Biological Interventions to Improve Cognition in Children with Sickle Cell Disease

by

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In loving memory of my mother.
Children with sickle cell disease (SCD) experience widespread cognitive deficits along with numerous other medical consequences including stroke, acute chest syndrome, and premature death. Molecular changes within sickled cells reduce the oxygen-carrying capacity of the blood, but the specific mechanisms by which cognitive deficits occur are not yet fully understood. Therefore, cognition remains a critical target, but currently, biological interventions for children with SCD aim to improve health and disease outcomes, but none are aimed at improving cognition.

The goal of the present study was to determine whether blood transfusion, an essential and life-saving biological intervention which increases oxygen carrying capacity, would improve cognition in children with SCD. Our study focused on executive abilities given their importance in school readiness and academic performance and had three specific aims. The first aim assessed for differences in executive abilities between children with SCD receiving transfusion (both near and far from transfusion), children with SCD receiving Hydroxyurea (HU; a commonly used drug that increases overall blood flow), and a cohort of healthy children tested at two time points. The second aim assessed the relationship between behavioral functioning and
cognition in children with SCD. Finally, the third aim assessed the relationship between blood biomarkers of SCD and executive abilities in children receiving transfusion.

The results of the study found that children with SCD (transfusion and HU) had poorer executive abilities than healthy children. Importantly, children near transfusion (high oxygen delivery) had improved executive abilities compared to far from transfusion (poor oxygen delivery). They also had better executive abilities near transfusion than children with SCD receiving HU at their first test session, despite having greater disease severity. Health-related quality of life emerged as the aspect of behavioral functioning most strongly related to executive abilities. Lastly, when blood biomarkers remained high over a 4 – 6 week interval (e.g., hemoglobin) executive abilities remained high further from transfusion. Our study demonstrates that executive abilities are vulnerable, yet malleable in children with SCD receiving transfusion. The findings provide new information that could influence the development of future treatment options tailored to the specific needs of this population struggling with SCD.
1. INTRODUCTION

1.1 Overview

Sickle cell disease (SCD) is the collective term for a group of autosomal recessive hemoglobinopathies that are characterized by the production of abnormal hemoglobin in red blood cells (RBCs) (Rees, Williams, & Gladwin, 2010). Approximately 3.5% of the global population carries the hemoglobinopathy mutation, but most hemoglobin gene variants are rare and many are harmless. Some variants, however, are more common and persist because individuals who are carriers (healthy heterozygotes) gain some protective advantage from malaria and are less likely than others to die from the disease. In populations in which malaria is (or was) endemic, up to 40% of individuals carry some combination of hemoglobin S, C, E, D Punjab, $\beta^+$ thalassemia, $\beta^0$ thalassemia, which are the significant gene variants that form the group of SCD disorders (Modell & Darlison, 2008; Platt et al., 1994).

SCD is most common in individuals of African ancestry, but a minority of individuals with SCD are of Hispanic, Asian Indian, or Middle Eastern descent (Centers for Disease Control and Prevention, 2015). In the United States, the number of individuals homozygous for SCD, and therefore experiencing the most severe form of the disease, approaches 100,000 (Hassell, 2010). SCD is caused by a single nucleotide mutation (A/T) within $\beta$-globin gene ($HBB$), which codes for a hemoglobin protein subunit. The mutation results in the production of sickle hemoglobin, (Ashley-Koch, Yang, & Olney, 2000) in RBCs, which polymerizes following the release of oxygen and distorts the shape of RBCs into a rigid sickle shape, which dramatically alters the mechanical and rheological properties of RBCs (Ashley-Koch et al., 2000; Frenette & Atweh, 2007; Stuart & Nagel, 2004).
These alterations result in two key pathological processes. First, abnormalities in the morphology, stiffness, and membrane pliability of sickled cells limit their flow through the vasculature. As such, blood vessels may become occluded, which impedes the delivery of oxygen to tissues and organs throughout the body (Rees et al., 2010; Switzer, Hess, Nichols, & Adams, 2006). Recurring vaso-occlusive crises, which are often precipitated by external factors such as dehydration, infection, cold temperature, exercise, alcohol consumption, and pregnancy (Stuart & Nagel, 2004), result in the pain syndrome associated with SCD due to damage to bones, joints, and organs (Platt et al., 1991; Rees et al., 2010).

The second key pathological process associated with SCD is hemolysis, which is the premature destruction and removal of healthy RBCs. Hemolytic anemia develops because the bone marrow cannot produce RBCs as quickly as they are destroyed. The severity of anemia depends on the extent of RBC destruction and whether the onset of hemolysis is abrupt or gradual (Lonergan, Cline, & Abbondanzo, 2001). Individuals with SCD commonly experience hypoxia (no oxygen) and hypoxemia (low oxygen) due to RBC destruction, which along with vaso-occlusion contributes to poor oxygen delivery throughout the body (Caboot & Allen, 2014).

Although the chronic oxygen deprivation associated with SCD causes multi-system medical complications (Rees et al., 2010); neurologic complications are especially severe and particularly relevant to the current investigation. Children with SCD are 300 times more likely than healthy children to experience cerebral infarction due to ischemia in the brain (DeBaun et al., 2012; Lee et al., 2006; Ohene-Frempong et al., 1998). The precise mechanisms underlying cerebral infarction are unknown, but associated factors include abnormal cerebral blood flow (CBF), anemia, vaso-occlusion in the internal carotid and cerebral arteries, endothelial damage, hemolysis, and reduced oxygen saturation (Hillery & Panepinto, 2004).
There are two primary presentations of cerebral infarction in individuals with SCD—stroke and silent cerebral infarct (SCI). Stroke reflects the presence of overt neurologic signs such as hemiplegia and aphasia (Ohene-Frempong et al., 1998). In contrast, SCI lacks the characteristic overt neurologic signs of stroke, but abnormalities observed on brain imaging are consistent with cerebral infarction (DeBaun et al., 2014). These serious neurologic complications begin in early childhood, with the highest incidence of stroke in children occurring between 2 and 5 years of age (Ohene-Frempong et al., 1998). Additionally, 25% of children with sickle cell anemia (SCA or HbS), will have a silent cerebral infarction (SCI) on magnetic resonance imaging (MRI) before age 18 years. The prevalence increases linearly with age, reaching nearly 50% by 30 years (Debaun et al., 2014; Lynch, Hirtz, DeVeber, & Nelson, 2002; Morton & Key, 2002; Ohene-Frempong et al., 1998; Pegelow et al., 1995).

These findings highlight the importance of therapeutic interventions to reduce cerebral infarction in children with SCD. As such, we next discuss therapies that are often initiated to prevent organ injury and improve prognosis in children with SCD (Inati, 2009). We first discuss antibiotics, vaccines, and stem-cell transplantation. We then turn to the administration of hydroxycarbamide (hydroxyurea; HU) and blood transfusion, which are the therapeutic foci of the present study.

1.2 Treatments for SCD

**Prophylactic antibiotics and vaccines.** Prophylactic antibiotics and vaccines are among the few interventions available that improve medical outcomes and quality of life for children with SCD. These interventions should be started in infancy because children with SCD have a 600-fold increase in risk of fatal invasive pneumococcal disease compared to the general population (Overturf, 1998). In fact, before widespread immunizations, pneumococcal disease
was the leading cause of death in children with SCD aged 1 to 3 years (Hamideh & Alvarez, 2013). In addition to pneumococcus, other infectious organisms are often harbored in damaged tissues, which further contribute to morbidity (Hirst & Owusu-Ofori, 2014).

**Stem cell transplantation.** Stem cell transplantation of hematopoietic pluripotent stem cells from HLA-matched related donors remains the only curative therapy for SCD (Bernaudin et al., 2007). Most successful stem cell transplantations for SCD have been in children, with a 5-year overall and 5-year event-free survival rate approaching 90% (Gluckman et al., 2017). The goal of transplantation is to eliminate sickled RBCs and their cellular progenitors and replace these with cells in which HbS is absent. The process produces HbS levels similar to those seen in individuals with sickle cell trait (i.e., heterozygous for the SCD gene) (Copelan, 2006) and prevents the most severe complications of SCD such as vaso-occlusive crises, stroke, and acute chest syndrome (Shenoy et al., 2017).

Although stem cell transplantation has been successful, its application is highly restricted because only 10 to 20% of children have an unaffected matched donor. In addition, transplantation is not without risk. The chemotherapy and/or radiation therapy administered before transplantation compromises the immune system of children who are already at high risk for infection (Walters et al., 1996). In addition, because graft-versus-host disease can lead to chronic problems across a range of organ systems, the benefits of curing SCD must be weighed carefully against the possibility that a child will develop another serious chronic condition (Shenoy et al., 2017).

**Hydroxyurea.** HU is a pharmacological agent that interferes with the DNA synthesis involved in RBC precursor maturation. As such, the expression of fetal hemoglobin is increased, which decreases the sickling of RBCs (Yarbro, 1992). HU is generally well tolerated by
individuals with SCD, with associated improvements in blood flow, hemoglobin levels, and mean corpuscular volume (Steinberg et al., 2010; Ware, 2010; Ware, Zimmerman, & Schultz, 1999). Hospital admissions and the duration of hospital stays are also decreased (Ferster et al., 1996).

There are risks associated with HU, such as reversible decreases in reticulocyte, white blood cell, and platelet counts, as well as increases in serum bilirubin (Brawley et al., 2008; Zimmerman et al., 2004). HU has also been shown to compromise the already limited fertility of adult men with SCD (DeBaun, 2014). Additionally, the large-scale Stroke with Transfusions Changing to Hydroxyurea (SWiTCH) trial was halted early because children receiving HU experienced more strokes than children receiving blood transfusion therapy (Ware & Helms, 2012). The subsequent Transcranial Doppler with Transfusions Changing to Hydroxyurea (TWiTCH) trial, however, showed that HU could be substituted for continued blood transfusion to maintain normal blood velocities and decrease stroke occurrence in children who had received at least one year of blood transfusion (Ware et al., 2016).

**Blood transfusion.** Blood transfusion is a life-saving component of clinical care in SCD and the primary intervention used to prevent the occurrence and recurrence of cerebral infarction (Josephson, Su, Hillyer, & Hillyer, 2007). Blood transfusion improves oxygen saturation via increased arterial oxygen pressure and hemoglobin oxygen affinity through the addition of healthy hemoglobin. This process reduces RBC sickling, RBC hemolysis, and prevents tissue hypoxia (Switzer et al., 2006).

The Stroke Prevention Trial in Sickle Cell Anemia (STOP) demonstrated that chronic blood transfusion increases the probability that children with SCD at high risk for stroke (i.e., those with high blood velocity measured via transcranial doppler ultrasonography; TCD) remain
stroke-free. Subsequently, STOP II randomized children with SCD who had normal blood velocity following transfusion to either continued or discontinued transfusion arms. This trial was terminated early because 34% of children in the discontinued transfusion arm had increased TCD blood velocities, which indicated they were at high risk for stroke (Abboud, Yim, Musallam, Adams, 2011). Although STOP and STOP II showed the efficacy of blood transfusion in reducing stroke risk, there is no consensus regarding the optimal duration of transfusion, and long-term side effects such as iron overload and risk of serious viral infection must be considered carefully (Beverung et al., 2015; Inati, 2009; Marouf, 2011).

1.3 Blood Biomarkers of SCD Severity

Blood biomarkers reflect changes in the composition and flow of blood following HU and blood transfusion therapies. They provide insights into how these treatments reduce SCD symptom severity. For example, hemoglobin levels are viewed as a surrogate marker for oxygen delivery to the brain (Vichinsky et al., 2010), and lower hemoglobin levels are associated with increased risk of SCI in children with SCD (DeBaun et al., 2012). Other common blood biomarkers include RBC count (number of RBCs), reticulocyte count (number of immature RBCs), hematocrit (percentage of blood by volume comprising RBCs), HbS concentration (abnormal hemoglobin), and HbA concentration (healthy hemoglobin). These biomarkers provide prognostic information in the management of SCD (Damanhour et al., 2015), particularly regarding transfusion.

In an early study, Venketasubramanian et al. (1994) measured hematocrit and used TCD to measure middle cerebral artery (MCA) blood velocity in children and young adults with SCD (including 6 with cerebral infarction). Blood velocity measurements were taken at baseline, at 30-minute intervals during transfusion, and the day after transfusion. Hematocrit was measured
at baseline immediately after transfusion. The study showed that blood velocity fell within 30 minutes of transfusion and continued to decline at a rapid rate during the first 3 hours (approximately 6% per hour) before remaining stable at lower values for the next 24 hours. Baseline MCA blood velocity was lower in infarcted than non-infarcted territories in individuals with cerebral infarction, but the rate of reduction in blood velocity during transfusion was the same. In terms of hematocrit, this value rose at a similar magnitude to the fall in MCA blood velocity, with an almost perfect correlation at all time points. These results suggest that blood transfusion normalized hematocrit, at least in the short-term (Venketasubramanian, Prohovnik, Hurlet, Mohr, & Piomelli, 1994).

Nahavandi et al. (2004) provided further evidence of short-term improvements in oxygen delivery following transfusion, albeit in an adult sample of individuals with SCD. Pre-and-post blood transfusion, they used cerebral oximetry to measure mixed arterial and venous oxygen saturation and collected blood biomarkers (e.g., hemoglobin and hematocrit) in individuals with no history of stroke. Findings showed that blood transfusion significantly increased cerebral oxygen saturation, HbA, and hematocrit, and significantly reduced HbS. Finally, Kwiatowski et al. (2011) assessed children with SCD without history of stroke receiving chronic transfusion (mean of 23 months) who had abnormal blood velocity prior to transfusion. They found that the probability of converting to normal blood velocity during transfusion increased by 26.6% for each 1 g/dl increase in pre-transfusion hemoglobin levels after controlling for initial blood velocity, reticulocyte count, and pre-transfusion HbS levels (Kwiatkowski, Yim, Miller, & Adams, 2011).

These studies demonstrate that blood biomarkers improve following transfusion, which is associated with lower risk of cerebral infarction. In addition to cerebral infarction, however,
children with SCD often experience other significant complications, such as poorer behavioral functioning, poorer quality of life, and widespread cognitive deficits in comparison to healthy children. In the sections following, we first discuss behavioral functioning and quality of life, and then, of primary importance to the present study, describe the significant cognitive deficits associated with SCD.

1.4 Behavioral Functioning and Quality of Life in SCD

Children with SCD face considerable challenges, but in comparison to other pediatric populations with serious medical illness, there are few studies that assess behavioral functioning or psychosocial outcomes. This is particularly surprising given the intense chronic treatment regimen associated with SCD and its potential to affect behavior. Most of the small number of studies that have focused on children with SCD have assessed internalizing disorders such as anxiety and depression, whereas others have focused on health-related quality of life (HRQOL). Finding from these studies are discussed next.

Studies assessing internalizing disorders have shown that depression is common in children with SCD, with prevalence estimates of 25-56% (Barbarin, Whitten, & Bonds, 1994; Benton, Ifeagwu, & Smith-Whitley, 2007). Jerrell et al. (2011) conducted a large-scale retrospective study examining data from over 1000 children with SCD and found that 46% were diagnosed with either major depressive disorder or dysthymia. Less than 20% of children diagnosed with depression were prescribed an antidepressant, and the average length of treatment was only 9 months. At present, the prevalence of anxiety disorders is unknown, but both depression and anxiety disorders in children with SCD have been associated with higher rates of pain (Gil et al., 2003; Ünal, Toros, Kütük, & Uyankır, 2011), behavioral disinhibition (Carpentier, Elkin, & Starnes, 2009), poorer HRQOL (Barakat, Patterson, Daniel, & Dampier,
Comparisons between children with SCD and peer and sibling controls have resulted in mixed findings. Morgan et al. (1986) found that children with SCD reported less satisfaction and more symptoms of depression than demographically-matched healthy children (Morgan & Jackson, 1986). Three studies found that caregivers reported more internalizing problems for children with SCD in comparison to matched classmates (Ekinci, Çelik, Ünal, & Özer, 2012; Trzepacz, Vannatta, Gerhardt, Ramey, & Noll, 2004) and siblings (Hijmans et al., 2009). Two other studies found high rates of depression and anxiety in children with SCD compared to national rates, although these high rates of psychopathology were similar to demographically matched classmates (Kelly et al., 2015; Yang, Cepeda, Price, Shah, & Mankad, 1994). Finally, Lee et al. (1997) found that non-SCD siblings actually experienced higher rates of depression and hopelessness than adolescents with SCD (Lee, Phoenix, Brown, & Jackson, 1997).

HRQOL is the most commonly assessed psychosocial outcome in children with SCD. Poorer HRQOL has been associated with increased pain (Dampier et al., 2010; Fisak, Belkin, Von Lehe, & Bansal, 2012; Schlenz, Schatz, McClellan, & Roberts, 2012), increased age, female gender, rural residence, low family income, presence of disease-related complications, and frequent hospital admissions (Amr, Amin, & Al-Omair, 2011). Perhaps counterintuitively, poorer HRQOL has also been associated with better medical adherence (Barakat, Lutz, Smith-Whitley, & Ohene-Frempong, 2005). Finally, Bhatia et al. (2015) found that HRQOL improved one year after stem cell transplantation.

Comparisons with controls paint a clear picture of poorer HRQOL for children with SCD (Ojelabi, Graham, & Ling, 2017). Children with SCD have poorer HRQOL than previously
published scores of healthy children (Dale, Cochran, Roy, Jernigan, & Buchanan, 2011; Wrotniak, Schall, Brault, Balmer, & Stallings, 2014) and demographically-matched healthy children (Adeyemo, Ojewunmi, Diaku-Akinwumi, Ayinde, & Akanmu, 2015; Menezes, Len, Hilário, Terreri, & Braga, 2013; Palermo, Schwartz, Drotar, & McGowan, 2002; Panepinto, Pajewski, Foerster, Sabnis, & Hoffmann, 2009). That said, one study found poorer HRQOL in children with SCD compared to published norms, but their HRQOL was similar to that of siblings (Hijmans et al., 2010).

The studies reviewed indicate that children with SCD experience high rates of internalizing disorders and generally poorer HRQOL. Pain crises, parental coping and support, and illness severity influence HRQOL, and the presence of psychopathology likely contributes to poorer long-term outcomes for children with SCD. Importantly, as medical advances have shifted from survival to management of a chronic lifelong disease, there is a great need to develop interventions to prevent and treat comorbid psychological conditions and improve HRQOL in children with SCD.

1.5 Cognition in SCD

Along with and often because of severe neurologic complications, children with SCD experience cognitive deficits including decreased intelligence (IQ), as well as impairment across a range of cognitive domains such as language, memory, visuospatial abilities, processing speed, attention, and executive abilities in comparison to siblings, peers, and normative test samples (Hood et al., 2017 under review). Children with SCD and stroke experience the most pronounced cognitive deficits, followed by children with SCI, and finally by children with normal-appearing CT or MRI (Berkelhammer et al., 2007; Brandling-Bennett, White, Armstrong, Christ, & DeBaun, 2003; Knight, Singhal, Thomas, & Serjeant, 1995; Nabors & Freymuth, 2002).
When cognition has been examined in relation to cerebral imaging findings, cognitive deficits in children with SCD were associated with higher blood velocity and cerebral blood flow (CBF); reduced white matter, gray matter, and basilar artery volume; poorer white matter integrity; delayed auditory cognitive evoked potentials; and decreased BOLD signal (Hood et al., under review). However, no clear pattern has emerged on the basis of neurologic status (e.g., stroke, SCI). This is primarily because studies that examined cognition in relation to imaging findings often failed to explore the cognition-imaging relationship based on neurologic status or only assessed one group of children with SCD (e.g., only children with normal-appearing CT or MRI) (Hood et al., under review).

Although children with SCD with normal-appearing CT or MRI have less pronounced cognitive deficits in comparison to children with stroke and SCI, they nonetheless experience deficits in comparison to healthy siblings and peers (Brown et al., 2000; Schatz, Finke, Kellett, & Kramer, 2002; Steen, Xiong, Mulhern, Langston, & Wang, 1999). Children with normal-appearing CT or MRI experience cognitive deficits in the absence of severe structural tissue injury and/or necrosis due to chronically reduced oxygen delivery that produces hypoxic changes in the brain (Cboot & Allen, 2014). Indeed, there is evidence of subtle brain abnormalities on quantitative T1-weighted MRI in children with normal-appearing conventional MRI findings (Steen et al., 1996).

Despite the long-held knowledge that all children with SCD experience chronic oxygen deprivation in the brain, there are currently only four studies that have evaluated the effect of improved oxygen delivery on cognition in children with SCD. In the first study, Wilmas et al. (1980) assessed full-scale, verbal, and performance IQ (i.e., IQ, VIQ, and PIQ, respectively) at baseline and at three subsequent timepoints over 6-month intervals in 12 children with SCD and
stroke who received blood transfusions over a 2-year period. They observed that IQ, VIQ, and PIQ for children with stroke were in the intellectually deficient range (< 70) at baseline but improved at the second evaluation. However, after recurrent stroke, IQ, VIQ, and PIQ reverted to baseline levels.

After Wilimas et al. (1980) showed that blood transfusion produced small improvements in IQ, VIQ, and PIQ, it would be 34 years before cognition was again assessed within the context of transfusion in children with SCD. The Silent Cerebral Infarct Multi-Center Clinical (SIT) trial randomized children with SCI to blood transfusion or observation groups for a median of 3 years. Children completed the Wechsler Abbreviated Scale of Intelligence (WASI) at three timepoints (baseline, interim, and study exit). In contrast to the findings of Wilimas et al. (1980), the large-scale SIT trial found that IQ, VIQ, and PIQ were similar at baseline and study exit, both within and between children with SCI in the transfusion and observation groups (DeBaun et al., 2014).

Burkhardt et al. (2016) then compared IQ, VIQ, PIQ, and executive abilities in children with SCD with no history of stroke who were either receiving blood transfusion, HU, or standard care (neither transfusion or HU). They found that IQ, VIQ, PIQ, and executive abilities were not significantly higher for the HU and standard care groups compared to the transfusion group compared to the HU and standard care groups. However, power to detect statistically significant differences was poor because there were only 3 children in the transfusion group. In fact, in absolute terms, the transfusion group had IQ, VIQ, PIQ, and executive abilities close to one standard deviation below those of the HU and standard care groups.

Finally, Puffer et al. (2007) assessed whether improved oxygen delivery through HU influenced cognition in children with SCD with no history of stroke. They compared overall
cognition (using a global cognitive index), language and visuospatial abilities, and short-term memory in children who received HU for a median of 41 months to that of children not receiving HU. They found that children receiving HU, who were at higher risk for stroke, had significantly better overall cognition and language and visuospatial abilities than children not receiving HU who were at lower risk for stroke.

Findings from this small set of studies are mixed. There is some support for the hypothesis that improved oxygen delivery improves cognition (Puffer, Schatz, & Roberts, 2007; Wilimas, Goff, Anderson, Langston, & Thompson, 1980), but findings from the large-scale SIT trial suggest similar IQ, VIQ, and PIQ for children with SCI receiving transfusion compared to children not receiving transfusion. Importantly, because the SIT trial was limited to the measurement of IQ, VIQ, and PIQ, it only provided the broadest information regarding cognition. Additionally, only Burkhardt et al. (2016) examined executive abilities, and in that study, there were only 3 children in the transfusion group. Currently, the influence of improved oxygen delivery through blood transfusion on specific cognitive domains (e.g., executive abilities) has not been assessed adequately in children with SCD.

Thus far we have discussed cognitive deficits and blood biomarkers in SCD separately. However, changes in blood biomarkers of oxygen delivery to the brain likely predict changes in cognition in children with SCD. Therefore, we next discuss research that assessed the relationship between blood biomarkers of oxygen delivery and cognition in children with SCD.

### 1.6 Cognition and Blood Biomarkers of SCD Severity

Hemoglobin concentration and hematocrit are the most commonly measured blood biomarkers in relation to cognition. Regarding hemoglobin, a number of studies found no relationship to IQ (Knight et al., 1995; Krejza et al., 2012; Oluwole, Noll, Winger, Akinyanju, &
Novelli, 2016; Smith, Patterson, Szabo, Tarazi, & Barakat, 2013; Swift et al., 1989; Yarboi et al., 2015), short-term memory and attention (Grueneich et al., 2004), or processing speed (Oluwole et al., 2016). In contrast, a few studies found that hemoglobin significantly predicted IQ and visual memory (Brown et al., 1993), verbal short-term memory (Hijmans et al., 2011), and executive abilities (Ruffieux et al., 2013). Apart from Hijmans et al. (2011), studies assessing hemoglobin and cognition in children with SCD included children in which neurologic status was unclear or children who had no history of stroke determined via neurologic examination (e.g., MRI was not conducted).

A number of studies have identified a relationship between hematocrit and IQ (Kral et al., 2006; Puffer, Schatz, & Roberts, 2010, 2014; Schatz, Finke, & Roberts, 2004; Steen, Xiong, Mulhern, Langston, & Wang, 1999), vocabulary and visual matching (Schatz et al., 2004), VIQ and short-term memory (Kral et al., 2003), and executive and visuospatial abilities (Kral et al., 2006). Only one study found no relationship between hematocrit and IQ (Knight et al., 1995). Reticulocyte count and HbF level are the only other blood biomarkers that have been assessed in relation to cognition in children with SCD. Hijmans et al. (2011) found that, in children with SCI and normal-appearing MRI, higher reticulocyte count was associated with poorer working memory but not inhibitory control, whereas Ruffieux et al. (2013) found that children with lower HbF had poorer executive abilities and sustained attention.

Overall, findings from the studies reviewed suggest that hematocrit may have a stronger relationship to cognition than hemoglobin concentration. This may be because hematocrit is a major determinant of whole blood viscosity. As viscosity increases so does hematocrit, along with diminished circulation of blood in small vessels and subsequent reductions in oxygen delivery (Rosse, Narla, Petz, & Steinberg, 2000).
Research discussed thus far indicates that children with SCD face significant medical, psychosocial, and cognitive problems. Blood transfusion and HU have been used successfully to treat medical problems, but there is no targeted treatment for cognitive problems in children with SCD. In addition, the small number of studies conducted to date suggest that HU but not blood transfusion improves IQ in children with SCD. There is, however, a great need for additional research with larger samples of children with SCD that assesses function across a range of specific cognitive domains.

1.7 Improved Oxygen Delivery in a Healthy Population

There has been one study assessing whether changes in blood hemoglobin influence cognition, but the study was conducted in non-SCD adults. Weiskopf et al. (2000) assessed healthy adults who completed three cognitive tasks measuring processing speed, attention, and immediate and delayed recall at five timepoints. Cognitive testing occurred at baseline (hemoglobin of 14 g/dl), after blood was removed to obtain hemoglobin of 7, 6, and 5g/dl, and finally after blood transfusion that returned hemoglobin to 7g/dl. Participants also completed cognitive testing at 5 timepoints the next day (over a similar duration) without blood removal to alter hemoglobin.

It was found that processing speed and delayed recall were similar at baseline and following blood transfusion (i.e., hemoglobin level of 7 g/dl) and that attention was similar at all hemoglobin levels for healthy adults. Reaction time was significantly poorer at a hemoglobin level of 6 g/dl compared to baseline. At a hemoglobin level of 5 g/dl, reaction time and immediate and delayed recall were significantly poorer compared to baseline. The following day, when hemoglobin returned to 14 g/dl, processing speed, attention, and immediate and delayed recall were similar at all five testing timepoints (Weiskopf et al., 2000).
This study demonstrated that when hemoglobin was reduced to anemic levels (5 and 6 g/dl) some aspects of cognition were poorer in healthy adults. Importantly, some aspects of cognition improved after blood transfusion increased hemoglobin to 7 g/dl, even though this hemoglobin level remained indicative of anemia. This study has clinical implications for SCD, suggesting that blood transfusion, even when an individual remains anemic, may improve in cognition.

1.8 Study Overview

Our overarching goal was to determine whether blood transfusion improves cognition in children with SCD. We believed that, similar to findings from healthy adults, blood transfusion would improve blood biomarkers of oxygen delivery and subsequently cognition. The focus of most studies of cognition in children with SCD has been IQ and, in general, transfusion has not been associated with improvements in IQ (e.g., DeBaun et al., 2014). This may, however, be because IQ is essentially an average across multiple cognitive domains, and it is possible that improvements in some cognitive domains may have been obscured by lack of improvement in others when combined to create a global IQ. As such, in the present study we chose to focus on executive abilities, a specific cognitive domain in which children with SCD experience particular difficulty (Hood et al., under review). In addition to examining possible change in executive abilities within children with SCD receiving blood transfusion, we also conducted comparisons of executive abilities across children with SCD receiving transfusion, children with SCD receiving HU, and data from a demographically-matched normative sample.
1.9 Specific Aims

Specific Aim 1. Determine whether executive abilities are poorer in children with SCD receiving blood transfusion or HU compared to a demographically-matched sample of healthy children.

This comparison was of importance to assess the clinical significance of impairments in executive abilities in children with SCD. We hypothesized that executive abilities would be poorer in children with SCD compared to the normative sample.

Sub-aim a. Determine whether executive abilities in children with SCD improve following blood transfusion.

To explore whether executive abilities improve following transfusion, children receiving transfusion as a component of their clinical care were administered tests of executive abilities and non-executive abilities within three days following transfusion (near transfusion) and then again within three days before their next transfusion (far from transfusion). We hypothesized that executive abilities would improve near transfusion relative to far from transfusion and that non-executive abilities would remain stable.

Sub-aim b. Determine whether executive abilities improve in children with SCD receiving blood transfusion compared to children with SCD receiving HU.

We compared executive abilities in children receiving HU at two timepoints within a timeframe comparable to that of children near and far from transfusion. Children with SCD receiving HU have similar demographic and medical characteristics to those receiving transfusion, although their symptoms are most often less severe. We hypothesized that children receiving transfusion, despite having greater disease severity,
would have improved executive abilities compared to children receiving HU when near, but not far from transfusion.

**Specific Aim 2. Determine whether executive abilities are related to behavioral functioning in children with SCD.**

Children with SCD experience behavioral problems (Barbarin, Whitten, & Bonds, 1994; Benton, Ifeagwu, & Smith-Whitley, 2007; Ojelabi, Graham, & Ling, 2017), and behavioral functioning has been related to cognition (Ruffieux et al., 2013). However, the relationship between executive abilities and behavioral functioning in children with SCD is largely unexplored. *We hypothesized that poorer executive abilities would be associated with poorer behavioral functioning (i.e., attention, emotional problems, HRQOL, and executive functioning) in children with SCD receiving either blood transfusion or HU.*

**Specific Aim 3. Determine whether executive abilities are related to blood biomarkers in children with SCD receiving blood transfusion.**

Blood biomarkers such as hemoglobin concentration, HbA%, RBC count, and HbS% are indicative of disease severity in children with SCD (Nahavandi et al., 2004; Kwiatowski et al., 2011) and have been related to cognition (Ruffieux et al., 2013). However, the relationship between executive abilities and biomarkers of disease severity in children with SCD is, again, largely unexplored. *We hypothesized that biomarkers would be associated with executive abilities in children with SCD receiving blood transfusion, such that change in biomarkers (collected after near transfusion and before far from transfusion) would be associated with improvements in executive abilities over the 4 – 6 week interval.*
2. METHODS

2.1 Participants

2.1.1 Patients with SCD

Patients were recruited through the Sickle Cell Program at St. Louis Children’s Hospital, which provides care to over 365 children with SCD each year. Recruitment occurred over the course of 18 months. Members of the SCD healthcare team (i.e., hematologists and nurses) identified patients who met initial eligibility criteria during routine hematology or blood transfusion appointments. Inclusion criteria included: (1) diagnosis of SCD confirmed by hemoglobin analysis; (2) receipt of either blood transfusion at four to six week intervals or HU for at least six months; and (3) age of 4 years or older at time of study enrollment. Exclusion criteria included: (1) history of bone marrow transplant; (2) congenital brain malformation; (3) severe developmental disability diagnosed through neuropsychological testing (e.g., autism); and (4) visual, auditory, language, or motor impairment that prevented use of a tablet computer as assessed by report of the researcher, a parent/guardian, or a health care provider. Seventy six patients and their families were approached and asked to participate in the study. As a result of our exclusion criteria, 1 patient was excluded due to severe developmental delay, and 1 patient was excluded due to verbal and motor impairment. After initial contact, 7 patients declined study participation, 4 patients did not respond to requests to schedule a study session, and 2 patients did not attend the first scheduled study session.

Sixty-one patients participated in the study, of which 59 completed the two required study sessions (information regarding demographic characteristics appears in Table 1 in the Results section). Regarding our treatment groups, medical providers determined treatment course (transfusion or HU) in consultation with patients and parents/guardians as part of standard
clinical care. Patients in the transfusion group (n = 27) were transfused with leukocyte poor, HbS negative, packed RBCs (10–15 ml/kg per transfusion) at a rate that did not exceed 5 ml/kg/hr over approximately four hours to decrease the number of HbS RBCs. Blood was matched for ABO, Rh antigens, and C, E, D, and Kill antigens. Medically necessitated reasons for transfusion were overt stroke or SCI (67%), pain (15%), abnormal TCD (> 200 cm/sec) (11%), hepatic sequestration (4%), and acute chest syndrome (3%). Patients in the HU group (n = 34) were prescribed HU to increase fetal hemoglobin (HbF) production in RBCs, which reduces the severe medical complications of SCD. Length of time patients had received HU ranged from 6-101 months (M = 46.2, SD = 23.8). Medically necessitated reasons for HU were acute chest syndrome (29%), pain (32%), acute chest syndrome plus pain (27%), SCI (9%), and severe anemia (3%).

2.1.2 Parents/Guardians

Parents/guardians completed questionnaires for 51 patients (10 patients over 18 years of age attended sessions alone). Parents/guardians were primarily mothers (86%), followed by fathers (8%), grandparents (4%), and an aunt (2%) and ranged in age from 26-75 years (M = 40.4, SD = 9.04). Most parents/guardians self-identified as African-American/Black (92%), followed by Caucasian/White (6%), and mixed-race (2%). Parent/guardian yearly income was available for 75% families, with values ranging from $1,750 to $198,000 (M = 30,278, SD = 34,450). Parents/guardians provided mother’s education level for all patients; 28% completed some college with no degree, 20% graduated from high school, 16% received an associate’s degree, 16% neither completed high school nor received an equivalent diploma, 8% received a bachelor’s degree, 6% received a master’s degree, and 6% received a GED.
2.1.3 Demographically-Matched Normative Sample of Children

For comparison with data from our groups of children with SCD, we accessed the cognitive data of a normative sample who completed the NIH Toolbox (described in Materials section below). This freely available dataset resulted from a large national study (dataverse.harvard.edu). The NIH Toolbox sample includes 4,859 participants, ages 3-85 years and is representative of the U.S. population. Of the 4,859 participants, 537 completed cognitive testing at two timepoints (Weintraub et al., 2013). For the present study, we matched children in the NIH Toolbox sample with children with SCD in the present study on age, gender, race, and ethnicity. Socioeconomic status (SES) data was not available, so we also matched on mother’s education as a proxy for SES. We only included children with cognitive data at two timepoints. Using this method, we extracted the data of 41 African-American/Black Non-Hispanic participants aged 4-21 years ($M = 11.2, SD = 3.4$) who completed testing at two timepoints over a one-week interval. NIH Toolbox data collection did not screen for SCD or sickle cell trait, which suggests that 8% (3 children) may have SCD or sickle trait in the extracted sample. However, we believe this sample provided reasonable normative data from African-American/Black individuals in the U.S.

2.2 Procedures

This study was approved by the institutional review board at Washington University. Parents/guardians provided informed consent for all patients under 18 years of age. Patients between 10 and 18 years of age provided assent and patients over 18 provided consent.

Patients receiving HU and transfusion were tested twice over 4-6 weeks using the same study protocol. During each of the two study visits, patients completed executive and non-executive testing and behavioral questionnaires, whereas parents/guardians completed
demographic questionnaires. Children receiving transfusion were tested within three days following transfusion (near transfusion) and then again within three days before their next transfusion (far from transfusion) \((M_{days} = 31.38, \ SD = 5.95, \ range = 23 – 42 \ days)\). This design was chosen to mitigate the influence of practice effects (e.g., familiarity with testing materials and environment). When the same test is repeated within a brief period, improvements in performance may be attributed to practice effects rather than intervention. Because we predicted that executive abilities would be better near rather than far from transfusion, we tested in that order. With this design, any practice effects worked against our prediction that executive abilities would be better near than far from transfusion.

For the transfusion group, the first test session occurred less than 72 hours after a transfusion \((M = 29.4, \ SD = 22.5, \ range = 1 – 72 \ hours)\) and the second test session occurred less than 72 hours before the next transfusion 4-6 weeks later \((M = 30.8, \ SD = 6.2, \ range = 23 – 42 \ hours)\). The second testing session occurred 4 – 6 weeks after the first transfusion \((M_{days} = 30.73, \ SD = 6.02, \ range = 23 – 42 \ days)\). For 5 patients, we were unable to complete the second test session within the above timeframe (e.g., unable to test before the very next transfusion). The reasons for missing the second study session included transition to adult care, change of legal guardianship, hospitalization, and time constraints. In these cases, the second test session occurred less than 72 hours before the next transfusion based on patient availability. All patients maintained continuous blood transfusions in the interim between study sessions.

Trained examiners administered all testing according to instructions in testing manuals or accompanying the NIH Toolbox. No patient had received cognitive testing within 1 year of study participation. Because many of our patients had significant neurologic injury (see Table 1), examiners read items from behavioral questionnaires aloud and recorded responses for all
patients (regardless of neurologic status). Each test session lasted 1-1½ hours and was conducted in a quiet, private room. Patients received $50 for their participation after each test session, and families were provided with transportation (e.g., cabs) or mileage reimbursement.

2.3 Materials

2.3.1 NIH Toolbox Cognition Module

The NIH Toolbox (www.nihtoolbox.org) (Weintraub et al., 2013) is a standardized battery of measures comprising four modules: motor, sensation, emotion, and cognition. The cognition module comprising 7 tests was administered on a tablet computer to evaluate attention, memory, language, and executive abilities. Convergent validity for all NIH Toolbox cognition tests and similar cognitive measures (e.g., Pattern Comparison Processing Speed Test and Wechsler Processing Speed Composite) is high, with correlations ranging from r = .48 to .93. Discriminant validity (e.g., Pattern Comparison Processing Speed Test and Wechsler Letter-Number Sequencing) is low, with correlations ranging from r = .05 to .30 (Weintraub et al., 2013).

The cognition module includes automated scoring; however, the examiner presented task instructions, monitored compliance, and ensured valid results. All instructions were presented visually on the tablet screen using the iPad app and also presented orally by the examiner. Patients completed the cognition module in 35–40 minutes. Age-corrected standard scores were used in analyses and interpreted similarly to the IQ which has a mean of 100 and standard deviation of 15.

2.3.1.1 NIH Toolbox Executive Abilities Composite

To reduce the number of analyses conducted, scores from the three tests measuring executive abilities (Dimensional Change Card Sort Test, Flanker Inhibitory Control and
Attention Test, List Sorting Working Memory Test) in the NIH Toolbox cognition module were combined to create an executive composite. Scores from all three tests were significantly correlated ($p < .01$ in all instances, $r = .32$ to .63). Each test comprising the executive abilities composite is described below.

**Dimensional Change Card Sort (DCCS):** This test measured aspects of cognitive flexibility such as task switching or set shifting (Miyake, Friedman, Emerson, Witzki, & Howarter, 2000).

During administration, participants were presented with two target pictures that varied along two dimensions (e.g., yellow balls and blue trucks). They were asked to match targets to test pictures, first according to one dimension (e.g., color) and then, after several trials, according to the other dimension (e.g., shape). The relevant criterion word (“color” or “shape”) appeared on the tablet screen, and for children younger than 12 years the word was also delivered orally. Participants were also presented with switch trials during which the dimension to be matched changed. For example, after three trials matching on shape, participants were asked to match on color on the next trial and then return to shape on the next trial. Participants were asked to respond to targets as quickly as possible without making mistakes. There were 40 trials, and scoring was based on a combination of accuracy and reaction time.

**Flanker Inhibitory and Attention Control:** This test measured the ability to inhibit or suppress visual information irrelevant to task demands (Eriksen & Eriksen, 1974). During administration, participants focused on a central directional target (fish for children younger than 8 years, arrows for ages 8 years and older) while inhibiting attention to similar stimuli flanking the target. On congruent trials, flankers pointed in the same direction as the target. On incongruent trials, flankers pointed in the opposite direction as the target. Participants were asked to indicate the
direction of the target and respond as quickly as possible without making mistakes. There were 20 trials for ages 8 years and older; for children aged 3–7 years, scores of $\geq 90\%$ using preliminary fish stimuli were followed that an additional 20 trials using arrows. Scoring was based on a combination of accuracy and reaction time.

**Listing Sorting Working Memory Test:** This test measured working memory and required immediate recall and sequencing of presented stimuli. During administration, participants observed a series of food (e.g., strawberry, banana) and animal (e.g., dog, horse) pictures that were accompanied by an audio recording and written text representing each pictorially presented item. They were asked to repeat the items to the examiner in order of size, from smallest to largest. In the first condition, all presented items were from one category (either food or animal). In the second condition, presented items were from both categories and participants were asked to report foods first in order from smallest to largest followed by animals in order from smallest to largest. The number of items in series increased from 2 to a maximum of 8. The test was discontinued when 2 trials at the same length were failed. Responses were entered by the examiner on a wireless keyboard. Children under 7 years did not complete this test. Scoring was based on the total number of items correctly recalled across all trials.

**2.3.1.2 NIH Toolbox Non-Executive Abilities Composite**

To reduce the number of analyses conducted, scores from the four tests measuring non-executive abilities (Picture Sequence Memory Test, Picture Vocabulary Test, Oral Reading Recognition Test, and Pattern Comparison Processing Speed Test) in the NIH Toolbox cognition module were combined to create a non-executive composite by averaging age-corrected standard scores ($M = 100$, $SD = 15$). Tests of non-executive abilities were significantly correlated ($p < .05$
in all instances, \( r = .22 \) to \( .51 \) except for the correlation between the Picture Vocabulary Test and the Pattern Comparison Processing Speed Test \( (r = 0.1) \). Each test comprising the non-executive abilities composite is described below.

**Picture Sequence Episodic Memory Test:** This test measured episodic memory, which involves the acquisition, storage, and effortful recall of new information (Tulving, 2002). The test required that participants recall a sequence of pictures that were thematically related but had no inherent order. A sequence of pictures was presented over two learning trials, with sequence length varying from 6 – 18 pictures, dependent on age. For each trial, pictures appeared in the center of the tablet screen and then were moved one at a time into a fixed spatial position around the edges of the screen as an audio recording simultaneously described the content of each picture (e.g., “Kick the ball”) until the entire sequence was displayed on the screen. The pictures then returned to the center of the screen in a random order and participants were asked to place the pictures back in the sequence demonstrated by touching and dragging the pictures to the correct location. Participants were given credit for each correctly placed adjacent pair of pictures. The maximum score is one less than the sequence length (e.g., if there were 18 pictures in the sequence, the maximum score was 17 because that was the number of adjacent pairs of pictures possible).

**Picture Vocabulary Test:** This test measured receptive vocabulary. During administration, participants were presented with an audio recording of a word and four photographic images (1 correct target and 3 distractors). They were then asked to select the picture that most closely matched the meaning of the word presented. Participants were permitted as much time as necessary to respond. The item bank contained 625 targets, although only 25 were presented.
The test was administered in a computerized adaptive format, with the difficulty of successive items estimated on the basis of correct responses to previously administered items. Scoring was based on the number of correct responses.

**Oral Reading Test:** This test measured expressive vocabulary. During administration, participants were presented with single printed words and/or letters one at a time and were asked to read and pronounce each aloud as accurately as possible. This test was also administered in a computerized adaptive format, and responses were entered by the examiner on a wireless keyboard (0 incorrect, 1 correct). The item bank contained 250 items, although only 30 – 40 were presented, depending on performance. Children under 7 years did not complete this test. Scoring was based on the number of correct responses.

**Pattern Comparison Processing Speed Test:** This test measured speed of processing by asking participants to use their index fingers to identify whether two side-by-side pictures presented on the tablet screen were the same (press “Yes” button) or were not (press “No” button) the same. Participants were given 90 seconds to respond to as many pictures as possible. The number of correct responses completed was scored, up to a maximum of 130. Children under 7 years did not complete this test.

### 2.3.2 Behavioral Questionnaires

Behavioral questionnaires were only available for children with SCD and are described below. For all measures, ratings were represented by T scores (M = 50, SD = 10) in analyses.

**Behavior Rating Inventory of Executive Function Screener (BRIEF-2 screener; Self-Report)**

(Gioia & Isquith, 2015): The BRIEF-2 screener is a 12-item questionnaire that assesses
impairment in self-regulation in children. Patients (aged 8.0–18.1 years) reported how well items described them or how frequently an event had happened in the past six months. Items were rated on a scale of “Never,” “Sometimes,” and “Often.” Patient report had an α = .73 in this sample.

Conners 3rd Edition-Short Form (Conners 3; Self-Report) (Conners, Pitkanen, & Rzepa, 2011): The Conners 3 is a 43-item questionnaire that assesses symptoms related to Attention Deficit/Hyperactivity Disorder (ADHD) and its most common co-morbid problems in children. Patients (aged 8.0–18.1 years) reported how well items described them or how frequently an event had happened in the past month. Items were rated on a scale of 0 = “Not true at all” to 3 = “Very much true.” For the present study, the inattention and hyperactivity/impulsivity subscales were averaged to create an ADHD symptom composite. Patient report had an α = .86 in this sample.

Conners’ Adult ADHD Rating Scales–Short Version (CAARS-S; Self-Report) (Conners, Erhardt, & Sparrow, 1999): The CAARS-S is a 26-item questionnaire that assesses symptoms related to ADHD in adults. Patients (aged 19 years and older) reported how well an item described them or how frequently an event had happened in the past month. Items were rated on a scale of 0 = “Not at all” to 3 = “Very much, very frequently.” For the present study, the inattention/memory problems and hyperactivity/restlessness subscales were averaged to create an ADHD symptom composite. Because only 7 patients completed this questionnaire, α was not calculated.

Behavioral and Emotional Screening System (BESS; Self and Caregiver Report) (Reynolds & Kamphaus, 2015): The BESS is a 28-item questionnaire that assesses a wide array of behaviors
that represent both behavioral problems and strengths, including internalizing or externalizing problems, issues in school, and adaptive skills. Patients (aged 4.0–18.1 years) reported how they had behaved in the last several months. Items were rated on a scale of “Never” to “Almost always.” Patient report had an $\alpha = .67$ in this sample, which demonstrated low internal consistency.

The Pediatric Quality of Life Inventory Sickle Cell Disease Module (PedsQL; Self and Caregiver Report) (Varni, Seid, & Rode, 1999): The PedsQL is a 43-item questionnaire with 9 dimensions that assesses HRQOL in individuals with SCD. The present study used a modified version of the PedsQL that included 5 of the 9 dimensions (i.e., pain and hurt, pain management and control, worry I and II, and emotions). Patients were asked to think about the past day, rather than the past week, because we wished to determine HRQOL for patients in the day immediately after and before a transfusion. Patients (aged 5 – 21 years) and parents/guardians rated how much of a problem an issue had been on a scale of 0 = “Never” to 4 = “Almost Always.” A total raw score from the 5 dimensions was used in analyses. Patient report had an $\alpha = .88$ in this sample.

General Health Questionnaire: Parents/guardians or patients over 18 years completed a general questionnaire that provided demographic, health, educational, and occupational information about the patient and her/his family. Responses were primarily yes/no, with some free responses.

2.3.3 Blood biomarkers of SCD

We reviewed laboratory data that were collected as part of standard clinical care to assess blood biomarkers of SCD severity including hemoglobin concentration, HbA%, RBC count, and HbS%. For children receiving blood transfusion, blood draws to assess these biomarkers were obtained before ($M_{hours} = 38.28, SD = 24.73, \text{ range } = 4 – 72 \text{ hours}$) and after ($M_{hours} = 31.2, SD$
= 24.16, range = .75 – 68.75 hours) each transfusion. For children receiving HU, blood draws to assess these biomarkers were obtained at clinic visits closest to each study session. Additional variables from medical records (e.g., body mass index, neurologic status, number of hospitalizations) were also examined to evaluate possible differences between our transfusion and HU groups.

3. STATISTICAL ANALYSES

All analyses were conducted in the R environment (R Development Core Team, 2014). We conducted preliminary analyses using independent samples t-tests and Chi-squared tests to identify differences between children with SCD receiving transfusion and HU in terms of demographics (e.g., age, gender), medical outcomes (e.g., BMI, oxygen saturation), disease severity (e.g., neurologic status, number of hospitalizations), and education (e.g., grade retention, utilization of special education services).

We then conducted analyses to examine executive and non-executive abilities, blood biomarkers, and psychological outcomes using linear mixed-effects models in the lme4 package (Bates, Sarkar, Bates, & Matrix, 2007). In all models, participants were specified as a random factor to control for their associated intraclass correlation and were fitted using Restricted Maximum Likelihood t-tests. We used adjusted group means of interactions between timepoint (e.g., near and far from transfusion) and group (e.g., children receiving transfusion, children receiving HU, demographically-matched healthy children). An advantage of mixed-effects models is that all participants’ data were included in analyses, even when some data were missing. The phia package was used to compute p-values for interaction means (Rosario-Martinez, 2013), and post hoc tests used Holm adjustments to control for Type I error. Graphs displaying within-subject differences use Cousineau–Morey confidence intervals (CI). These CIs
center the data to remove between-subject differences and integrate a correction factor to de-bias the standard errors obtained from the normalized data (Baguley, 2012).

We conducted analyses of executive and non-executive abilities between children with SCD receiving transfusion, children with SCD receiving HU, and demographically-matched healthy children. Hematologic, psychological, and HRQOL analyses were only available for children with SCD receiving either transfusion or HU. Finally, we conducted Pearson correlations to assess the relationships between hematologic, psychological, and HRQOL outcomes and executive abilities in children with SCD receiving either transfusion or HU adjusted for multiple comparisons using false discovery rate (FDR).

4. RESULTS

4.1 Preliminary Analyses

To begin, we provide a detailed description of our SCD groups in Table 1. Values displayed are collapsed over both timepoints. Initial analyses demonstrated that our groups of children receiving transfusion and HU did not differ significantly on most assessed variables, including age, race, gender, genotype, oxygen saturation, grade retention, or utilization of special education services ($p > .05$ in all instances). As expected, however, children receiving transfusion experienced greater disease severity as indicated by a significantly higher incidence of stroke and SCI, $X^2 (1, 60) = 13.92, p < .001, d = 1.14$, and significantly more hospitalizations within the year before testing, $t(26.55) = -2.36, p = .03, d = .64$, than children receiving HU. In addition, children receiving transfusion had significantly higher body mass index (BMI), $t(48.011) = -2.18, p = .04, d = .55$, than children receiving HU.

Visual inspection of the data as well as skew and kurtosis analyses indicated that the distributions of executive and non-executive abilities scores were normal. For illustrative
purposes, distributions of individual test scores from the NIH Toolbox cognitive module are displayed in boxplots collapsed across both timepoints and separated by group in Figure 1. Below we describe our main findings using mixed linear effects models and tests of the factor interactions using adjusted means within the context of our aims/sub-aims and hypotheses.

4.2 Executive Abilities

Specific Aim 1. Determine whether executive abilities are poorer in children with SCD receiving blood transfusion or HU compared to a demographically-matched sample of healthy children.

As a starting point, we conducted analyses to examine change over time in executive abilities and differences among children with SCD receiving transfusion, children with SCD receiving HU, and demographically-matched healthy children. Our mixed model ANOVA including executive abilities revealed no significant main effect of timepoint, $F(1, 104) = 1.18, p = .28$, but a significant main effect of group, $F(2, 104) = 22.08, p < .0001$, indicating that demographically-matched healthy children had better executive abilities than children with SCD receiving transfusion and HU regardless of timepoint. Of greatest interest, there was also a significant interaction between timepoint and group, $F(2, 104) = 12.84, p < .0001, r = .23$.

Crucially, results supported our hypothesis, as executive abilities for children near transfusion, $\chi^2(1) = 6.07, p = .03$ (M = 91.40, SE = 2.03) and far from transfusion $\chi^2(1) = 42.82, p < .001$ (M = 82.04, SE = 2.06), and executive abilities for children receiving HU at their first test session $\chi^2(1) = 27.61, p < .001$ (M = 86.13, SE = 1.76) and second test session $\chi^2(1) = 19.26, p < .001$ (M = 88.98, SE = 1.76), were both significantly poorer than executive abilities of demographically-matched healthy children at their first (M = 97.54, SE = 1.60) and second (M =
98.51, SE = 1.60) test sessions. Additional analyses also showed that executive abilities for demographically-matched healthy children were similar at the first and second test sessions, \( \chi^2(1) = 0.39, p = .53 \).

**In our first sub-aim of Specific Aim 1, we examined whether executive abilities in children with SCD improve following blood transfusion.** We found support for our hypothesis that executive abilities in children with SCD receiving transfusion would improve near transfusion compared to far from transfusion. We found that executive abilities for children with SCD near transfusion (M = 91.40, SE = 2.03) were significantly better than executive abilities far from transfusion (M = 82.04, SE = 2.06), \( \chi^2(1) = 23.69, p < .001 \), indicating that transfusion was associated with improved executive abilities.

**In our second sub-aim of Specific Aim 1, we hypothesized that executive abilities would better for children near transfusion than in children receiving HU.** To test this hypothesis, we first compared executive abilities assessed in children near transfusion to those of children receiving HU at their first test session. We found that executive abilities for children near transfusion (M = 91.40, SE = 2.03) were significantly better than executive abilities for children receiving HU at their first test session (M = 86.13, SE = 1.76), \( \chi^2(1) = 3.88, p = .04 \), indicating that children near transfusion, despite having greater disease severity, had better executive abilities than children receiving HU. We also compared executive abilities assessed in children far from transfusion to those of children receiving HU at their second test session. We found that executive abilities for children far from transfusion (M = 82.04, SE = 2.06) were significantly poorer than executive abilities for children receiving HU at their second test session (M = 88.98, SE = 1.76), \( \chi^2(1) = 6.66, p = .03 \).
Additional analyses revealed that, just like demographically-match controls, executive abilities for children receiving HU were similar at both timepoints $\chi^2(1) = 2.83, p = .19$. This result indicates that children receiving HU had stable executive abilities over the 4 – 6-week interval, which is in contrast to children receiving transfusion who had a large improvement in executive abilities near compared with far from transfusion. More specifically, children receiving HU had an increase of just under 3 points in executive abilities, whereas children receiving transfusion had a decrease of just under 10 points in executive abilities. These results indicate that, although children receiving transfusion had greater disease severity (e.g., higher risk of stroke) than children receiving HU, differences in executive abilities depended on whether children were near or far from transfusion, which further highlights our previous finding that transfusion improves executive abilities (see Figure 2).

4.3 Non-Executive Abilities

Although executive abilities were the focus of our study, determining change in non-executive abilities between children receiving transfusion and children receiving HU provides an important counterpoint to our primary hypotheses. A mixed effect ANOVA including non-executive abilities revealed a significant main effect of timepoint, $F(1, 104) = 29.14, p < .0001$, demonstrating that children with SCD and demographically matched children had better non-executive abilities at the second, compared to, first testing session. There was also a significant main effect of group, $F(2, 104) = 3.98, p = .02$, demographically-matched healthy children had better non-executive abilities than children with SCD receiving transfusion, but not children receiving HU. There was not, however, a significant interaction between timepoint and group, $F(2, 104) = .57, p = .57$. 
Regarding our significant main effect of timepoint, we found that non-executive abilities were significantly better for demographically-matched healthy children at the second test session (M = 99.77, SE = 1.61) than at the first test session (M = 93.32, SE = 1.61), $\chi^2(1) = 18.00, p < .001$, for children far from transfusion (M = 93.20, SE = 2.07) than near transfusion (M = 89.03, SE = 2.05), $\chi^2(1) = 4.79, p = .03$, and for children receiving HU at the second test session (M = 94.91, SE = 1.77) than at the first test session (M = 90.37, SE = 1.77), $\chi^2(1) = 7.37, p = .01$. These results suggest the presence of a practice effect for demographically-matched healthy children and children with SCD receiving transfusion and HU. Specifically, demographically-matched healthy children had an increase of just over 6 points in non-executive abilities compared with the 4–4.5 point increase for children with SCD receiving transfusion and HU, respectively. It is important to note, however, that the interval between the first and second test session for demographically-matched healthy children was only one week, whereas, the interval for children with SCD was 4–6 weeks.

Regarding our significant main effect of group, as noted above demographically-matched healthy children had better non-executive abilities than children with SCD; however, there was not a significant group by timepoint interaction. Specifically, we found that non-executive abilities were similar for demographically-matched healthy children at their first session and children near transfusion, $\chi^2(1) = 2.92, p = .35$ and to children receiving HU at their first test session $\chi^2(1) = 1.84, p = .53$. Additionally, children near transfusion and children receiving HU at their first test session also had similar non-executive abilities, $\chi^2(1) = 0.25, p = 1$. Demographically-matched healthy children at their second test session also had similar non-executive abilities to children receiving HU at their second test session $\chi^2(1) = 5.01, p = .12$ (M = 94.91, SE = 1.77), and children far from transfusion had similar non-executive abilities to
children receiving HU at their second test session $\chi^2(1) = 0.40, p = 1$. In contrast, the difference in non-executive for demographically-matched healthy children and children far from transfusion tended towards significance $\chi^2(1) = 6.76, p = .06$, with demographically-matched healthy children having better non-executive abilities (see Figure 3).

These results indicate that, in contrast to our findings regarding executive abilities, non-executive abilities were generally similar for demographically-matched healthy children and children with SCD receiving transfusion and children receiving HU supporting the notion that, 1) executive, but not non-executive abilities, are particularly vulnerable in children with SCD and 2) children being near or far from transfusion does not appear to influence non-executive abilities. In fact, for children near transfusion, executive abilities and non-executive abilities were comparable, with a difference of just over 2 points. In contrast, for children far from transfusion, executive abilities were significantly poorer than non-executive abilities, $p < .0001$, with a difference of just over 11 points (two-thirds of a SD).

4.4 Executive Abilities Relationship to Behavioral Functioning in Children with SCD

Before assessing relationships between executive abilities and behavioral functioning, we first conducted separate linear mixed models to determine change over time in patient report of attention problems, executive functioning problems, behavioral and emotional problems, and HRQOL, as well as differences between children with SCD receiving transfusion and children with SCD receiving HU.

Turning first to patient-reported attention (Conners-3 ADHD Composite), a linear mixed model revealed no significant main effect of timepoint, $F(1, 49) = .12, p = .72$, group, $F(1, 55) = 1.15, p = .29$, or significant interaction between timepoint and group, $F(1, 49) = .31, p = .58, r = .02$. Turning next patient-reported executive functioning (BRIEF-2), a linear mixed model also
revealed no significant main effect of timepoint, $F(1, 44) = 1.45, p = .24$, group, $F(1, 46) = .24, p = .62$, or significant interaction between timepoint and group, $F(1, 44) = .25, p = .62, r = .01$.

Regarding patient-reported behavioral and emotional problems (BESS), a linear mixed model revealed no significant main effect of timepoint, $F(1, 43) = .17, p = .68$. There was, however, a significant main effect of group, $F(1, 45) = 5.02, p = .03$, but no significant interaction between timepoint and group, $F(1, 43) = .02, p = .88, r = .08$. These results indicate that, across both timepoints and regardless of whether children were near or far from transfusion, children receiving transfusion reported more behavioral and emotional problems than children receiving HU.

Finally, regarding patient-reported HRQOL (PedsQL), a linear mixed model revealed a significant main effect of timepoint $F(1, 58) = 4.51, p = .04$, a trend toward a significant effect of group $F(1, 59) = 3.26, p = .08$, and a trend toward a significant interaction between timepoint and group, $F(1, 58) = 3.51, p = .07, r = .06$. Analyses determined that children receiving transfusion reported significantly poorer HRQOL (including increased pain and worry) near transfusion ($M = 30.59, SE = 3.36$) than far from transfusion ($M = 23.92, SE = 3.38$), $p = .01$ (see Figure 4). In addition, children receiving transfusion reported significantly poorer HRQOL near transfusion than children receiving HU at their first test session ($M = 19.32, SE = 2.99$), $p = .04$.

Now turning to relationships between executive abilities and behavioral functioning for children receiving transfusion, Pearson correlations revealed that patient-reported attention, executive functioning, and behavioral and emotional problems were not significantly related to executive or non-executive abilities for children near transfusion, $p > .05$. Poorer patient-reported HRQOL, however, was significantly related to poorer executive abilities ($r = -.44, p = .02$) and
non-executive abilities \((r = -0.47, p = .01)\) for children near transfusion. For children far from transfusion, patient-reported attention, executive functioning, and behavioral and emotional problems were not significantly related to executive or non-executive abilities for children far from transfusion, \(p > .05\). Poorer patient-reported HRQOL, however, was significantly related to poorer non-executive abilities \((r = -0.42, p = .03)\), but not executive abilities for children far from transfusion (see Table 2).

Turning next to children receiving HU; patient-reported attention, executive functioning, and emotional and behavioral problems were not significantly related to executive and non-executive abilities at their first test session, \(p > .05\). Poorer patient-reported HRQOL, however, was significantly related to both poorer executive abilities \((r = -0.38, p = .03)\) and non-executive abilities \((r = -0.54, p < .001)\) at the first test session for children receiving HU. For children receiving HU at their second test session, patient-reported attention and HRQOL were not significantly related to executive and non-executive abilities at their first test session, \(p > .05\). Poorer patient-reported behavioral and emotional problems \((r = -0.45, p = .02)\) and executive functioning \((r = -0.42, p = .03)\) were both significantly related to poorer executive abilities, but not non-executive abilities, for children receiving HU at the second test session (see Table 3).

These results indicate that for children receiving transfusion and HU across the measures of behavioral functioning assessed, poorer HRQOL (more pain and worry) emerged as the variable most often related to poorer executive and non-executive abilities.

### 4.5 Executive Abilities Relationship to Blood Biomarkers in Children with SCD Receiving Blood Transfusion

Before assessing relationships between executive abilities and behavioral functioning, we first conducted separate linear mixed models to determine change over time in blood biomarkers
and differences among children receiving transfusion and children receiving HU. Hemoglobin concentration and RBC were the only biomarkers available for children receiving HU. Thus, only biomarkers collected for children before transfusion were analyzed, as they best matched those collected from children receiving HU collected before the testing session. A mixed effects ANOVA including hemoglobin concentration revealed no significant main effect of timepoint, $F(1, 54) = .006, p = .94$, group, $F(1, 59) = 1.70, p = .20$, or significant interaction between timepoint and group, $F(1, 54) = .06, p = .81, r = .03$.

Children receiving transfusion had similar hemoglobin concentration collected immediately before their near transfusion test session ($M = 9.26, SE = .25$) and hemoglobin concentration collected immediately before their far from transfusion test session ($M = 9.27, SE = .25$), $\chi^2(1) = .01, p = 1$. Children receiving HU also had similar hemoglobin concentration collected immediately before their first test session ($M = 8.87, SE = .22$) and hemoglobin concentration collected immediately before their second test session ($M = 8.84, SE = .22$), $\chi^2(1) = .05, p = 1$. Finally, children receiving transfusion had similar hemoglobin concentration than children receiving HU at the first $\chi^2(1) = 1.37, p = .38$ and second test session $\chi^2(1) = 1.72, p = .38$.

A mixed effects ANOVA including RBC revealed no significant main effect of timepoint, $F(1, 51) = .03, p = .85$, but there was a significant main effect of group, $F(1, 59) = 15.63, p < .0001$, but there was not a significant interaction between timepoint and group, $F(1, 51) = .08, p = .78, r = .20$. Children receiving transfusion had similar RBC collected immediately before their near transfusion test session ($M = 3.17, SE = .09$) and RBC collected immediately before their far from transfusion test session ($M = 3.18, SE = .09$), $\chi^2(1) = .09, p = 1$. Children receiving HU also had similar RBC collected immediately before their first test session ($M =
2.71, SE = .08) and RBC collected immediately before their second test session (M = 2.71, SE = .08), \( \chi^2(1) = .01, p = 1 \). Children receiving transfusion, however, had significantly higher RBC than children receiving HU at the first \( \chi^2(1) = 14.26, p < .0001 \) and second test session \( \chi^2(1) = 15.03, p < .0001 \). These results indicate that “baseline” levels of hemoglobin concentration are similar for children receiving transfusion (e.g., before the addition of healthy hemoglobin), but in contrast, RBC levels are higher for children before transfusion.

Before assessing relationships between executive abilities and blood biomarkers for children receiving transfusion, we first conducted analyses to determine change in hemoglobin concentration, HbA\%, RBC count, and HbS\% collected immediately before and immediately after the near transfusion test session and collected immediately before and immediately after the far from transfusion test session. We collapsed blood biomarker data across timepoints. Paired samples t-tests revealed that hemoglobin concentration, \( t(25) = -5.91, p < .0001, d = 1.16 \), HbA\%, \( t(24) = -8.31, p < .0001, d = 1.66 \), and RBC count, \( t(23) = -8.15, p < .0001, d = 1.66 \), all increased after transfusion, whereas HbS\%, \( t(25) = -6.12, p < .0001, d = 1.20 \), decreased. These findings demonstrated that transfusion immediately improved blood biomarkers of SCD severity (see Figure 5).

Turning to relationships between blood biomarkers and executive and non-executive abilities for children near transfusion, Pearson correlations revealed that hemoglobin concentration, HbA\%, RBC, HbS\% collected before their near transfusion test session were not significantly related to executive and non-executive abilities assessed immediately after their near transfusion test session, \( ps > .05 \) (see Table 4).

Pearson correlations revealed that hemoglobin concentration, HbA\%, and HbS\% collected after their near transfusion test session were not significantly related to executive and
non-executive abilities for children assessed after their near transfusion test session, ps > .05. Higher RBC collected after their near transfusion test session, however, was significantly related to better non-executive abilities ($r = -.41, p = .02$), but not executive abilities, for children measured after their near transfusion (see Table 5).

Finally, Pearson correlations revealed that hemoglobin concentration and HbS% collected before their far from transfusion test session were not significantly related to executive and non-executive abilities for children assessed before their far from transfusion test session, ps > .05. Higher HBA% collected before their far from transfusion test session, however, was significantly related to better non-executive abilities ($r = -.51, p < .001$), but not executive abilities, measured immediately before their far from transfusion. Additionally, Higher RBC collected immediately before their far from transfusion test session was significantly related to better executive abilities ($r = -.54, p < 001$ ) and non-executive abilities ($r = -.51, p = .01$) measured before their far from transfusion (see Table 6).

Because we found that children receiving transfusion had improved executive abilities near transfusion, we examined whether blood biomarkers collected after near transfusion test session (e.g., after the addition of healthy hemoglobin) were related to a smaller difference in executive abilities (i.e., less improvement in executive abilities) for children near and far from transfusion. Pearson correlations revealed that HBA% and HBS% were not related to change in executive abilities in children receiving transfusion, ps > .05. In contrast, hemoglobin concentration ($r = .59, p < .001$) and RBC count ($r = .49, p = .01$) collected after near transfusion test session were significantly related to change in executive abilities in children receiving transfusion. Specifically, higher hemoglobin concentration and RBC count after near
transfusion test session were associated with a smaller difference (i.e., sustained improvement) in executive abilities over the 4 – 6 week interval (see Figure 6).

Finally, we also assessed whether change in blood biomarkers collected after near transfusion test session and before far from transfusion test session were significantly related to change in executive abilities in children near and far from transfusion. Pearson correlations revealed that change in HBA%, RBC, and HBS% were not related to change in executive abilities in children receiving transfusion, ps > .05. In contrast, change in hemoglobin concentration (r = .43, p = .03) was significantly related to change in executive abilities in children receiving transfusion. Specifically, a smaller change in hemoglobin concentration over 4 – 6 week interval was associated with a smaller difference (i.e., sustained improvement) in executive abilities over the 4 – 6 week interval (see Figure 7).

5. DISCUSSION

Cognitive deficits in children with SCD are well-documented (Berkelhammer et al., 2007) and have been shown in children with stroke, SCI, and normal-appearing MRI (Hood et al., 2017 under review). Much less is known about how we can improve cognition in children with SCD and whether current biological interventions (e.g., transfusion) are the avenue through which improvements can be identified. The present study aimed to help answer this question by determining whether cognition could be improved in children receiving transfusion. Therefore, we compared cognition in children receiving transfusion to children with SCD receiving HU and demographically-matched healthy children.

Our study provides evidence that executive and non-executive abilities are differentially affected in children with SCD such that executive abilities are poorer, but importantly, they can
also show the largest improvement after biological intervention. Beginning at the broadest level, we found that in comparison to demographically matched healthy children, children with SCD receiving transfusion and HU had significantly worse executive abilities, but had similar non-executive abilities, for both the first and second testing sessions. Additionally, children receiving transfusion had improved executive abilities near transfusion compared to children receiving HU and had worse executive abilities far from transfusion than children receiving HU, despite having worse disease severity (e.g., cerebral infarcts, more hospitalizations).

Overall, our findings indicate a sharp contrast between executive abilities and non-executive abilities for children with SCD. Although not the focus of the present study, our findings regarding non-executive abilities suggest that assessing IQ or some other composite comprised of executive and non-executive abilities likely will not provide the most accurate picture of cognitive deficits in children with SCD. In comparison to demographically-matched healthy children, children with SCD struggle considerably more on tasks of attention, working memory, and cognitive flexibility, than they do on tasks of vocabulary knowledge and episodic memory. Thus, unless we change our methodology and use measures that capture specific cognitive domains, we will continue to have contradictory results when these tasks are “clumped” together and not analyzed separately.

Results from the present study converge on three important findings: (1) executive abilities improved near compared with far from blood transfusion, (2) children with SCD had poorer HRQOL near transfusion, which was in turn related to poorer executive abilities near transfusion, and (3) children with the smallest improvement in executive abilities near compared with far from transfusion had better biomarkers of SCD disease severity (i.e., higher hemoglobin concentration and RBC count. We now discuss the possible mechanisms and implications of
these three principal findings.

Turning first to our finding that executive abilities improved soon after transfusion, we also showed that blood transfusion improved blood biomarkers of SCD severity. Previous research has shown that improvements in blood biomarkers after transfusion increases oxygen carrying capacity and delivery (Rees et al., 2010). The biological mechanisms by which blood biomarkers improve oxygen delivery are complex, but because the brain is the most metabolically active organ in the body, we can reasonably extrapolate that increased oxygen delivery following transfusion increases oxygen availability to the brain.

Improvements in executive abilities through improved oxygen delivery following transfusion have not previously been demonstrated in children with SCD. Increased oxygen delivery through the transient administration of highly concentrated oxygen has been shown to improve cognition in healthy adults (Moss & Scholey, 1996), and complex cognitive processing may require increased oxygen availability (Toichi et al., 2004). As such, we suggest that increased oxygen delivery after blood transfusion increased oxygen availability to the brain and therefore improved executive abilities in children soon after transfusion.

It is also important to note that we found improvements in executive, but not non-executive abilities, soon after transfusion. One plausible explanation for this finding is that non-executive abilities are “crystalized” and therefore less susceptible to short-term changes in oxygen delivery to the brain. This explanation is consistent with the notion that crystalized knowledge is more dependent on experience and less affected by changes in biological processes, particularly during childhood (Rindermann & Baumeister, 2015). Another explanation is that non-executive abilities for children receiving transfusion were already close to ceiling before transfusion, with little room for improvement even after improved oxygen delivery. This
notion is supported by the finding that, for children far from transfusion and demographically-matched controls, there was just over a 6-point difference in non-executive abilities, whereas there was more than a 16.5-point (> 1 SD) difference in executive abilities.

Of greatest significance, our findings demonstrated that, although executive abilities for children with SCD are vulnerable, they are also malleable. Executive abilities for children with SCD improved by just over 10 points (> 2/3 SD) near transfusion. This is a considerable improvement and indicates that executive abilities could easily be the target of future interventions, especially given the importance of executive abilities in school readiness and academic performance. The malleability of executive abilities also has implications for medical care, neuropsychological function, and academic success.

From a medical perspective, our results suggest that healthcare providers may wish to time explanations of medical procedures (e.g., stem cell transplantation), changes in medication regimens (e.g., beginning HU), and/or changes in medical providers (e.g., transitioning to adult care) to occur soon after transfusion. The decision making required to consider related options requires executive abilities (e.g., attention, working memory, and cognitive flexibility), which improved soon after transfusion in the present study. In addition, children with SCD receive multicomponent interventions that require complex adherence regimens, and our findings suggest that children will best be able to understand these complexities soon after transfusion.

From a neuropsychological perspective, our results suggest that performance on some tests for children with SCD receiving transfusion will differ depending on how long ago their last transfusion occurred. Neuropsychological evaluations require good cooperation and effort so that the test findings are a reliable estimate of current functioning in the areas assessed. Even if children with SCD meet these expectations, neuropsychologists may not be accurately capturing
the optimal performance of children when they are far from transfusion. Our findings suggest that neuropsychological reports for children with SCD should indicate not only current treatment type (e.g., transfusion), but additionally document whether children are near or far from transfusion to accurately interpret findings.

From an academic perspective, teachers and family members may wish to time important tests (e.g., final examinations, standardized achievement tests, college entrance examinations) to occur soon after blood transfusion to maximize children’s performance. Children with SCD already likely have difficulty at school-based tasks that require executive abilities. Being far from transfusion may compound these preexisting difficulties. Similar to neuropsychological evaluations, academic tests may only adequately capture “optimal” performance when children are near rather than far from transfusion.

Finally, we would be remiss if we did not discuss whether cognitive interventions could be helpful in improving executive abilities in children with SCD. A small number of studies have assessed cognitive interventions in children with SCD. Yerys et al. (2003) and King et al. (2007) demonstrated that, in small samples of children with SCD and stroke, a school-based memory rehabilitation program improved performance on the trained memory tests (e.g., digit span and word-list learning). Additionally, King et al. (2007) found a small but significant improvement on math and spelling tests. More recently, Hardy et al. (2016) found that children with SCD with unclear neurologic status who completed a home-based computerized memory training intervention (Cogmed) had improved performance on trained tests, including better verbal and visuospatial working memory.

There is extensive evidence beyond the SCD population that supports these findings and shows that cognitive interventions improve performance on the trained tasks. There is less
evidence, however, that cognitive interventions improve performance on closely related tasks, and there is even less evidence that training enhances performance on distantly related tasks or everyday cognitive activities (Simons et al., 2016).

With regard to our next important finding, HRQOL (including pain and worry) was poorer soon after than far from transfusion. This finding is opposite to that which was predicted, and it is unclear why children reported poorer HRQOL soon after transfusion. One possibility is that, although transfusion is used to reduce the pain associated with vaso-occlusive crises (Miller et al., 2001), the process of receiving transfusion is itself painful and worrisome. Because HRQOL was assessed soon after transfusion, the pain and worry associated with transfusion may have been especially salient. In contrast, 4-6 weeks had passed when HRQOL was assessed for the far from transfusion timepoint, perhaps making the associated pain and worry less salient.

In addition to our finding that children experienced poorer HRQOL soon after transfusion, poorer HRQOL was also associated with poorer executive abilities soon after transfusion. Prior research has demonstrated that pain may limit the ability to engage in demanding cognitive processing (Eccleston & Crombez, 1999) such as executive abilities. In addition, it is possible that children receiving transfusion felt little control over their pain and worry, which could have been influenced by a negative anticipatory evaluation of the pain experience (Arnsten, 2009). This finding does, however, provide an interesting target for intervention.

Overall, our findings that children with SCD report poorer HRQOL near transfusion and that poorer HRQOL is related to poorer executive abilities has important medical and psychological implications. Medical providers and family members may wish to monitor HRQOL around the time of transfusion, as children with poorer HRQOL may have less ability to
engage in demanding cognitive processing. Psychologically, our findings suggest that improving HRQOL through evidence-based coping treatments and strategies (e.g., Acceptance and Commitment Therapy and diaphragmatic breathing) may improve executive abilities for children with SCD.

We finally turn to our findings that children with the sustained improvement, e.g., smaller difference in executive abilities near compared with far from transfusion had better biomarkers of SCD disease severity after transfusion (i.e., higher hemoglobin concentration and RBC count). Additionally, sustained improvement in executive abilities was also associated with sustained improvement in hemoglobin concentration, such that children whose hemoglobin concentration levels dropped less over the 4 – 6 week interval also maintained improved executive abilities provided by the oxygen rich blood transfusion. This finding points to possible mechanisms by which executive abilities are improved in children with SCD. In previous research, hemoglobin concentration was not associated with cognition in children with SCD (Knight et al., 1995; Krejza et al., 2012; Oluwole et al., 2016; Smith et al., 2013; Swift et al., 1989; Yarboi et al., 2015), but this may be because most previous research in children with SCD focused on IQ. In the only study to examine hemoglobin concentration in relation to executive abilities, there was a significant correlation (Ruffieux et al., 2013), which is in line with our findings.

Taken together, our findings point to the value of blood transfusion not only for improving medical outcomes in children with SCD but also for improving executive abilities. Our study also highlights the importance of timing and methodology when assessing cognition in children receiving transfusion. Cognitive testing far from transfusion and combining scores from executive and non-executive tasks (e.g., assessing IQ) may not capture optimal performance. In addition, our findings indicate that brief assessment batteries such as the NIH toolbox will be of
utility in clinical trials to assess interventions that may affect executive abilities in children with SCD. Finally, brief assessment batteries will be of value in terms of determining which children with SCD should be referred for further neuropsychological evaluation to determine eligibility for special education services and academic accommodations.

5.1 Limitations and Future Research

There were limitations to the present study that should be noted. For example, although our sample included a relatively large number of children with SCD compared with previous studies, sample size may have limited statistical power to detect between-group effects. That said, we believe it is unlikely that our overall pattern of findings would change with a larger sample. Another limitation was that assignment to treatment group was not random. Healthcare providers determined the best treatment for patients prior to study enrollment as a component of clinical care. This limitation is common in medical research due to ethical and medical concerns around withholding efficacious treatment.

Also of note, in the present study we collected data at only two timepoints. In future research, it will be important to collect additional timepoints to determine whether short-term improvements in executive abilities occur with consistency near transfusion. It will also be crucial to examine the long-term effects of blood transfusion on executive abilities, because prior research regarding the long-term effects of blood transfusion on cognition has focused on IQ. Finally, a significant next step in this line of research will be to replicate the current study with the addition of neuroimaging to identify how improved oxygen delivery changes brain function soon after blood transfusion.
5.2 Conclusion

There is a critical need to identify interventions that improve clinical and functional outcomes for children with SCD. Findings from the present study indicated that blood transfusion is one such intervention, at least over the short-term. Importantly, executive but not non-executive abilities improved soon after transfusion, pointing to specificity in the effects of blood transfusion on cognition. Future research is needed to determine whether the observed short-term improvements in executive abilities extend over the longer term and to identify the brain mechanisms underlying such improvements.
### Table 1. Description of SCD Study Groups

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<td>Transfusion (n = 27)</td>
<td>HU (n = 34)</td>
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<td>1.7 (2.8)</td>
<td>4.3 (8.7)</td>
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<td></td>
<td>Range</td>
<td>0 – 39</td>
<td>0 – 10</td>
<td>0 – 39</td>
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<td><strong>Grade retention</strong></td>
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<td>6</td>
<td>7</td>
<td>13</td>
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<td></td>
<td>No</td>
<td>21</td>
<td>27</td>
<td>48</td>
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<tr>
<td><strong>Special education</strong></td>
<td>IEP</td>
<td>13</td>
<td>17</td>
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<td>504 plan</td>
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<td>No formalized program</td>
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<td>6</td>
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<tr>
<td></td>
<td>After school program</td>
<td>12</td>
<td>12</td>
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Notes: HbSS = sickle cell anemia; HbS-beta thal + = Hemoglobin beta plus thalassemia; HbS-beta thal zero =
Hemoglobin beta zero thalassemia; HbD = Hemoglobin beta D-Los Angeles; SD = Standard deviation; BMI = body mass index; MRI = Magnetic resonance imaging; SCI = Silent Infarct; MRA = Magnetic resonance angiography; TCD = Transcranial Doppler Imaging; IEP = individualized education plan. * = significant difference between Transfusion and HU groups, $p < .05$. 
Table 2. Correlations between behavioral functioning and executive and non-executive abilities for children receiving transfusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>1.</th>
<th>2.</th>
<th>3.</th>
<th>4.</th>
<th>5.</th>
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<tbody>
<tr>
<td><strong>Children near transfusion</strong></td>
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<td>1. Patient-report Attention</td>
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<tr>
<td>2. Patient-report HRQOL</td>
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<td></td>
</tr>
<tr>
<td>3. Patient-report Executive Functioning</td>
<td>.71**</td>
<td>.48*</td>
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</tr>
<tr>
<td>4. Patient-report BESS</td>
<td>.73**</td>
<td>.49*</td>
<td>.68**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Executive Abilities</td>
<td>.18</td>
<td>-.44*</td>
<td>.02</td>
<td>-.09</td>
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</tr>
<tr>
<td>6. Non-executive abilities</td>
<td>-.21</td>
<td>-.47*</td>
<td>-.38</td>
<td>-.46</td>
<td>.74**</td>
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<tr>
<td><strong>Children far from transfusion</strong></td>
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</tr>
<tr>
<td>1. Patient-report Attention</td>
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<td></td>
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</tr>
<tr>
<td>2. Patient-report HRQOL</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Patient-report Executive Functioning</td>
<td>.54*</td>
<td>.46*</td>
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<tr>
<td>4. Patient-report BESS</td>
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<td>.20</td>
<td>.47*</td>
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<tr>
<td>5. Executive Abilities</td>
<td>.23</td>
<td>-.15</td>
<td>-.21</td>
<td>.08</td>
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</tr>
<tr>
<td>6. Non-executive abilities</td>
<td>-.14</td>
<td>-.42*</td>
<td>-.45</td>
<td>-.28</td>
<td>.66**</td>
</tr>
</tbody>
</table>

Note. HRQOL = Health-related quality of life; BESS = Behavior and Emotional Problems; * indicates $p < .05$; ** indicates $p < .01$. 
### Table 3. Correlations between behavioral functioning and executive and non-executive abilities for children receiving HU

**First test session**

<table>
<thead>
<tr>
<th>Variable</th>
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<tbody>
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</tr>
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<td>3. Patient-report Executive Functioning</td>
<td>.67**</td>
<td>.29</td>
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<tr>
<td>4. Patient-report BESS</td>
<td>.44*</td>
<td>.34</td>
<td>.42*</td>
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<td></td>
</tr>
<tr>
<td>5. Executive Abilities</td>
<td>.12</td>
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<td>-.03</td>
<td>.03</td>
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</tr>
<tr>
<td>6. Non-executive abilities</td>
<td>-.20</td>
<td>-.54**</td>
<td>-.36</td>
<td>-.34</td>
<td>.58**</td>
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**Second test session**

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<td>1. Patient-report Attention</td>
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<td></td>
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<td>2. Patient-report HRQOL</td>
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<td>3. Patient-report Executive Functioning</td>
<td>.72*</td>
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<td>-.01</td>
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<td>-.45*</td>
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</tr>
<tr>
<td>6. Non-executive abilities</td>
<td>-.21</td>
<td>-.29</td>
<td>-.29</td>
<td>-.30</td>
<td>.65**</td>
</tr>
</tbody>
</table>

**Note.** HRQOL = Health-related quality of life; BESS = Behavior and Emotional Problems; * indicates $p < .05$; ** indicates $p < .01$. 
Table 4. Correlations between blood biomarkers collected before transfusion and executive and non-executive abilities assessed for children near transfusion

<table>
<thead>
<tr>
<th>Variable</th>
<th>1.</th>
<th>2.</th>
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<th>4.</th>
<th>5.</th>
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<tr>
<td>1. Hemoglobin concentration</td>
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<td></td>
</tr>
<tr>
<td>2. HbA%</td>
<td>-.07</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>3. RBC</td>
<td>.92**</td>
<td>.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. HbS%</td>
<td>.09</td>
<td>-.99**</td>
<td>-.10</td>
<td></td>
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<tr>
<td>5. Executive abilities</td>
<td>-.08</td>
<td>.11</td>
<td>.08</td>
<td>-.16</td>
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<tr>
<td>6. Non-executive abilities</td>
<td>.05</td>
<td>.11</td>
<td>.19</td>
<td>-.15</td>
<td>.74**</td>
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</tbody>
</table>

Note HbA% = adult hemoglobin percentage; RBC = red blood cell count; HbS% = abnormal hemoglobin percentage; * indicates $p < .05$; ** indicates $p < .01$. 
Table 5. Correlations between blood biomarkers collected after transfusion and executive and non-executive abilities assessed for children near transfusion

<table>
<thead>
<tr>
<th>Variable</th>
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<th>2.</th>
<th>3.</th>
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<th>5.</th>
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<td>1. Hemoglobin concentration</td>
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<td></td>
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</tr>
<tr>
<td>2. HbA%</td>
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<tr>
<td>3. RBC</td>
<td>.88**</td>
<td>.38</td>
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<td>4. HbS%</td>
<td>-.29</td>
<td>-.99**</td>
<td>-.42*</td>
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<td>5. Executive abilities</td>
<td>.10</td>
<td>.24</td>
<td>.28</td>
<td>-.29</td>
<td></td>
</tr>
<tr>
<td>6. Non-executive abilities</td>
<td>.27</td>
<td>.15</td>
<td>.41*</td>
<td>-.17</td>
<td>.74*</td>
</tr>
</tbody>
</table>

Note: HbA% = adult hemoglobin percentage; RBC = red blood cell count; HbS% = abnormal hemoglobin percentage; * indicates $p < .05$; ** indicates $p < .01$. 
Table 6. Correlations between blood biomarkers collected *before* transfusion and executive and non-executive abilities assessed for children *far from* transfusion

<table>
<thead>
<tr>
<th>Variable</th>
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<th>2.</th>
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<th>4.</th>
<th>5.</th>
</tr>
</thead>
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<td>1. Hemoglobin concentration</td>
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<td></td>
</tr>
<tr>
<td>2. HbA%</td>
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<td></td>
<td></td>
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<tr>
<td>3. RBC</td>
<td>.87**</td>
<td>.14</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4. HbS%</td>
<td>.03</td>
<td>-.99**</td>
<td>-.17</td>
<td></td>
<td></td>
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<tr>
<td>5. Executive abilities</td>
<td>.27</td>
<td>.25</td>
<td>.54**</td>
<td>-.32</td>
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</tr>
<tr>
<td>6. Non-executive abilities</td>
<td>.38</td>
<td>.51**</td>
<td>.51*</td>
<td>-.04</td>
<td>.66**</td>
</tr>
</tbody>
</table>

*Note* HbA% = adult hemoglobin percentage; RBC = red blood cell count; HbS% = abnormal hemoglobin percentage; * indicates $p < .05$; ** indicates $p < .01$. 
Executive and Non-Executive Abilities from the NIH Toolbox for children receiving transfusion, children receiving HU, and demographically-matched healthy children. The dashed line represents the mean (100) of most intelligence test batteries. Flanker: Flanker Inhibitory Control; WM: Working Memory List Sorting; DCCS, Dimensional Card Change Sort; Proc: Pattern Comparison; Voc: Picture Vocabulary; PicSeq: Picture Sequence, Read: Oral Reading. Black dots outside of the whiskers represent outliers for each test.

**Figure 1. Distribution of Cognitive Subtests**
Demographically-matched children, children receiving HU at their first and second test session, and children near and far from transfusion. Near transfusion (within 3 days after transfusion); Far from transfusion (within 3 days before next transfusion after 4 to 6 week interval). Error bars represent 95% confidence intervals. * indicates a significant difference; * = $p < .05$, ** = $p < .01$, *** = $p < .001$.

**Figure 2.** Executive Abilities
Demographically-matched children, children receiving HU at their first and second test session, and children near and far from transfusion. Near transfusion (within 3 days after transfusion); Far from transfusion (within 3 days before next transfusion after 4 to 6 week interval). Error bars represent 95% confidence intervals. * indicates a significant difference; * = $p < .05$, ** = $p < .01$, *** = $p < .001$.

**Figure 3.** Non-Executive Abilities
Near Transfusion (within 3 days after transfusion); Far From Transfusion (within 3 days before next transfusion after 4 to 6-week interval). Error bars represent Cousineau-Morey within-subject confidence intervals. * indicates a significant difference; * = p < .05, ** = p < .01, *** = p < .001.

**Figure 4.** Heath-Related Quality of Life for Children Near and Far from Transfusion
Figure 5. Change in Blood Biomarkers Immediately Before and After Transfusion

Error bars represent Cousineau-Morey within-subject confidence intervals. * = indicates a significant difference between before and after transfusion; * = p < .05, ** = p < .01, *** = p < .001.
Over a 4- to 6-week interval for children receiving transfusion.

**Figure 6.** Correlations Between Blood Biomarkers and Change in Executive Abilities
Over a 4- to 6-week interval for children receiving transfusion.

**Figure 7:** Correlations Between Change in RBC and Change in Executive Abilities
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