Title:

Executive Abilities are Higher Following a Blood Transfusion in Children and Young Adults with Sickle Cell Disease

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Abbreviations	Word or Phrase
SCD	sickle cell disease
HU	Hydroxyurea
TCD	transcranial doppler imaging
SCI	silent cerebral infarct
Intelligence Quotient	IQ
Hb	hemoglobin concentration
BMI	Body Mass Index
M	Mean
SE	Standard Error
SD	Standard Deviation

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Abstract

Individuals with sickle cell disease (SCD) experience cognitive deficits; however, it remains unclear whether medical treatments for SCD improve cognition. Given that executive abilities are typically impaired in individuals with SCD, they were the focus of the current study. Our primary hypothesis was that executive abilities would be higher acutely soon after a blood transfusion in children and young adults with SCD. We used tests from the NIH Toolbox to assess executive abilities in 27 participants with SCD receiving chronic transfusion in comparison to 34 participants with SCD receiving hydroxyurea (HU) and 41 non-SCD demographically-matched controls, all of whom were tested at 2 timepoints. Participants in the transfusion group completed cognitive testing within 3 days after a transfusion (soon-after transfusion) and then within 3 days before their next transfusion (long-after transfusion) over an interval of 3 – 7 weeks. We found that executive abilities were significantly poorer for the transfusion and HU groups than the control group. In support of our primary hypothesis, executive abilities for the transfusion group were significantly better soon-after a transfusion compared to long-after a transfusion, $\chi^2(1) = 17.8$, $p < .0001$. Our results demonstrate that executive abilities were higher acutely following a blood transfusion. These findings have implications for daily functioning, medical decision making, and academic achievement in children and young adults with SCD.

INTRODUCTION

Individuals with sickle cell disease (SCD) are at high risk for neurologic[1] and cognitive morbidity.[2] The two primary treatments that reduce the multi-organ complications of SCD are chronic blood transfusion, which is the primary medical treatment for stroke prevention[3,4] and hydroxyurea (HU), which improves cerebral oxygen delivery.[5,6] However, despite long-held knowledge regarding the presence of cognitive deficits in individuals with SCD, there is little information as to whether these therapies improve cognition.

Findings from the small body of relevant research are mixed. For example, one study showed that the intelligence quotient (IQ) improved in children with SCD-related stroke who received chronic transfusion. IQ was impaired at baseline (after initial stroke), but there were some small improvements in IQ 6-months later. IQ subsequently declined in 7/10 of children following recurrent stroke.[7] In another study, cognition was higher in children with SCD with no history of stroke who received HU.[8] In contrast, findings from a large-scale trial showed that IQ was similar among children with SCI who received chronic transfusion for 3 years and children with SCI who did not receive chronic transfusion; however, IQ testing was not timed to occur soon after a transfusion.[9] Similarly, there were no differences in IQ and executive abilities among a very small sample of children with SCD with no history of stroke who received either chronic transfusion, HU, or neither treatment.[10] IQ was also similar in children with no history of stroke who did and did not receive HU.[11]

As just illustrated, the focus of most previous studies has been on changes in IQ. In general, chronic transfusion has not been associated with improvement in IQ.[10,12] However, IQ is a cognitive composite that essentially averages performance across a number of different cognitive domains. Additionally, no previous study has focused on possible acute improvements

in cognition within days following a transfusion. Therefore, the question of whether specific cognitive domains improve soon after a blood transfusion in individuals with SCD has not been adequately addressed.

One study in non-SCD adults found that attention and recall were poorer at low hemoglobin levels compared to baseline, but improved following transfusion.[13] We believed that, similar to findings from non-SCD adults, blood transfusion would improve oxygen delivery and subsequently cognition. Thus, we tested the hypothesis that cognition would be higher acutely soon after compared with longer after a blood transfusion in individuals with SCD.

Using tests from the NIH Toolbox, we focused on executive abilities, a cognitive domain in which individuals with SCD experience particular difficulty.[2,14,15] Non-executive abilities were also evaluated to determine whether change was specific to executive abilities or more general. In addition, we compared executive and non-executive abilities in individuals with SCD receiving chronic transfusion to individuals with SCD receiving HU, who share some of the same comorbidities as individuals receiving transfusion, and to demographically-matched controls. All groups were tested at two timepoints. Given that our sample comprised children and young adults, we also assessed the influence of age on study findings.

METHODS

Participants

Participants with SCD were recruited during regularly scheduled appointments at the St. Louis Children's Hospital hematology clinic. Medical providers determined treatment (e.g., chronic blood transfusion or HU) in consultation with participants and parents/guardians as a component of standard clinical care. Study inclusion criteria were diagnosis of SCD by capillary

gel electrophoresis or genotyping, treatment with chronic blood transfusion (every 3 – 7 weeks) or HU for at least 6 months before enrollment, and 4 years of age or older at study enrollment. No participant was receiving both transfusion and HU at time of testing. Exclusion criteria were non-severe disease as defined by lack of clinical symptoms (painful episodes, acute chest syndrome, stroke, SCI, abnormal TCD, or severe anemia), history of hematopoietic stem cell transplant, congenital brain malformation, previously diagnosed severe developmental disability (e.g., autism and/or IQ < 60), or impairment that would prevent use of a computer tablet.

Seventy-six individuals were invited to participate in the study. Two were excluded due to severe developmental disabilities. After initial contact, 11 participants declined study participation, and 2 did not attend the first scheduled study session. Data from 61 participants with SCD were available for analyses, of which 59 completed both test sessions (see Table 1).

Demographically-Matched Normative Control Sample. We accessed the cognitive data of individuals from a large national study conducted at 10 sites across the United States (dataverse.harvard.edu). They completed tests from the NIH Toolbox in 2011 during 2 test sessions conducted 1 week apart. The NIH Toolbox sample includes 4,859 participants, ages 3-85 years and is representative of the U.S. population. We matched individuals in this sample to our participants with SCD based on age, gender, race, ethnicity, and maternal education.

Procedures

The institutional review board at Washington University in St. Louis approved our study. All participants or their parents/guardians provided informed consent in accordance with the Declaration of Helsinki. Participants receiving transfusion were first tested within 3 days after a

transfusion (soon-after a transfusion; test session 1) and then again within 3 days before their next transfusion (long-after a transfusion; test session 2). Time between transfusions and test sessions was 3 – 7 weeks. We chose this design because any practice effect resulting from repeat testing would work against our primary hypothesis (i.e., executive abilities are higher soon-after a transfusion). In addition to cognitive testing, blood was drawn as a component of clinical care before and after each transfusion to assess hemoglobin (Hb) (see Figure 1).

Five participants were unable to complete their long-after a transfusion test session within the above timeframe (i.e., unable to complete testing before their very next transfusion). Reasons for missing the test session included transition to the adult SCD clinic, change of legal guardianship, hospitalization, and time constraints. In these cases, the long-after transfusion test session occurred within 3 days before the next available transfusion. These participants continued their regularly scheduled chronic transfusions in the interim between test sessions.

Participants with SCD receiving HU were tested at their earliest convenience for test session 1, and test session 2 occurred 3 – 7 weeks later. During each test session, participants with SCD completed tests from the NIH Toolbox (described in Materials) and caregivers completed general health and information questionnaires. Each session lasted 1 – 1.5 hours. Trained examiners administered the NIH Toolbox Cognition Module in 35–40 minutes in a quiet, private room.

Materials

Cognition Battery. The NIH Toolbox Cognition Module is a standardized cognitive battery comprising 7 tests that are validated and normed based on age and maternal education [16,17]. Using standardized procedures, instructions were presented visually on a tablet computer

using an iPad app and also orally by an examiner. Detailed descriptions of individual tests have been published extensively elsewhere (see Supplementary Table 1 for additional information regarding the abilities measured by the Cognition Module).[17,18]

Briefly, on the Dimensional Change Card Sort Test participants were presented with two pictures that varied along two dimensions ("color" or "shape") and participants matched a series of test pictures to the target pictures, switching between matching dimensions. On the Flanker Inhibitory Control and Attention Test participants focused on a central stimulus ("fish" or "arrow") and responded while inhibiting attention to a similar flanking stimulus. On the List Sorting Test, pictures of foods and animals were presented along with audio recordings and written text. Participants reported the items based on size from smallest to largest, first within a single dimension (i.e., food or animals) and then on two dimensions (i.e., food then animals). On the Picture Vocabulary Test participants heard a word presented with four photographic images (1 correct target and 3 distractors). Participants selected the picture that best corresponded to the meaning of the word. On the Oral Reading Recognition Test, participants read and pronounced letters and words as accurately as possible. On the Picture Sequence Memory Test participants recalled the order of increasingly longer series of pictured objects and activities as an audio recording simultaneously described the content of each picture. Participants recalled the sequence of the pictures over two learning trials. Lastly, on the Pattern Comparison Test participants decided whether pairs of side-by-side pictures and designs were or were different quickly as possible.

For theoretical purposes and to increase statistical power, we categorized tests of the NIH Toolbox as executive (Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test, List Sorting Test) and non-executive abilities (Picture Vocabulary Test, Oral

Reading Recognition Test, Picture Sequence Memory Test). The NIH Toolbox provides similar composites (e.g., Fluid and Crystalized). However, the Fluid composite contains the Pattern Comparison Test, which measures processing speed. Processing speed is not an executive skill. Therefore, we did not include it in our executive abilities composite, but instead assessed it separately. Composite scores of executive and non-executive abilities were computed by averaging standard scores (M = 100, SD = 15). Participants aged 4 – 6 years did not complete the List Sorting and Pattern Comparison tests because they were younger than the recommended age range.

Medical Chart Review. Hb, HbA%, HbS%, body mass index (BMI), neurologic status (i.e., history of stroke or SCI verified by MRI and neurologic examination), and number of hospitalizations in the year before enrollment were extracted from the medical record. All information was obtained for clinical care, not specifically for the study protocol. Information extracted occurred closest to each transfusion or test session.

STATISTICAL ANALYSES

Analyses were conducted in the R environment.[19] A priori sample-size calculations,[20] indicated that we had > 90% power to detect medium sized effects in mixed model repeated measures ANOVAs (two-tailed α of .05). Preliminary analyses related to demographic variables used independent samples t-tests and Chi-squared tests with Cohen's *d* as the measure of effect size. Primary analyses related to executive and non-executive abilities used linear mixed-effects models with adjusted group means and post hoc tests used Holm adjustments to control for Type 1 error.[21] Paired sample t-tests assessed change in Hb following a transfusion. Pearson correlations assessed relationships between Hb and executive abilities in participants with SCD

receiving either transfusion or HU and were adjusted for multiple comparisons using the false discovery rate.

Analyses were conducted with and without the five participants who were unable to complete their long-after transfusion test session within the timeframe shown in Figure 1. However, as the pattern of findings were the same, analyses reported include all transfused participants. Additionally, analyses of processing speed pointed to the presence of a consistent practice effect from test session 1 to test session 2 (see Supplementary Table for individual test standard scores). Processing speed was not included in either the executive or non-executive composites.

RESULTS

A description of participants with SCD is provided in Table 1 with values displayed averaged across both test sessions. Participants with SCD completed test sessions over a 3 – 7-week interval (M_{days}= 31.4, SD = 6.0, range = 23 – 42 days). Transfusion and HU groups did not differ significantly on most variables, including age, race, gender, genotype, oxygen saturation, grade retention, or utilization of special education services, $p > .05$ in all instances. However, in comparison to the HU group, the transfusion group had a significantly higher prevalence of stroke and/or SCI, X^2 (1, 60) = 13.92, $p < .001$, $d = 1.14$, significantly more hospitalizations within the year before testing, $t(26.55) = -2.36$, $p = .03$, $d = .64$, and a significantly higher BMI, $t(48.01) = -2.18$, $p = .04$, $d = .55$, indicating greater disease severity.

Demographically matched controls were 41 African-American/Black Non-Hispanic participants aged 4 – 21 years (M = 11.2, SD = 3.4). Scores on executive and non-executive abilities tests for our extracted control sample (see Supplemental Table 2) were similar to the

scores of all African-American children on the NIH Toolbox. [22]

Executive Abilities

Our primary analyses examined differences in executive abilities across age, test sessions, and study groups (i.e., transfusion, HU, control). A mixed model ANOVA revealed significant main effects of age, $F(1, 98) = 37.69$, $p < .0001$ and group, $F(2, 98) = 12.96$, $p < .0001$, but not a significant main effect of test session, $F(1, 98) = 1.11$, $p = .29$. Of greater interest, there was a significant interaction between test session and group, $F(2, 98) = 11.33$, $p < .0001$, $r = .29$, but no three-way interaction (age x test session x group), $F(2, 98) = .73$, $p = .48$.

Post hoc analyses controlling for multiple comparisons showed that older children had poorer executive abilities ($r = -.44$). Additionally, executive abilities were better for the control group at test session 1 (M = 97.5, SE = 1.6) and test session 2 (M = 98.5, SE = 1.6) than for the transfusion group soon-after a transfusion (test session 1) (M = 91.4, SE = 2.0) and long-after a transfusion (test session 2) (M = 82.0, SE = 2.1). Similarly, executive abilities were better for the control group at both test sessions than for the HU group at test session 1 (M = 86.1, SE = 1.8) and test session 2 (M = 89.0, SE = 1.8).

In support of our primary hypothesis, executive abilities for the transfusion group were significantly better soon-after a transfusion (test session 1) than long-after a transfusion (test session 2). In contrast, there was no significant difference in executive abilities across test sessions for either the control or HU groups. Importantly, executive abilities soon-after a transfusion (test session 1) were significantly better than those of the HU group at test session 1. In contrast, executive abilities long-after a transfusion (test session 2) were significantly poorer than those of the HU group at test session 2. Overall, these results indicated that although older

children had poorer executive abilities they did not differ as a function of group or test session. Further, executive abilities remained relatively stable over time for the control and HU groups (changes of only ~1 and 3 points, respectively), whereas executive abilities were significantly better soon-after compared to long-after a transfusion (change of ~9 points) for the transfusion group (see Figure 2 and Table 2 for statistical values).

Non-Executive Abilities

To provide a counterpoint to our executive abilities results, we examined differences in non-executive abilities across age, test sessions, and study groups (i.e., transfusion, HU, control). A mixed model ANOVA revealed significant main effects of age, $F(1, 98) = 4.53$, $p = .03$ and test session, $F(1, 98) = 7.50$, $p = .007$, but there was not a main effect of group, $F(2, 98) = 1.26$, $p = .29$. There was also not an interaction between test session and group, $F(2, 98) = .37$, $p = .69$ and no three-way interaction (age x test session x group), $F(2, 98) = .02$, $p = .98$.

Post hoc analyses controlling for multiple comparisons showed that older children had poorer non-executive abilities ($r = -.24$), but the control and HU groups had similar non-executive abilities at test session 1 and 2. The transfusion group also had similar non-executive abilities soon vs. long-after a transfusion (see Figure 3 and Table 3 for statistical values).

Relationship between Hemoglobin and Executive Abilities

Hb was obtained only for participants with SCD. To best match the HU group, we conducted between group comparisons using Hb collected before test session 2 in the transfusion group (i.e., long-after a transfusion). A mixed effect ANOVA revealed no significant effect of test session, $p = .94$, group, $p = .20$, or interaction between test session and group, $p = .81$,

indicating that Hb collected long-after a transfusion was comparable to the HU group (M = 8.9, SE = .02).

We conducted analyses within the transfusion group to determine change in Hb immediately following transfusion. Analyses revealed that Hb, $t(25) = 5.9$, $d = 1.2$, and HbA%, $t(24) = 8.3$, $d = 1.7$, increased following transfusion, whereas HbS%, $t(25) = -6.1$, $d = 1.2$, decreased. Additionally, Hb, $t(25) = -6.5$, $d = 1.3$, and HbA%, $t(23) = -6.2$, $d = 1.3$, decreased and HbS%, $t(25) = 6.1$, $d = 1.3$, increased between soon-after a transfusion (test session 1) and long-after a transfusion (test session 2) timepoints, $ps < .001$ in all instances.

Given the observed changes in executive abilities, we also examined whether Hb collected soon-after a transfusion was related to change in executive abilities across test sessions. We found that higher Hb soon-after a transfusion was significantly related to a smaller change in executive abilities across test sessions, $r = .59$, $p < .001$. HbA% and HbS% were not related to change in executive abilities, $ps > .05$. Finally, we examined whether change in Hb between transfusions (soon-after to long-after) was related to change in executive abilities. Analyses revealed that a smaller change in Hb was significantly related to a smaller change in executive abilities, $r = .43$, $p = .03$. Change in HbA% and HbS% were not related to change in executive abilities, $ps > .05$. Overall, these results indicated that increased Hb following transfusion and less decline in Hb between transfusions was associated with less decline in executive abilities between transfusions.

DISCUSSION

Cognitive deficits in individuals with SCD are well documented.[2,23] Prior research, however, have been mixed as to whether medical treatments influence cognition in individuals

with SCD. [8,7,10,24] Additionally, most previous studies have assessed IQ rather than more specific cognitive domains. Our study focused on acute change in executive abilities following a transfusion, as this domain is typically impaired for individuals with SCD. We found that although older age predicted poorer executive and non-executive abilities, there was not an interaction between age, group, and timepoint. Of clinical relevance, we found that executive abilities were especially vulnerable compared to non-executive abilities in individuals with SCD (both chronic transfusion and HU). Strikingly, executive abilities were 9 points higher soon after a blood transfusion. Thus, executive abilities were vulnerable but nonetheless malleable in individuals with SCD.

When individuals were tested long after a transfusion, executive abilities were poorer than non-executive abilities. In contrast, executive but not non-executive abilities were substantially better soon after a transfusion. One plausible explanation for this differential finding is that executive abilities are more susceptible to short-term biological changes (i.e., acute changes with blood transfusion) because they are more "fluid" and represent the ability learn new information efficiently, perform novel tasks, and make complex decisions.[25] In comparison, non-executive abilities are less susceptible to short-term biological changes because they more "fixed" and represent the long-term accumulation of consolidated knowledge, facts, and skills.[26]

From a physiological perspective, we found that improvements in Hb soon after a transfusion were accompanied by greater sustained improvement in executive abilities between transfusions, suggesting that normalizing hemoglobin could improve executive abilities for individuals with SCD. Relatedly, lower Hb is associated with fatigue which is a commonly reported symptom of SCD[27] that can be improved following a transfusion.[28] Further, fatigue is

related to poorer parent-reported executive function in children with SCD.[29] Therefore, if individuals in this study were experiencing fatigue, a transfusion may have reduced symptoms contributing to the higher executive abilities observed. Prior research has also revealed compromised brain oxygen metabolism in individuals with SCD[30] that is mitigated soon after blood transfusion. By extension, it is likely that the changes in executive abilities observed in our study are related to reversible cerebral oxygen deficits, but this hypothesis requires further investigation.

Our findings indicate that examining IQ in isolation does not provide the most accurate picture of the cognitive strengths and weaknesses of individuals with SCD. We support using instruments that evaluate specific as well as general aspects of cognition. Consideration of time since last transfusion is also important when examining cognition in individuals with SCD. From a clinical perspective, our results suggest that providers may wish to time delivery of disease education soon after a blood transfusion as executive abilities may be better in the first few days after a transfusion. Lastly, executive abilities could be used as clinical endpoints in future studies of curative therapies and non-curative treatments.

There were limitations to our study. The control sample had not been screened for SCD or sickle cell trait and they were tested only one week apart, compared to the 3 – 7 week interval for individuals with SCD. Our smaller sample size limited statistical power; therefore, we created an executive composite that included tests that are highly correlated and have an underlying commonality, but are not identical and represent distinct abilities.[31] We also did not randomly assign participants to treatments. Instead, treatments were determined by participants' hematologists before study enrollment. Unfortunately, cognitive data were unavailable prior to the onset of medical treatment for participants receiving either chronic transfusion or HU,

prohibiting our ability to detect possible improvements in executive or non-executive abilities related to HU. Finally, because we collected data at only 2 timepoints, we could not determine whether short-term improvements in executive abilities soon after a transfusion persisted over the long-term.

CONCLUSION

In individuals with SCD, executive abilities were higher soon after a blood transfusion, and improvements were related to higher Hb. Importantly, executive but not non-executive abilities were higher soon after a transfusion, pointing to the particular vulnerability and malleability of executive abilities. Future research is needed to determine whether the observed acute changes in executive abilities extend over the long-term and to identify the brain mechanisms underlying acute transfusion-related improvements. However, our findings have implications for daily functioning, medical decision making, and academic achievement for individuals with SCD.

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Disclosures of conflicts of interest

Anna Hood, Allison King, Andria Ford, Kristin Guilliams, Monica Hulbert, and Desiree White declare they have no conflicts of interest. Melanie Fields has equity ownership in Proclara Biosciences.

Data Availability

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

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Authorship

Contribution: A.M.H and D.A.W. designed the experiment, analyzed and interpreted data, and prepared the manuscript. A.A.K. designed the experiment, interpreted data, and prepared the manuscript. M.E.F., A.L.F., K.P.G., M.L.H., J.M.L designed the experiment and interpreted data. All authors critically reviewed and approved the final version of the manuscript.

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TABLE 1. Characteristics of Participants with SCD

Characteristics	Transfusion (n = 27)	Hydroxyurea (n = 34)
Age (years)		
Mean (SD)	14.4 (5.1)	12.6 (4.2)
Range	4–23	5–21
Race		
Black	26	33
Bi-racial (Black/White)	1	1
Gender		
Male	9	17
Female	18	17
Sickle cell genotype		
HbSS	26	31
HbS-beta thal +	0	2
HbS-beta thal zero	0	1
HbSD	1	0
Treatment length (weeks)		
Mean (SD)	50.4 (38.7)	46.2 (23.8)
Range	6–139	6–101
BMI*		
Mean (SD)	20.8 (4.9)	18.6 (4.0)
Range	14.4–30.4	13.4–31.7
Oxygen saturation		
Mean (SD)	97.3 (2.0)	97.2 (2.3)
Range	92–100	90–100
# hospitalizations in last year*		
Mean (SD)	7.5 (12.0)	1.7 (2.8)
Range	0–39	0–10
% of participants in each group		
Neurologic status*		
Overt stroke	22.2	0
SCI	51.9	29.4
Both	7.4	0
Neither	18.5	70.6
MRA		
Abnormal	22	3

Normal	74	79
Unknown	4	18
TCD		
Abnormal	11	9
Conditional	7	18
Low	7	3
Normal	52	71
Unknown	0	22
Grade retention		
Yes	22	21
No	78	79
Special education		
IEP	52	50
504 plan	60	52

Notes: HbSS = sickle cell anemia; HbS-beta thal + = Hb beta plus thalassemia; HbS-beta thal zero = Hb beta zero thalassemia; HbSD = Hb S-D-Los Angeles; BMI indicates body mass index; HbS-beta thal +, hemoglobin beta plus thalassemia; HbS-beta thal zero, hemoglobin beta zero thalassemia; HbSD, hemoglobin S-D-Los Angeles; HbSS, sickle cell anemia; IEP, individualized education plan; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; SCI, silent cerebral infarct; TCD, transcranial Doppler imaging. * Indicates a significant difference between participants receiving transfusion and participants receiving HU ($p < .05$). Clinical indications for chronic transfusion were overt stroke or SCI (67%), recurrent vaso-occlusive pain (15%), abnormally elevated TCD (11%), recurrent hepatic sequestration (4%), and recurrent acute chest syndrome (3%). Clinical manifestations of those receiving HU were acute chest syndrome (29%), pain (32%), acute chest syndrome plus pain (27%), SCI (9%), and severe anemia (3%).

TABLE 2. Differences in Executive Abilities by Test Session and Group

	Difference	X^2	p
Within-group			
Controls Test Session 1 vs Controls Test Session 2	-0.7	0.2	0.7
HU Test Session 1 vs HU Test Session 1	-2.8	2.6	0.2
Soon-After Transfusion (Test Session 1) vs Long-After Transfusion (Test Session 1)	9.0	17.8	**< .0001**
Between-group			
Test Session 1			
Controls Test Session 1 vs HU Test Session 1	9.2	17.6	**.0001**
Controls Test Session 1 vs Soon-After Transfusion (Test Session 1)	3.9	2.3	0.13
HU Test Session 1 vs Soon-After Transfusion (Test Session 1)	-5.3	4.1	**.09**
Test Session 2			
Controls Test Session 2 vs HU Test Session 2	7.1	10.4	**.0005**
Controls Test Session 2 vs Long-After Transfusion (Test Session 2)	13.5	27.4	**< .0001**
HU Test Session 2 vs Long-After Transfusion (Test Session 2)	6.4	5.8	**.04**

HU = hydroxyurea. Difference indicates the change between Test Session 1 and Test Session 2 or difference between groups at Test Session 1 or Test Session 2. Negative difference values indicate lower values at Test Session 1 compared to Test Session 2 or lower values for first group compared to second group. Values in bold represent a significant difference.

TABLE 3. Differences in Non-Executive Abilities by Test Session and Group

	Difference	X^2	*p*
Within-group			
Controls Test Session 1 vs Controls Test Session 2	-3.2	3.8	.14
HU Test Session 1 vs HU Test Session 1	-1.7	.9	.35
Soon-After Transfusion (Test Session 1) vs Long-After Transfusion (Test Session 1)	-4.1	3.8	.14
Between-group			
Test Session 1			
Controls Test Session 1 vs HU Test Session 1	.09	.001	1
Controls Test Session 1 vs Soon-After Transfusion (Test Session 1)	2.3	.5	1
HU Test Session 1 vs Soon-After Transfusion (Test Session 1)	2.2	.5	1
Test Session 2			
Controls Test Session 2 vs HU Test Session 2	1.8	.5	1
Controls Test Session 2 vs Long-After Transfusion (Test Session 2)	1.6	.3	1
HU Test Session 2 vs Long-After Transfusion (Test Session 2)	-.2	.003	1

HU = hydroxyurea. Difference indicates the change between Test Session 1 and Test Session 2 or difference between groups at Test Session 1 or Test Session 2. Negative difference values indicate lower values at Test Session 1 compared to Test Session 2 or lower values for first group compared to second group. Values in bold represent a significant difference.

Supporting Information

SUPPLEMENTARY TABLE S1. Description of NIH Toolbox Cognitive Domains

Cognitive Domain	NIH Toolbox Tests	Validation Measures	Description
Executive Abilities			
Set shifting	Dimensional Change Card Sort	WISC-IV and WPPSI-III Block Design (3–6 years)	The ability to unconsciously shift conceptual frameworks
Response inhibition	Flanker Inhibitory Control and Attention	D-KEFS Color Word Interference (8–15 years)	The ability to control attention/behavior to override strong internal or external distractions
Working memory	List Sorting	NEPSY-II Sentence Repetition (3–6 years) WISC-IV Letter Number Sequencing (8–15 years)	The capacity to process information across a series of tasks and modalities, hold information in a short-term buffer, manipulate the information, and hold the products in the same short-term buffer
Non-Executive Abilities			
Receptive vocabulary	Picture Vocabulary	Peabody Picture Vocabulary Test 4th Edition	How many concepts/words an individual understands through listening, signing, or print
Expressive vocabulary	Oral Reading Recognition	Wide Range Achievement Test 4th Edition Reading Subtest	Translation of shared symbols (e.g., words, gestures) for the purpose of communication
Episodic memory	Picture Sequence Memory	NEPSY-II Sentence Repetition (3–6 years) Rey Auditory-Verbal Learning Test (8–15 years) Brief Visuospatial Memory Test-Revised (8–15 years)	The capacity for storing and retrieving information, it is critical for the acquisition of knowledge and for building adaptive skills.
Processing Speed	Pattern Comparison	WPPSI-III or WISC-IV Processing Speed Composite Paced Auditory Serial Addition Test (8–15 years)	The speed with which simple cognitive operations can be performed

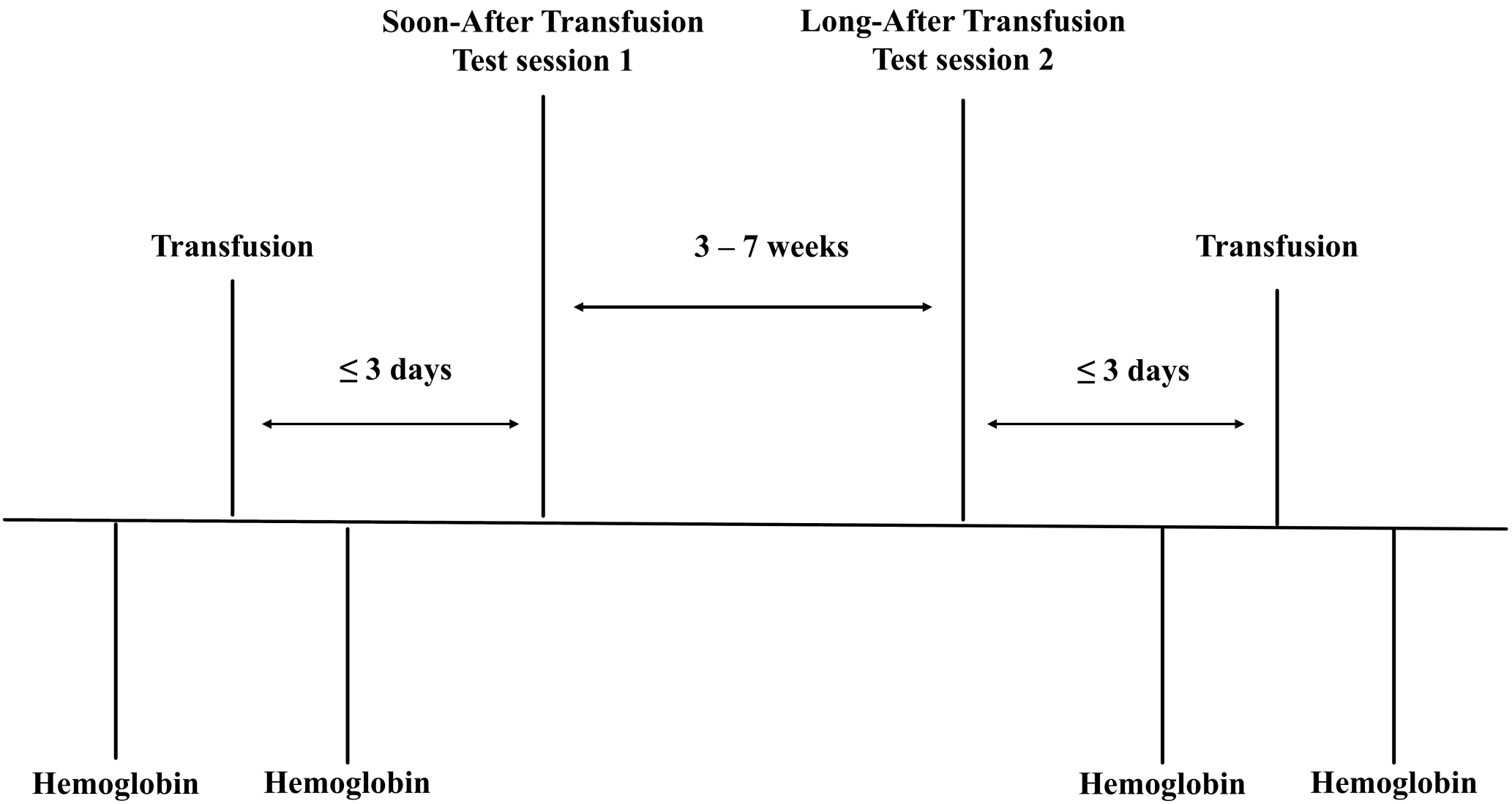
Notes: NIH = National Institutes of Health; WISC-IV = The Wechsler Intelligence Scale for Children Fourth Edition; WPPSI-III = The Wechsler Preschool and Primary Scale of Intelligence Third Edition; D-KEFS = Delis-Kaplan Executive Function System

Supporting Information

SUPPLEMENTARY TABLE 2. Standard Scores for Individual Tests on the NIH Toolbox by Test Session and Group

NIH Toolbox Tests	Controls M (SD)		HU M (SD)		Transfusion M (SD)	
	Test Session 1	Test Session 2	Test Session 1	Test Session 2	Soon-After	Long-After
Executive Abilities						
Dimensional Change Card Sort	97.9 (14.2)	95.8 (13.7)	87.5 (13.6)	89.9 (15.5)	89.6 (16.5)	82.9 (13.2)
Flanker Inhibitory Control and Attention	95.8 (16.4)	98.5 (15.3)	84.6 (12.5)	86.1 (12.1)	84.7 (15.7)	80.2 (14.9)
List Sorting	97.0 (14.8)	99.3 (15.8)	92.0 (14.2)	96.4 (13.2)	94.1 (10.5)	77.4 (10.4)
Non-Executive Abilities						
Picture Vocabulary	93.2 (18.1)	94.1 (16.7)	92.0 (13.6)	92.2 (13.1)	87.2 (9.9)	90.5 (11.1)
Oral Reading Recognition	94.1 (12.8)	95.6 (16.9)	91.2 (14.1)	92.8 (14.6)	81.5 (13.5)	84.6 (13.3)
Picture Sequence Memory	91.8 (14.8)	97.0 (14.3)	95.8 (14.7)	100.0 (15.9)	91.0 (11.6)	96.88 (18.1)
Processing Speed						
Pattern Comparison	96.2 (16.2)	106.4 (15.8)	86.71 (24.3)	102.0 (18.9)	89.2 (24.0)	93.6 (17.8)

Note: HU = hydroxyurea; M = Mean; SD = Standard Deviation; Soon-After = Soon after a transfusion; Long-After = Long after a transfusion


Soon-After Transfusion
Test session 1
Long-After Transfusion
Test session 2
Transfusion
3 – 7 weeks
Transfusion
≤ 3 days
≤ 3 days
Hemoglobin
Hemoglobin
Hemoglobin
Hemoglobin

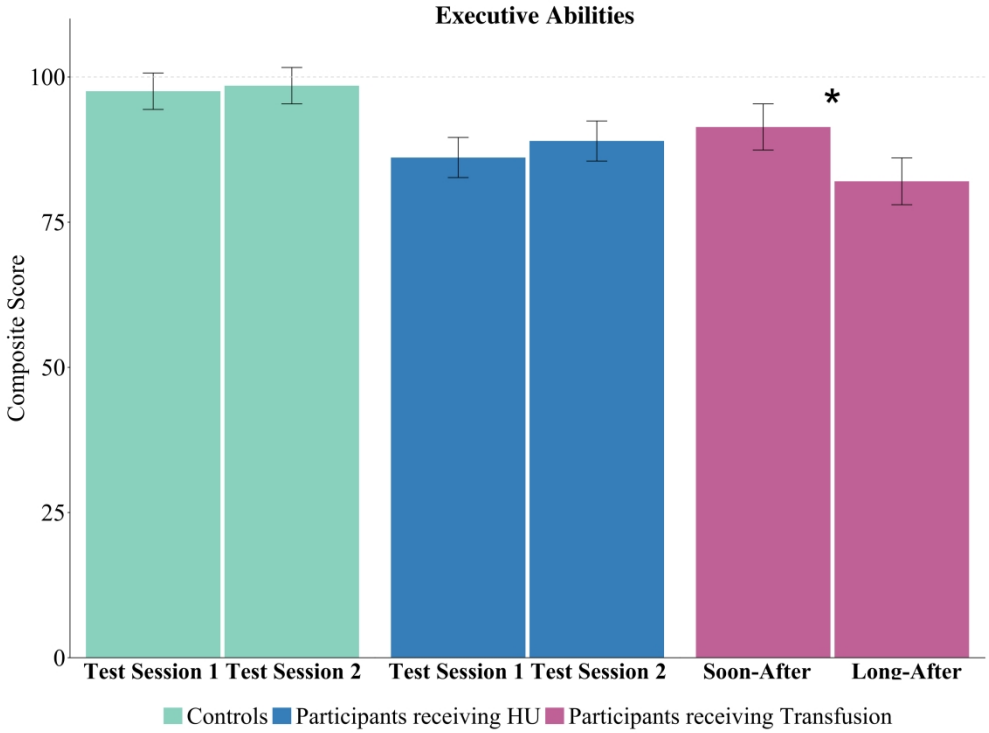


Figure 2. Executive abilities for control and HU groups at test session 1 and 2, and for the transfusion group soon-after a transfusion (test session 1) and long-after a transfusion (test session 2). Composite score = Executive Abilities Composite, which was computed by averaging standard scores (M = 100, SD = 15) of individual tests (i.e., Dimensional Change Card Sort Test, Flanker Inhibitory Control and Attention Test, List Sorting Test). Error bars represent 95% confidence intervals. * = $p < .05$ represents significant difference between test session 1 and test session 2 (i.e., soon-after vs long-after transfusion). Dashed gray line represents mean scores for NIH Cognition Module; HU = Hydroxyurea.

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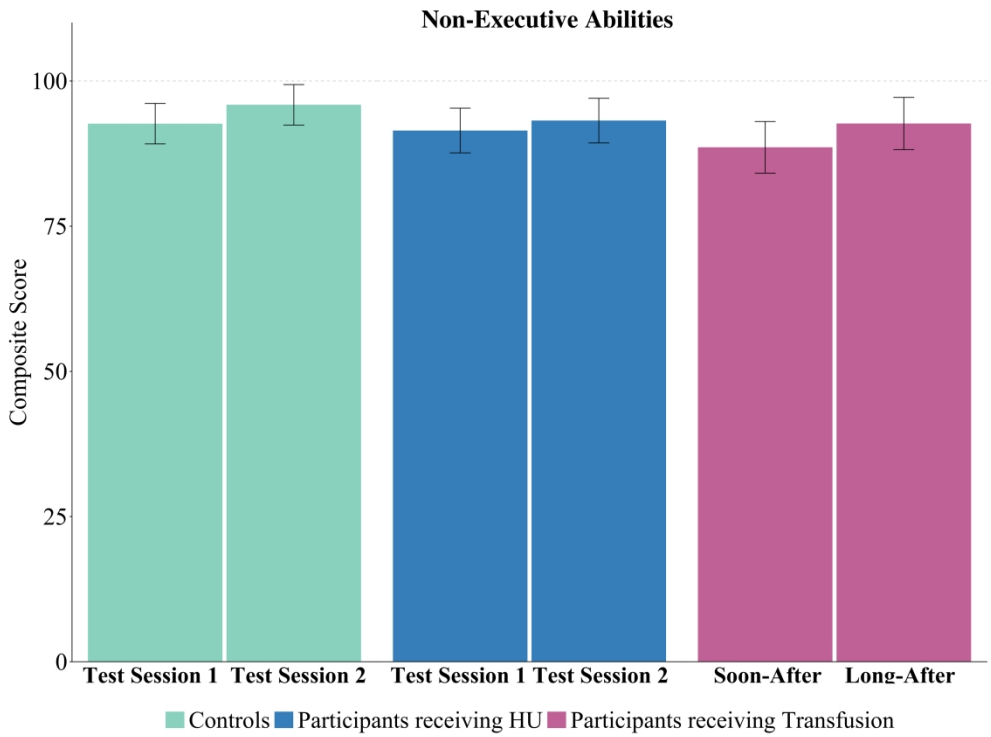

Figure 3. Non-executive abilities for control and HU groups at test sessions 1 and 2, and for the transfusion group soon-after (test session 1) and long-after (test session 2) transfusion. Composite score = Non-Executive Abilities Composite, which was computed by averaging standard scores (M = 100, SD = 15) of individual tests (i.e., Picture Vocabulary Test, Oral Reading Recognition Test, Picture Sequence Memory Test). Dashed gray line represents mean scores for NIH Cognition Module; HU = Hydroxyurea.

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