<sup>18,19</sup> HU treatment is positively associated with neurocognitive performance in SCD. Across genotypes, those treated with HU at the time of their neurocognitive evaluation demonstrated an approximately 6-point elevation in IQ compared to their untreated peers. The effect of HU on neurocognition appeared to have different mechanisms that were dependent on the patient's genotype. Among those with HbSS/HbS $\beta^0$ -thalassaemia, the effect of HU was partially mediated by HbF, such that HU treatment was associated with increased HbF, which influenced neurocognitive functioning. Although HU reduces anaemia and improves oxygen delivery,<sup>15,39</sup> our present data suggest an alternative pathway to impact cognition through increased HbF production without affecting the degree of anaemia. These results are consistent with prior studies that have observed a positive association between HbF and neurocognitive performance.<sup>9,40</sup> In contrast, there was no relationship between HbF and IQ among patients with HbSC/HbS $\beta^+$ -thalassaemia. Mechanisms to account for the relationship between HU treatment and neurocognitive functioning in HbSC/HbS $\beta^+$ -thalassaemia require further research.

The present study is the first to demonstrate that the age of HU initiation is clinically meaningful. Patients with HbSS/HbS $\beta^0$ -thalassaemia who started treatment at an older age displayed significantly poorer neurocognitive performance after adjustment for covariates, than those who initiated at an earlier age. Thus, beginning HU treatment earlier may mitigate some of the neurocognitive effects of SCD. HU displayed a protective effect across age groups and genotypes, offering support for improving access to HU treatment for all patients with SCD. Longitudinal research with a larger sample is needed to further explore these relationships.

Increased age was associated with poorer neurocognitive performance across most domains for patients with HbSS/HbS $\beta^0$ -thalassaemia but not for patients with HbSC/HbS $\beta^+$ -thalassaemia. The largest (negative) effects of age were seen on measures of academic knowledge and fluency. These findings likely reflect a combination of the neurological burden of SCD, large amounts of school absences and reduced academic resources. Children living in poverty, regardless of disease status, tend to show slowed development of academic

skills and reduced academic attainment.<sup>41,42</sup> Most of our present patients live within low-income households and attend schools that are underfunded and understaffed, placing them at risk of falling further behind academic expectations. The presence of chronic disease, such as haemophilia or cystic fibrosis, may increase risk of neurocognitive and academic difficulties; however, deficits generally do not significantly differ from normative expectations.<sup>43</sup>

The present study has several strengths including a large, representative, sample of patients that span school age to young adulthood. Extensive information on clinical characteristics was collected allowing for exploration of numerous predictors of neurocognitive functioning. The study included a wide range of neurocognitive outcomes that are sensitive to the effects of SCD. Yet, several limitations exist. Cross-sectional analyses limited the conclusions that could be drawn from our present data. Due to HU being standard of care, it was not possible/ethical to randomise patients to treatment approaches, so frequency matching was used to mitigate this limitation. Additionally, only patients with a clinical indication received neuroimaging. Based on previous research, it is likely that silent cerebral infarcts account for some of the variance in neurocognitive outcomes for these patients.<sup>44–46</sup> The relationship between age, HU treatment and neurocognitive functioning may be altered after considering the presence of cerebral infarcts. Information on sociodemographic factors was also limited to the neighbourhood level, and we did not account for household factors such as family income or parental education, all potential predictors of neurocognitive functioning.<sup>7,47</sup> Because we did not utilise a demographically matched or sibling-control group we cannot rule out the possibility that the age-related effects are primarily due to environmental factors rather than disease or treatment factors. In the future, we plan to collect more individualised sociodemographic data to better characterise the contribution of social determinants of health to neurocognitive outcomes in SCD.

To conclude, our present cross-sectional analyses suggest that patients with SCD demonstrate increasing neurocognitive deficits as they age, particularly among patients with HbSS/HbS $\beta^0$ -thalassaemia. Early treatment with HU potentially provides some protection against the neurocognitive burden of SCD, although more research is needed to determine how the timing of this treatment affects outcomes. Despite assessing many relevant medical, treatment and demographic factors, we only captured a small amount of the variance in overall IQ. Accounting for neuroimaging and genetic factors is needed to better predict neurocognitive outcomes. Longitudinal studies that follow patients into adulthood are needed to fully understand neurocognitive functioning across the lifespan in SCD.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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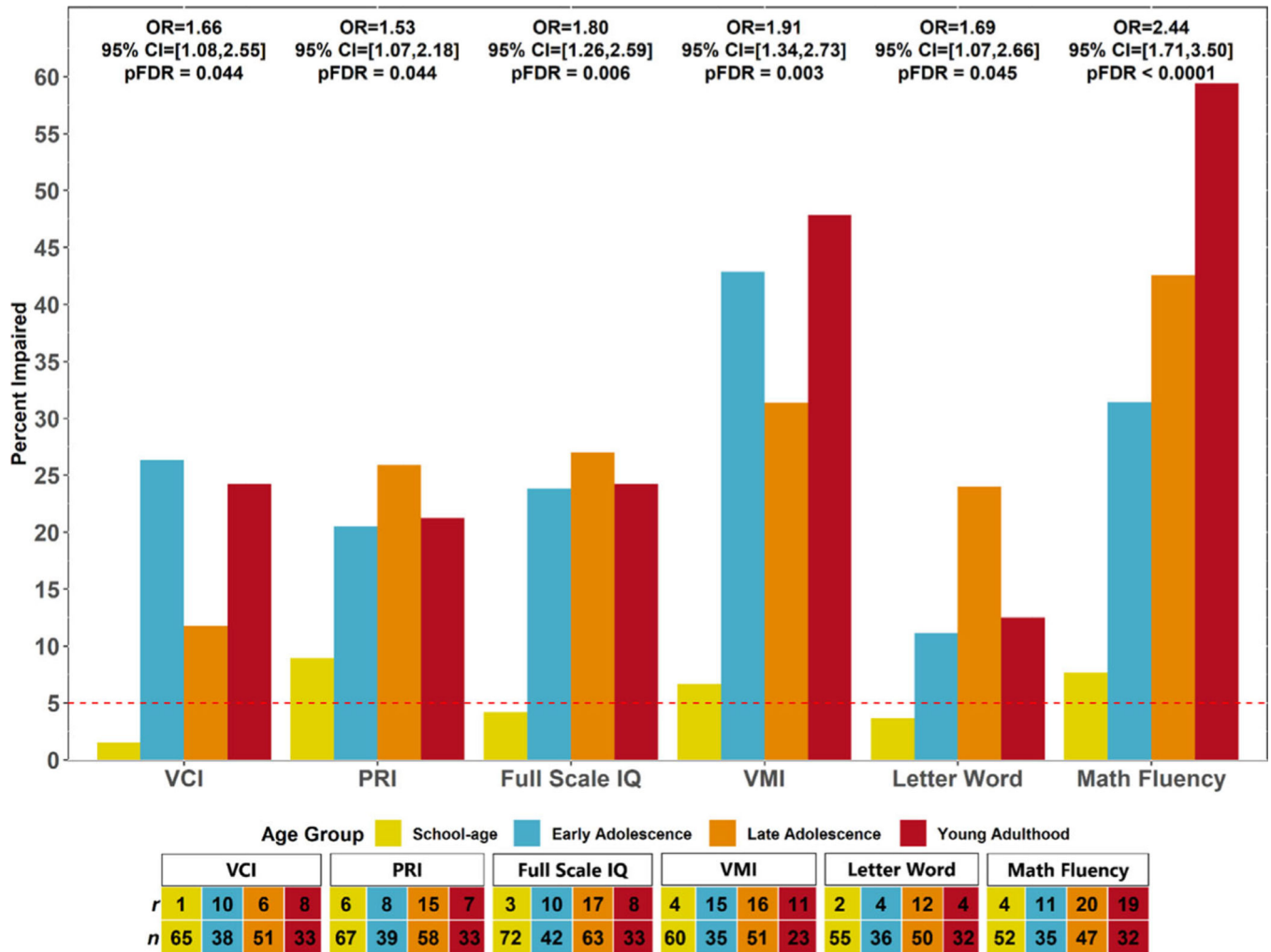
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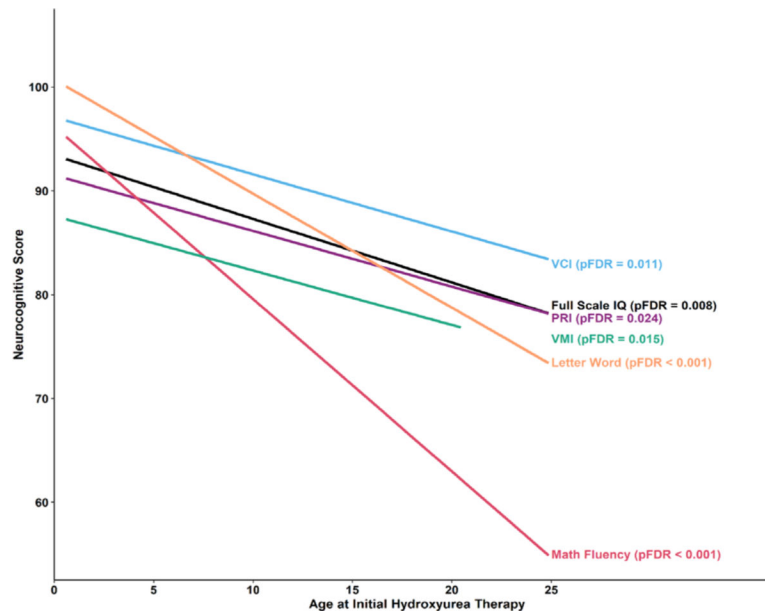
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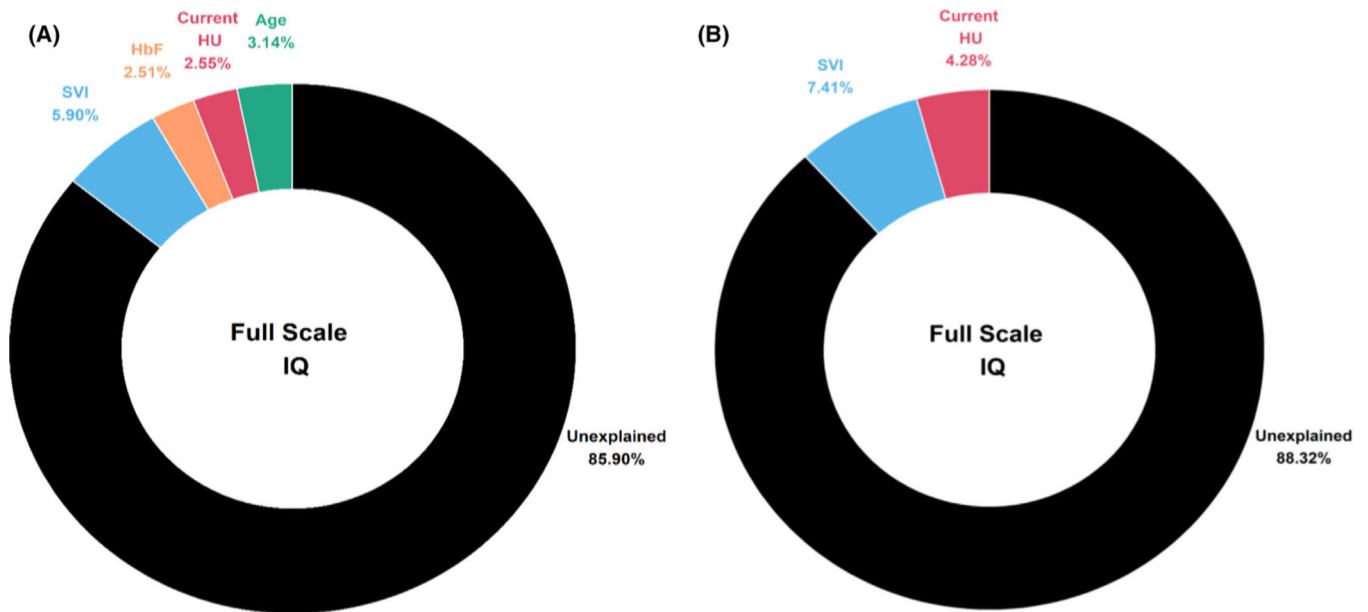


**Fig 1.** Frequency of neurocognitive impairment increases across age groups for patients with HbSS/HbS $\beta^0$ -thalassaemia. FDR, false discovery rate adjustment for 23 neurocognitive outcomes; HU, hydroxyurea; OR, odds ratio; PRI, Perceptual Reasoning Index; VCI, Verbal Comprehension Index; VMI, Visual Motor Integration. Age groups include school-age (8–9 years), early adolescence (12–13 years), late adolescence (16–17 years), and young adulthood (19–24 years). ORs reflect the effect of a 1-unit increase in age group (where 0 = school age) at assessment on impairment (scoring at or below the 5th percentile) compared to no impairment after accounting for sex, social vulnerability, and current HU use. *p*FDR is FDR adjusted *P*value. The Verbal Comprehension Index, Perceptual Reasoning Index, and Full-Scale intelligence quotient (IQ) were measured with the Wechsler Abbreviated Scale of Intelligence, Second Edition. Visual Motor Integration was measured using the Beery Visual Motor Integration Test, Sixth Edition. Letter-Word and Math Fluency were measured with the Woodcock–Johnson Academic Achievement Test, Third Edition. Dashed line represents percentage of individuals expected to display clinically significant impairment (i.e. <5th percentile) in the normative population



**Fig 2.**

Older age at treatment initiation is associated with poorer neurocognitive performance in patients with HbSS/HbS $\beta^0$ -thalassaemia. FDR, false discovery rate adjustment for 23 neurocognitive outcomes; HU, hydroxyurea; PRI, Perceptual Reasoning Index; VCI, Verbal Comprehension Index; VMI, Visual Motor Integration. The *p*FDR reflects the effect of age at initial HU therapy on neurocognitive performance after accounting for duration of HU treatment, social vulnerability, and sex. All neurocognitive scores are presented as standard scores with a mean (SD) of 100 (15). The Verbal Comprehension Index, Perceptual Reasoning Index, and Full-Scale intelligence quotient (IQ) were measured with the Wechsler Abbreviated Scale of Intelligence, Second Edition. Visual Motor Integration was measured using the Beery Visual Motor Integration Test, Sixth Edition. Letter-Word and Math Fluency were measured with the Woodcock–Johnson Academic Achievement Test, Third Edition



**Fig 3.**

Variance in full-scale intelligence quotient (IQ) explained by biological, treatment, and demographic factors in patients with sickle cell disease separated by genotype. SVI, social vulnerability index; HbF, fetal haemoglobin; HU, current hydroxyurea treatment status. **(A)** Variance explained for patients with HbSS/HbSβ<sup>0</sup>-thalassaemia. **(B)** Variance explained for patients with HbSC/HbSβ<sup>+</sup>-thalassaemia. Separate models built for HbSS/HbSβ<sup>0</sup>-thalassaemia and HbSC/HbSβ<sup>+</sup>-thalassaemia. Age, SVI, sex, HU, HbF, total haemoglobin, platelet count, and haemoglobin oxygen saturation were included in the initial model. Covariates with significant associations at  $P < 0.10$  were included in the multivariable analyses to obtain the final model using stepwise model selection with the final model only including variables reaching  $P < 0.05$ . Values are coefficient of determination ( $R^2$ ), calculated from linear regression model. The Full-Scale IQ was measured with the Wechsler Abbreviated Scale of Intelligence, Second Edition

**Table 1.**

Participant characteristics by HU for the overall group and by genotype.

	HbSS/HbSβ <sup>0</sup> -thalassaemia		HbSC/HbSβ <sup>+</sup> -thalassaemia		PFDR
	HU n = 152	No HU n = 63	HU n = 29	No HU n = 119	
N(%)					N = 148
Sex					
Female	70 (46.05)	34 (53.97)	15 (51.72)	63 (52.94)	0.91
Male	82 (53.95)	29 (46.03)	14 (48.28)	56 (47.06)	
Race					
African American	151 (99.34)	63 (100.00)	29 (100.00)	119 (100.00)	.
Other	1 (0.66)	0 (0.00)			.
Overall vulnerability summary ranking*					
Very low (0.15-99)	8 (5.26)	4 (6.35)	3 (10.34)	6 (5.04)	0.72
Low (16.26-99)	5 (3.29)	3 (4.76)	3 (10.34)	7 (5.88)	
Moderate (27.37-99)	8 (5.26)	3 (4.76)	2 (6.90)	7 (5.88)	
High (38.48-99)	12 (7.89)	5 (7.94)	2 (6.90)	12 (10.08)	
Very high (49.100)	118 (77.63)	48 (76.19)	19 (65.52)	87 (73.11)	
Chronic transfusion at time of evaluation	2 (1.32)	7 (11.11)			.
HU treatment gap <sup>†</sup>	27 (17.76)		3 (10.34)		.
Transcranial Doppler <sup>‡</sup>					
Normal	98 (67.12)	39 (65.00)			.
Conditional	35 (23.97)	11 (18.33)	0.40		.
Abnormal	13 (8.90)	10 (16.67)			.
Age group					
School age	50 (32.89)	24 (38.10)	4 (13.79)	45 (37.82)	0.02
Early adolescent	27 (17.76)	17 (26.98)	5 (17.24)	27 (22.69)	
Late adolescent	51 (33.55)	13 (20.63)	13 (44.83)	39 (32.77)	
Young adult	24 (15.79)	9 (14.29)	7 (24.14)	8 (6.72)	
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>

	HbSS/HbSβ <sup>0</sup> -thalassaemia		PFDR		HbSC/HbSβ <sup>+</sup> -thalassaemia		PFDR	
	HU n = 152	No HU n = 63	HU n = 215	No HU n = 119	HU n = 29	No HU n = 148	HU n = 29	No HU n = 148
Age at evaluation, years	14.34 (4.93)	13.69 (4.95)	0.54	0.007	16.60 (4.80)	13.29 (4.31)	0.007	0.007
Age at HU initiation, years	7.95 (4.73)		.	.	12.90 (5.43)		.	.
Duration of HU treatment, years	6.27 (4.27)		.	.	3.74 (3.34)		.	.
HU dose, mg/kg	25.66 (5.75)		.	.	18.83 (5.45)		.	.
Haemoglobin, g/l	93.7 (12.8)	87.5 (10.3)	0.002	0.72	114.2 (15.7)	116.9 (10.8)	0.72	0.72
WBC count, x 10 <sup>9</sup> /l	9.25 (3.98)	11.95 (3.87)	<0.0001	0.17	7.21 (3.45)	8.02 (3.29)	0.17	0.17
Fetal haemoglobin, %	17.73 (9.11)	10.98 (7.54)	<0.0001	0.72	5.57 (6.45)	4.65 (6.07)	0.72	0.72
Platelet count, x 10 <sup>9</sup> /l	389.81 (185.44)	391.01 (123.38)	0.36	0.72	252.45 (138.62)	248.74 (98.89)	0.72	0.72
Haemoglobin oxygen saturation, %	99.16 (1.25)	98.72 (1.57)	0.40	0.42	99.48 (0.77)	99.64 (0.77)	0.42	0.42

FDR, false discovery rate; HbF, fetal haemoglobin; HU, hydroxyurea; n, sample size; SD, standard deviation; WBC, white blood cell.

P values based on chi-square or Fisher's Exact test for categorical variables and ANOVA or Kruskal-Wallis for continuous variables. FDR adjusted P (PFDR) < 0.05 were considered significant. Haematological indices were the average value of measurements collected within 3 months of or the one closest to neurocognitive assessment.

\* Classifies individuals based on social vulnerabilities at the neighbourhood level (e.g. poverty, education, housing data); a higher percentile score indicates higher social vulnerability.

<sup>†</sup> Percentage of patients currently on HU that had a gap in treatment of 1 year at any time.

<sup>‡</sup> Only performed on patients with Hb SS/HbSβ<sup>0</sup>-thalassaemia. Transcranial Doppler mean flow velocity values for each artery: normal (<170 cm/s), conditional (170–199 cm/s), and abnormal (>200 cm/s).



**Table II.**

Effect of current hydroxyurea treatment status on neurocognitive performance.

Domain	Measure	Score*	HbSS/HbSβ <sup>0</sup> -thalassaemia			HbSC/HbSβ <sup>0</sup> -thalassaemia				
			Estimate <sup>†</sup>	SE	Raw P	PFDR <sup>‡</sup>	Estimate <sup>†</sup>	SE	Raw P	PFDR <sup>‡</sup>
Reasoning	WASI-II	Verbal comprehension index	6.50	2.18	0.003	<b>0.019</b>	6.99	2.75	0.012	0.093
		Perceptual reasoning index	4.95	1.99	0.014	0.062	5.52	2.69	0.042	0.112
Processing speed	WISC-IV or WAIS-IV	Full-Scale IQ	6.29	1.94	0.001	<b>0.019</b>	6.93	2.48	0.006	0.093
		Coding	0.56	0.34	0.104	0.239	0.8	0.59	0.182	0.262
Working memory	WISC-IV or WAIS-IV	Digit span total	0.75	0.38	0.051	0.166	0.86	0.6	0.154	0.236
		Story memory initial	0.02	0.44	0.972	0.972	1.25	0.61	0.043	0.112
Visuomotor	Beery VMI	Visual motor integration	1.83	2.43	0.454	0.652	4.72	2.69	0.082	0.188
		Fine motor dominant	0.08	0.28	0.779	0.918	0.71	0.48	0.144	0.236
Academic achievement	WJ Achievement-3	Letter word	2.97	2.46	0.23	0.441	4.44	3.52	0.21	0.262
		Math fluency	2.67	2.54	0.295	0.521	1.16	3.66	0.752	0.752

FDR, false discovery rate; SE, standard error; WASI-II, The Wechsler Abbreviated Scale of Intelligence, Second Edition; WAIS-IV, Wechsler Adult Intelligence Scale, Fourth Edition; WISC-IV, Wechsler Intelligence Scales for Children, Fourth Edition; VMI, Beery-Buktenica Visual Motor Integration Test, Sixth Edition; WJ Achievement-3, Woodcock-Johnson Test of Achievement, Third Edition; WRAML-2, The Wide Range Assessment of Memory and Learning, Second Edition.

Groups represent HU treatment status at the time of neurocognitive evaluation.

Bold values statistically significant at  $P < 0.05$ .

\* Scaled scores with mean (SD) of 10 (3); Digit Span Total, Story Memory Initial; standard scores with a mean (SD) of 100 (15); Verbal Comprehension Index, Perceptual Reasoning Index, Full-Scale IQ, Visual Motor Integration, Letter Word, Math Fluency; z-scores with a mean (SD) of 0 (1); Fine Motor Dominant.

<sup>†</sup> Estimates for effect of current use of HU on neurocognitive performance from linear regression model: neurocognitive measure = current use of HU + participant age at neurocognitive assessment + sex (ref = female) + social vulnerability.

<sup>‡</sup> FDR adjustment for 23 neurocognitive outcomes.

Table III.

Duration of hydroxyurea exposure and age at first exposure effect on neurocognitive performance.

Domain	Measure	Score*	HbSS/HbSp <sup>0</sup> -thalassaemia				HbSC/HbSp <sup>+</sup> -thalassaemia							
			All patients		Patients on HU		All patients		Patients on HU					
			Estimate	SE	PFDR <sup>†</sup>	M2: adjusted effect of duration of HU treatment	Estimate	SE	PFDR <sup>†</sup>	M2: adjusted effect of age at initial HU treatment	Estimate	SE	PFDR <sup>†</sup>	M2: adjusted effect of age at initial HU treatment
Reasoning	WASI-II	Verbal comprehension index	0.59	0.24	0.07	-0.77	0.27	<b>0.01</b>	1.01	0.49	0.16	-0.66	0.49	0.56
			0.61	0.21	<b>0.03</b>	-0.62	0.25	<b>0.02</b>	0.74	0.49	0.21	0.58	0.49	0.57
			0.69	0.21	<b>0.01</b>	-0.77	0.25	<b>0.01</b>	1.02	0.46	0.16	-0.13	0.44	0.81
Processing speed	WISC-IV / WAIS-IV	Coding	0.04	0.04	0.34	-0.13	0.05	<b>0.01</b>	0.07	0.11	0.51	0.16	0.09	0.52
			0.05	0.04	0.36	-0.15	0.05	<b>0.01</b>	0.19	0.11	0.18	0.06	0.08	0.65
Memory	WRAML-2	Story memory initial	0.1	0.05	0.10	-0.17	0.05	<b>0.004</b>	0.28	0.12	0.15	-0.23	0.11	0.52
Visionmotor	Beery VMI	Visual motor integration	0.13	0.26	0.65	-0.84	0.31	<b>0.02</b>	1.06	0.51	0.15	0.37	0.39	0.58
Motor	Grooved pegboard	Fine motor dominant	-0.01	0.03	0.82	-0.07	0.03	<b>0.04</b>	0.2	0.1	0.16	0.09	0.06	0.56
Academic achievement	WJ Achievement-3	Letter word	0.56	0.25	0.09	-1.56	0.3	<b>&lt;0.001</b>	0.76	0.62	0.31	0.12	0.4	0.81
		Math fluency	0.43	0.27	0.22	-2.4	0.31	<b>&lt;0.001</b>	0.46	0.66	0.51	0.37	0.56	0.67

FDR, false discovery rate; HU, hydroxyurea; SE, standard error; VMI, Beery-Buktenica Visual Motor Integration Test, Sixth Edition; WASI-II, The Wechsler Abbreviated Scale of Intelligence, Second Edition; WAIS-IV, Wechsler Adult Intelligence Scale, Fourth Edition; WISC-IV, Wechsler Intelligence Scales for Children, Fourth Edition; WJ Achievement-3, Woodcock-Johnson Test of Achievement, Third Edition; WRAML-2, The Wide Range Assessment of Memory and Learning, Second Edition.

Model 1 (M1): Score = duration of HU treatment + age at neurocognitive assessment + sex + social vulnerability. Model 2 (M2): Score = duration of HU treatment + age at initial HU treatment + sex + social vulnerability. For M1, if patients were not on HU treatment at the time of evaluation, then their duration of HU treatment is set as 0.

Bold values statistically significant at  $P < 0.05$ .

\* Scaled scores with mean (SD) of 10 (3): Digit Span Total, Story Memory Initial; standard scores with a mean (SD) of 100 (15): Verbal Comprehension Index, Perceptual Reasoning Index, Full-Scale IQ, Visual Motor Integration, Letter Word, Math Fluency; z-scores with a mean (SD) of 0 (1): Fine Motor Dominant.

FDR adjustment for 23 neurocognitive outcomes.

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