The Development of Neuroimaging Biomarkers for Cognitive Decline in Sickle Cell Disease

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KEYWORDS

• Sickle cell disease • Silent cerebral infarcts • Neurologic complications

KEY POINTS

- Patients with sickle cell disease, even in the absence of vasculopathy or stroke, experience cognitive dysfunction that progresses with age and the cognitive sequelae of sickle cell disease are likely underrepresented when examining measures of global intelligence alone.
- Transcranial Doppler ultrasound and structural brain MRI are currently used for primary and secondary stroke prevention, but laboratory or imaging biomarkers do not currently exist that are specific to the risk of cognitive dysfunction in patients with sickle cell disease.
- MR measures assessing cerebral hemodynamics, functional connectivity and the integrity of the white matter microstructure can potentially be used to define the impact of sickle cell disease on brain development.

COGNITIVE DYSFUNCTION IN THE ABSENCE OF STROKE

SCD is an autosomal recessive hemoglobinopathy caused by a mutation in the beta globin gene that results in hemoglobin with a decreased affinity for oxygen and a propensity for polymerization in the setting of hypoxia.[1] Sickled red blood cells flow abnormally through the vasculature, obstruct the microcirculation, and hemolyze, with resultant inflammation and endothelial activation.[2] While this physiologic process impacts all organ systems, patients with SCD are at risk for a host of neurologic complications, including vasculopathy, overt hemorrhagic or ischemic stroke, silent cerebral infarcts (SCIs), and cognitive dysfunction, all of which result in great morbidity.

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People with sickle cell disease (SCD), even in the absence of vasculopathy or stroke, have impaired cognitive function in comparison to people without SCD.[3–5] The effects of SCD on global intelligence in the absence of stroke or silent cerebral infarct (SCI) were demonstrated in a cross-sectional study performed by Steen and colleagues who found a significant decrease in full-scale, verbal and performance intelligence quotient (FSIQ, VIQ, and PIQ, all with $P < .01$) in children with hemoglobin SS (HbSS) disease and normal brain MRIs compared with non-sickle cell controls that were matched for age, sex, and race. Mean FSIQ, VIQ, and PIQ were 90.8, 92.4, and 91.0, respectively, in non-sickle cell controls in comparison to 77.9, 80.3, and 79.3 in children with sickle cell anemia (SCA) and normal brain MRIs, with an average 12-point decrease in each IQ measure. Similar findings were demonstrated when the authors controlled for parental education as a surrogate for socioeconomic status.[4] To support these cross-sectional data, a meta-analysis performed by Schatz and colleagues compared cognitive testing in children with SCD and normal brain MRIs versus healthy, demographically matched or sibling-matched controls. While the included studies varied in control population and definition of infarction (MRI vs clinical history), the meta-analysis found a mean 4 to 5-point decrease in IQ among SCD patients without silent or overt stroke in comparison to controls. Additionally, 10 of the 14 studies included in the meta-analysis found deficits within the specific cognitive subdomains of attention and executive function, verbal and language function, or memory.[3] All together, these data demonstrate the detrimental effects of SCD on cognition even in the absence of stroke, and stress the need for early intervention to mitigate neurocognitive sequelae.

The neurodevelopmental effects of SCD are often identified within the first years of life[6–9] and worsen with age.[6,7,10,11] In a cohort of 80 children with SCD at an average age of less than 2 years, mean cognitive performance as per the Bayley Scales of Infant Development was 1 SD below the population mean, with 17.5% having significant neurodevelopmental delay.[9] Longitudinally, infants with SCD that were evaluated at 3, 9, and 12 months of life using the Bayley Infant Neurodevelopmental Screener (BINS, a screening tool that assesses neurologic status, cognitive function, and language with lower scores suggestive of higher risk for neurodevelopmental delay) had higher risk BINS scores in comparison to healthy controls. Of note, the prevalence of high-risk scores increased between 3 and 9 months of age, and higher risk scores correlated with higher transcranial Doppler ultrasound (TCD) velocities.[7] Relatedly, infants and toddlers with SCD that were evaluated at 6, 12, 24, and 36 months of age were found to have a significant decrease in cognition between 12 and 24 months of age[6] supporting that deficits are present early in life with an increased prevalence as children age.

Not only does the prevalence of cognitive dysfunction increase over time, but the cognitive deficits associated with SCD accumulate and worsen with age.[3,4,10,12] While children with SCD and normal brain MRIs in the Cooperative Study of Sickle Cell Disease (CSSCD) cohort did not have a significant decline in FSIQ or PIQ, VIQ scores decreased by approximately 0.5 points per year on the Weschler Intelligence Scale for Children (WISC). Furthermore, these children were found to have a significant decline in coding performance, a measure of visual motor speed and coordination, by 0.2 points per year ($P < 0.01$) and in mathematics by 0.9 points per year ($P < 0.01$).[10] This is suggestive of the cumulative cognitive effects of this disease in the absence of any cerebrovascular accidents. The Silent Cerebral Infarct Multi-Center Clinical Trial (SIT) corroborated these longitudinal analyses through the multivariate modeling of full-scale IQ in 150 children with SCD (107 children with SCIs) showing an approximate decline of 1 point per year of life while controlling for hemoglobin oxygen saturation, presence of SCI, household income, and parental

education.[12] As expected with prior literature showing cognitive deficits that first manifest in childhood and progress over time, Vichinsky and colleagues reported that the Weschler Adult Intelligence Scale-III (WAIS-III) performance IQ score in adults with SCD without a history of stroke (silent or overt) or end-organ damage was significantly lower than that of healthy controls without SCD. Additionally, adults with SCD were found to have marked deficits in attention and processing speed.[5]

Stroke Further Exacerbates Cognitive Dysfunction Associated with Sickle Cell Disease

Children with SCD are at increased risk of both overt stroke and SCI, defined as ischemic lesions visualized on neuroimaging in the absence of clinical history or neurologic deficits associated with stroke. Historically, overt stroke impacted approximately 9% of patients with SCA by the age of 20 years.[13–15] Implementation of screening with TCD and chronic transfusion therapy (CTT)[16,17] has decreased the risk of overt stroke to 1.9%.[18] However, children with SCD remain at high risk for SCIs as TCD is not an effective screening tool for this neurologic complication.[18,19] SCIs occur in very young children, with 13.7% of patients having an SCI by 2 years of age,[18,20,21] 32.4% to 37% by 14 years of age, 39% by 18 years of age and extending into young adulthood without plateau.[18,22,23]

The cognitive implications of overt stroke and SCIs have been widely examined, with several studies demonstrating that children with SCD affected by stroke have poorer global intelligence.[7,10,15,24–26] Armstrong and colleagues found that children with SCD and a history of overt stroke had significantly lower FSIQ and PIQ than those with a history of SCI, and that those with SCIs had significantly lower VIQ (with a strong trend in FSIQ) in comparison to those with SCD and normal brain MRIs.[24] Similar findings were demonstrated by Hogan and colleagues, who compiled data from numerous studies and found that ethnically matched non-sickle cell controls had the highest mean FSIQ, followed by those with SCD and no evidence of stroke, then those with SCD and MRI evidence of SCI, and lastly, those with SCD and a history of overt stroke.[27] The CSSCD examined a cohort of pediatric SCD patients over a 10-year time period with standardized neuropsychiatric testing and brain MRIs, permitting cross-sectional comparisons of cognitive outcomes between patients with overt stroke, SCIs, and normal MRIs. The CSSCD found that those with SCIs had significantly lower FSIQ and VIQ scores in comparison to those with normal MRIs. At an average age of 12 years, the average FSIQ score for those with evidence of SCI was 77.2 in comparison to 84.8 in children with SCD and normal brain imaging, both of which are over a standard deviation below the expected normative average.[10]

While measures of IQ provide a global cognitive assessment, such comprehensive measurements may be less sensitive to the impact of SCD than evaluating specific cognitive subdomains. Infarction has been associated with specific deficits in vocabulary,[15,24] verbal comprehension,[15] processing speed,[26,28,29] visual motor speed and coordination (coding),[24,28] attention,[26] and executive function.[26] Thus, the cognitive sequelae of SCD are likely underrepresented when examining measures of global intelligence alone.

IMAGING BIOMARKERS FOR THE NEUROLOGIC COMPLICATIONS OF SICKLE CELL DISEASE

The two most common imaging modalities studied in SCD are TCD and MRI. TCD is currently used to identify patients with SCA at the highest risk for cerebral infarction and, relatedly, those who would benefit from the initiation of CTT for primary stroke

prevention.[16,17] While TCD continues to be used as a safe, noninvasive, and relatively low-cost means of identifying those at the highest risk of overt stroke, it has several limitations. First, TCD is unable to accurately predict susceptibility to SCIs.[18,19,22] Wang and colleagues specifically explored the relationship between TCD and MRI results in a cross-sectional cohort study, reporting that only 29% of the participants with SCIs had conditional or abnormal TCD results. The authors concluded that TCD and MRI findings are often discordant with regard to SCIs and there is a need to develop additional biomarkers for early neurologic complications of SCD.[19] Furthermore, patients with SCD that receive care per current guidelines for monitoring with TCD and initiation of CTT continue to develop SCIs.[18,22] Lastly, overt strokes still occur in those with TCD velocities <200 cm/s, and alternatively, do not always occur in patients with TCD velocities >200 cm/s.[16]

The guidelines from the American Society of Hematology also recommend a structural brain MRI in school-age children to screen for the presence of SCIs,[30] potentially prompting consideration for escalation of primary disease modification with CTT for secondary stroke prevention if infarction is identified.[31] Aside from recommended developmental screening,[30] laboratory or imaging biomarkers do not currently exist that are specific to the risk of cognitive dysfunction in patients with SCD. Thus, recent studies have focused on the utilization of advanced neuroimaging techniques to better understand the pathophysiology of cognitive dysfunction in patients with SCD, with the ultimate goal of developing alternative neuroimaging biomarkers to be used in risk prediction algorithms and to assess the efficacy of treatment options for patients with SCD. The remainder of this review focuses on introducing different physiologic metrics that can be quantified with MRI and the utilization of these advanced MRI sequences to understand the impact of SCD on brain development.

Cerebral Blood Flow and Cerebrovascular Reserve

MRI can be used to measure cerebral blood flow (CBF; **Table 1**), a measure of arterial blood delivery to brain parenchymal tissue. Cerebral oxygen delivery is the product of CBF and the oxygen content of the blood (CaO_2; see **Table 1**). CBF increases in the setting of anemia, or reduced CaO_2, to maintain adequate cerebral oxygen delivery.[32–39] As a result, the brain is left with a reduced ability to respond to additional hemodynamic stressors given that its vasculature is nearing maximal vasodilation. Cerebrovascular reactivity (CVR; see **Table 1**), defined as the remaining vasodilatory capacity in response to vasoactive challenge, is consequently reduced in the setting of elevated CBF.[39]

Resting cerebral blood flow is increased[34,39–45] and cerebrovascular reactivity is decreased[39,42,45] in patients with SCD compared with healthy age-matched controls. While not different between patients with hemoglobin SS versus hemoglobin S beta thalassemia zero ($HbS\beta^0$) disease,[46] CBF is significantly higher in those with HbSS and $HbS\beta^0$ disease compared with patients with hemoglobin SC or S beta thalassemia plus disease.[39] Various studies have reported age,[34,45] hemoglobin or oxygen content,[34,39,42,45,47] hemoglobin F,[39,48] and gray matter volume[34] to be predictors of CBF. However, the relationship between CBF and ongoing hemolysis, as measured by biomarkers such as lactate dehydrogenase reticulocyte count, and bilirubin, remains unclear.[39,45] The relationship between CBF and these known risk factors for the neurologic complications of SCD, in addition to Kim and colleagues' report of an association between decreased cerebrovascular reactivity and global cortical thinning in children with SCD,[49] suggests that chronically elevated CBF may impact the brain's structural development. As such, CBF and CVR have the potential for imaging biomarkers of cognitive risk prediction.

Table 1
MR metrics evaluating cerebral pathophysiology in sickle cell disease

Categories	MR-measured Metrics	Definitions	Typical Responses in Sickle Cell Disease
Hemodynamic Measures	Cerebral Blood Flow (mL/100 g/min)	Arterial blood delivery to brain parenchymal tissue	Cerebral blood flow increases in the setting of anemia, or reduced CaO_2, to maintain adequate cerebral oxygen delivery.[32–39]
	Cerebral Oxygen Delivery	Product of cerebral blood flow and the oxygen content of the blood (CaO_2)	
	Cerebral Vascular Reactivity	Increase in blood flow in response to vasodilatory challenge	Cerebral vascular reactivity is reduced in the setting of elevated cerebral blood flow.[39]
	Oxygen Extraction Fraction	The fraction of oxygen that the brain parenchyma extracts from the blood	Oxygen extraction fraction increases in people with sickle cell disease,[44,63–67] and regional elevation of oxygen extraction fraction co-localizes with regions of the brain at highest risk for microstructural impairment and stroke.[44,67] Utilizing a TRUST sequence, there are also reports of unchanged[69] and decreased[54,68] oxygen extraction fraction in people with sickle cell disease.
Microstructure	Diffusion Tensor Imaging	MRI sequence that characterizes the diffusion properties of water molecules	As water diffusion is typically restricted within the direction of healthy myelin, increased diffusivity and reduced anisotropy suggest damage if water diffusion is not contained within typical confines. Increased diffusivity and reduced anisotropy have been appreciated across different brain regions in people with sickle cell disease.[77–83]
	Mean/Radial/Axial Diffusivity ($10^{-3}mm^2s^{-1}$)	The restriction of water diffusion	
	Fractional Anisotropy	The directionality of water diffusion	
Function	Functional connectivity MRI	Directly measures cerebral hemodynamics and indirectly assesses neural activity by correlating the BOLD MR signal between brain regions	Altered functional connectivity has been reported in patients with sickle cell disease compared with healthy controls, evaluating both specific regions and large-scale functional networks with a variety of analysis methodologies.[95–102]
	Resting-state Functional Networks	Temporally associated fluctuations in the BOLD signal between functionally related regions of the brain	

SCIs most commonly occur in the border zone regions of the brain where CBF nadirs.[44,50,51] In the analysis of infarct density maps that were created from the SIT trial, Ford and colleagues demonstrated increased SCI density in the deep white matter of the frontal and parietal lobes that corresponded with regions that had the lowest CBF.[50] These findings suggest that (1) white matter potentially does not have the same compensatory vasodilatory mechanisms as the remainder of the brain and (2) it is these regions in which SCIs, a neurologic complication that is associated with cognitive dysfunction in patients with SCD, disproportionately occur.

The effects of elevated CBF on cognitive function in SCD were evaluated by Prussien and colleagues, who performed brain MRIs on 54 children and adults (6–31 years of age) with SCD. On multivariate analysis, hematocrit was positively correlated with fluid cognition, processing speed, and inhibitory control, and CBF was inversely related to working memory and inhibitory control (**Table 2**).[52]

Different MRI sequences can be used to acquire measurements of CBF, such as phase contrast (PC) MRI and arterial spin labeling (ASL) MRI. Several groups have evaluated sequence parameters that can be utilized to more accurately quantify CBF in the setting of SCD. In vivo measured or SCD cohort-specific blood relaxation times (T1), utilization of a two-compartment versus single compartment model, and consideration of the labeling efficiency can be used to improve CBF quantification.[53–55] While this review does not focus on the technical specifics of each imaging biomarker, accurate and noninvasive measurement of CBF will be required for successful utilization of this neuroimaging biomarker in risk prediction algorithms.

Oxygen extraction fraction

In the setting of significant anemia with a resultant decrease in CaO_2 and/or compromised cerebral perfusion, CBF increases via autoregulatory arteriolar dilation. Furthermore, oxygen extraction fraction (OEF; the fraction of oxygen that the brain parenchyma extracts from the blood, see **Table 1**) can be altered to maintain the cerebral metabolic rate of oxygen utilization ($CMRO_2$).[56–58] Ischemic infarction occurs if CBF and OEF are inadequate to maintain $CMRO_2$.[59] Thus, prognostic markers of cerebral hemo-metabolic disequilibrium, such as OEF, can potentially be utilized to gain insight into tissue-level hemodynamic relationships and may also predict neurocognitive complications in SCD.

Historically, OEF was primarily measured via $_{15}O$ PET, but newer methods utilizing MRI have allowed for OEF to be quantified more readily and with less risk to patients.[60–62] Children and adults with SCD have higher OEF in comparison to healthy controls.[44,63–67] Elevated OEF has been correlated to the severity of SCD, as there is a negative relationship between OEF and hemoglobin.[44,64] Jordan and colleagues demonstrated that OEF was highest in adult SCD patients with a greater degree of clinical impairment, as defined by the extent of vasculopathy, prior overt stroke, and/or chronic SCD-related pain necessitating routine blood transfusions.[63] Moreover, regions of higher OEF co-localize with regions of the brain at greatest risk for SCI.[44,67] Relatedly, Wang and colleagues demonstrated a spatial relationship between increased OEF and elevated mean diffusivity in adults with SCD, suggestive of the potential role of tissue-level metabolic stress in the underlying microstructural injury.[66]

OEF can be quantified using MRI at either a regional tissue level using an asymmetric spin echo sequence (ASE; voxel-wise measurement of OEF-dependent MR measurements of T2)[60,61] or a summed whole brain level using a T2-relaxation-under-spin-tagging (TRUST) sequence.[62] The T2 signal measured with TRUST is sensitive to both hematocrit and oxygenation. If hemoglobin and T2 are quantified in vivo,

Table 2
Investigations relating MRI biomarkers to cognitive outcomes in patients with sickle cell disease

Studies	Cohorts	Age (Years)	Overt Stroke	Silent Infarct	Chronic Transfusion	CBF	OEF	DTI	Functional Connectivity	Cognitive Tests Obtained
Prussien et al[52] 2021	49 HbSS 5 HbSB^0	SCD 6–17 HC 18–31	5 (9.3%)	20 (37.0%)	17 (31.5%)	pCASL	TRUST	-	-	Wechsler Working Memory Index NIHTB—CB
Scantlebury et al[76] 2011	11 HbSS 3 HbSC 1 HbSD 10 HC	SCD 11.7 HC 10.2	0	5 (33.3%)	Not stated	-	-	ADC	-	WISC/WAIS
Sun et al.[78]2012	30 HbSS 15 HC	SCD 15.2[a] HC 15.1	0	0	Not Stated	-	-	FA MD RD LD MO EAR	-	WASI D-KEFS CCPT
Kawadler et al.[79]2015	25 HbSS 14 HC	SCD 13.1 HC 13.7	0	0	2 (8%)	-	-	FA MD AD RD	-	WASI D-KEFS BRIEF
Stotesbury et al.[84]2018	82 HbSS 1 HbSB^0 32 HC	SCD -SCI 14.6 SCD + SCI 16.3 HC 15.3	0	37 (45%)	5 (6%)	-	-	FA MD RD ICVF ODI	-	WASI/WISC/WAIS
Chai et al.[81]2021	26 SCD 19 ACTL 21 HC	SCD 24.2 ACTL 26.1 HC 22.6	0	SCD 14 (53.8%) ACTL 8 (42.1%) HC 7 (33.3%)	SCD 4 (15.4%) ACTL 14 (73.7%)	-	-	FA	-	WISC/WAIS D-KEFS
Colombatti et al.[95] 2016	39 HbSS 1 HbSB^0 16 HC	SCD 8.1 HC 10.0	0	20 (50%)	9 (22.5%)	-	-	-	DMN	WISC/WPSSI

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Table 2
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Studies	Cohorts	Age (Years)	Overt Stroke	Silent Infarct	Chronic Transfusion	CBF	OEF	DTI	Functional Connectivity	Cognitive Tests Obtained
Sun et al.[96]2017	10 HbbSS 10 HC	SCD 15.3 HC 14.5	0	0	0	-	-	-	DMN	WASI/WISC D-KEFS CCPT Tower of London BRIEF WRAML Children's Memory Scale
Coloigner et al.[98]2017	17 HbSS 2 HbSB0 1 HbSC 12 ACTL 19 HC	SCD 19.7 ACTL 20.8 HC 22.1	0	SCD 4 (20%) ACTL 1 (8.3%)	12 (60%) ACTL 11 (91.7%)	PC	-	-	ALFF	WASI/WISC/WAIS D-KEFS CVLT REY-O BASC2
Fields et al.[101]2020	35 HbSS 5 HbSB^0 20 HC	SCD 10.0 HC 11.5	0	15 (39.5%)	0	-	ASE	-	SM Auditory Visual Cerebellum DAN VAN Memory DMN Salience CO FP Subcortical	WASI NIHTB-CB

ALFF, amplitude of low frequency fluctuations; ACTL, Non-sickle cell anemic control participants; ADC, Apparent diffusion coefficient; AD, Axial diffusivity; BASC, Behavior Assessment System for Children; BRIEF, Behavior Rating Inventory of Executive Function; CVLT, California Verbal Learning Test; CO; Cingulo-Opercular Network; CCPT, Conners' Continuous Performance Test; DAN, Dorsal Attention Network; DMN, Default mode network; DKEFS, Delis-Kaplan Executive Functioning System; DWI, Diffusion weighted imaging; FA, Fractional anisotropy; FP, Fronto-Parietal Network; HC, Healthy control; Hb, Hemoglobin; NIHTB-CB, NIH Toolbox Cognitive Battery; LD, Longitudinal diffusivity; MD, Mean diffusivity; PC, Phase contrast; RD, Radial diffusivity; Rey-O, Rey Osterrieth Complex Figure Test; SM, Sensory Motor Netowrk; SCD, Sickle cell disease; VAN, Ventral Attention Network; WASI, Wechsler Abbreviated Scale of Intelligence; WAIS, Wechsler Adult Intelligence Scales; WISC, Wechsler Intelligence Scale for Children; WPSSI, Wechsler Preschool Scale Intelligence; WRAML, Wide Range Assessment of Memory and Learning.

[a] Mean age for SCD cohort with normal structural MRI ($N = 15$)

oxygenation can be calculated via a predetermined calibration curve. However, the most appropriate calibration curve for patients with SCD remains unclear. In contrast with the aforementioned studies, OEF was found to be decreased in participants with SCD in comparison to healthy controls when utilizing a hemoglobin S-specific calibration curve[54,68] while there was not a significant difference in OEF between participants with SCD and healthy controls when using an individualized calibration curve per participant.[69] With the TRUST sequence, a single T2 measurement is obtained in the superior sagittal sinus, providing a global OEF measurement. The presence of microvascular cerebral shunting in the setting of increased transit time that prevents hemoglobin from fully offloading oxygen[70] could potentially explain a lower OEF in patients with SCD as measured by TRUST, which is supported by Juttukonda and colleagues' results showing a lower OEF in SCA patients with venous hyperintense signals on ASL because of increased transit time compared with those without venous hyperintensities.[65] All together, these studies highlight the need for future investigations to determine how these different quantification methods of OEF can be used to complement each other.

CTT is widely accepted as a means to mitigate stroke risk in SCD.[17,31] Guilliams and colleagues reported that both CBF and OEF decreased following exchange transfusion in children with SCD.[64] The effects of transfusion on cerebral hemodynamics were further evidenced in a study conducted by Juttukonda and colleagues, which showed that adults with SCD had significantly lower OEF following transfusion (with greater reductions in OEF appreciated following simple transfusion in comparison to exchange transfusion), whereas children with SCD had reductions in both CBF and OEF following exchange transfusion.[71] Hood and colleagues reported higher executive abilities immediately following transfusion in patients with SCD.[72] All together, these results suggest that transfusion decreases the risk of neurocognitive complications by mediating tissue-level cerebral metabolic stress.

Further solidifying that impaired tissue-level cerebral hemodynamics are implicated in the cognitive dysfunction appreciated in SCD, Prussien and colleagues reported that increased OEF was associated with decreased processing speed after controlling for age, income, and history of silent or overt infarction (see **Table 2**).[52] These findings highlight the potential use of OEF as a biomarker for cognitive dysfunction independent of its utility for stroke risk prediction.

Diffusion tensor imaging

Diffusion-tensor imaging (DTI) is an MRI sequence that identifies the diffusion properties of water molecules and provides insight into white matter microstructure. The utility of this imaging modality is based on the premise that various forms of tissue damage result in the degradation of the cellular barriers that typically function to restrict water diffusion.[73,74] As a result, the degree and directionality in which water is able to diffuse through various regions of the brain can be suggestive of underlying microvascular and microstructural injury.[74] Commonly used DTI metrics include mean diffusivity (MD), radial diffusivity (RD), axial diffusivity (AD), and the apparent diffusion coefficient (ADC), which measure the extent to which water diffusion is restricted, as well as fractional anisotropy (FA), which measures the directionality of water diffusion (see **Table 1**).[74,75] Given that white matter injury is common in SCD, DTI could be useful in evaluating microstructural changes in otherwise normal-appearing white matter that can predispose to further neurologic sequelae and result in subsequent cognitive dysfunction.

Increased diffusivity (MD, RD, and ADC) and reduced anisotropy (FA) are suggestive of microstructural white matter injury and have been appreciated across various

regions of the brain in children and adults with SCD.[76–82] The seven studies published thus far utilizing DTI to compare white matter microstructure in children with SCD compared with healthy controls are limited by small sample sizes (with 30 or less SCD participants) and utilize different analysis techniques (**Table 3**).

Microstructural white matter injury is also present in SCD in the absence of SCI (see **Table 3**).[76–79,81] While all of Kawadler and colleagues' analyses were limited to children with SCD unaffected by SCI,[79] Scantlebury and colleagues showed that increased regional ADC persisted in subgroup analyses comparing only children with SCD without SCI against healthy controls.[76] Utilizing two different analysis techniques, Sun and colleagues reported increased diffusivity in the left centrum ovale with tract-based spatial statistics and increased MD in the corpus callosum with regional analyses in children with SCD unaffected by SCI compared with healthy controls.[78] Moreover, the severity of SCD has been positively correlated with the extent of white matter injury (see **Table 3**).[77,78,81,83] These findings were expanded upon more recently by Jacob and colleagues in a larger cohort in Tanzania, which not only compared children with SCD with and without SCIs, but also showed that patients with SCD and mild/moderate vasculopathy had significantly reduced FA across widespread areas (particularly within the anterior regions of the brain) in comparison to those without vascular abnormalities.[83]

While the physiology of white matter injury in SCD in the absence of SCI remains unknown, associations have been described between markers of disease severity and disrupted white matter integrity. In a cohort of children with SCD that had no radiographical evidence of SCI, Kawadler et al. observed a significant negative relationship between RD and oxygen saturation ($P < .05$) in the genu of the corpus callosum, with a trend toward a negative relationship between RD in the midbody and posterior of the corpus callosum and hemoglobin ($P < .1$).[79]

Decreased white matter microstructural integrity has been associated with cognitive deficits in patients with SCD (see **Table 2**).[76,81,84] Scantlebury and colleagues reported a significant negative correlation between processing speed and ADC in the right frontal lobe in all participants (SCD and control participants), but this relationship ceased to exist when the cohort was included in the multivariate model predicting processing speed.[76] In a study performed by Stotesbury and colleagues, decreased FA and increased MD within specific regions were significantly associated with decreased processing speed in patients with SCD.[84] Most recently, Chai and colleagues investigated the relationship between FA in 11 different white matter tracts and 3 cognitive subdomains: processing speed, working memory, and executive function. They reported that a significant association between FA within the corpus callosum and processing speed, working memory, and executive function measures, all of which are known to be impacted in patients with SCD.[81] Overall, these studies highlight the potential utility of DTI as a neuroimaging biomarker to evaluate for microstructural changes that are not identified by standard-of-care screening modalities, particularly in white matter, where the majority of SCIs occur,[44,50] and are suggestive of a relationship between structural connectivity and clinical cognitive outcomes in SCD patients that warrants further investigation.

Functional connectivity

Functional connectivity MRI (fcMRI) is a noninvasive imaging modality that facilitates the exploration of neuronal connectivity via the blood-oxygen-level-dependent (BOLD) MR signal, which is dependent on the paramagnetic properties of deoxyhemoglobin. While neural activity increases local oxygen consumption, there is also a regional increase in cerebral blood flow with a resultant change in the ratio of oxy-to-

Table 3
Investigations utilizing diffusion tensor imaging in patients with sickle cell disease

Studies	Participants	Age (Years)	Overt Stroke	Silent Infarct	Chronic Transfusion	DTI Metrics	Impacted Regions (SCD without Infarct vs. HC)	Impacted Regions (SCD vs HC)	Impacted Regions (SCD with vs. without Infarct)
Scantlebury et al.[76]2011	11 HbSS 3 HbSC 1 HbSD 10 HC	SCD 11.7 HC 10.2	0	5 (33.3%)	Not stated	ADC	Frontal lobe Cerebellum	Frontal lobe Cerebellum Pons Vermis	No differences identified
Balci et al.[77]2012	16 HbSS 14 HC	SCD 25.4 HC 26.1	0	6 (37.5%)	Not stated	ADC FA Fiber Count	-	CC segment I, IV Frontal lobe Centrum semiovale Periventricular WM Brainstem Caudate Thalamus Pons	CC segment IV Centrum semiovale Superior frontal white matter Pons Occipital Temporal white matter
Sun et al.[78]2012	30 HbSS 15 HC	SCD 15.2[a] HC 15.1	0	0	0	EAR FA MD RD LD MO	Corpus callosum Centrum ovale	Corpus callosum Centrum ovale	Corpus callosum[b]
Kawadler et al.[79]2015	25 HbSS 14 HC	SCD 13.1 HC 13.7	0	0	2 (8%)	FA MD	Peduncles Cerebellum Frontal lobe Parietal lobe CC Subcortex Internal capsule	-	-

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Table 3
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Studies	Participants	Age (Years)	Overt Stroke	Silent Infarct	Chronic Transfusion	DTI Metrics	Impacted Regions (SCD without Infarct vs. HC)	Impacted Regions (SCD vs HC)	Impacted Regions (SCD with vs. without Infarct)
							ATR CST		
Kapustin et al.[80]2019	27 HbSS 12 HC	SCD -HU 15.3 SCD + HU 13.2 HC 14.0	0	15 (55.6%)	0	MD	-	-	-
Chai et al.[81]2020	26 SCD 19 ACTL 21 HC	SCD 24.2 ACTL 26.1 HC 22.6	0	SCD 14 (53.8%) ACTL 8 (42.1%) HC 7 (33.3%)	SCD 4 (15.4%) ACTL 14 (73.7%)	FA	CC CST ILF IFO SLF UNC	CC CST ILF IFO SLF UNC	SLF
Costa et al[82] 2021	28 SCD 26 HC	SCD 14.5 HC 15.0	11 (39.3%)	Not stated	17 (60.7%)	FA MD RD AD	-	All white matter	-

Abbreviations: ACTL, Non-sickle cell anemic control participants; ADC, apparent diffusion coefficient; AD, axial diffusivity; ATR, anterior thalamic radiation; CC, corpus callosum; CST, cortical spinal tract; FA, fractional anisotropy; HC, healthy control; Hb, Hemoglobin; IFO, Inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; LD, longitudinal diffusivity; MD, mean diffusivity; RD, radial diffusivity; SCD, sickle cell disease; SLF, superior longitudinal fasciculus; WM, white matter; UNC, uncinate.

[a] Mean age for SCD cohort with normal structural MRI ($N = 15$).

[b] SCD with mild gliosis versus SCD with a normal structural MR.

deoxyhemoglbin and BOLD signal. Hence, the BOLD signal directly measures cerebral hemodynamics while providing an indirect measure of neural activity (see **Table 1**).[85]

Various brain regions have known fluctuations in the BOLD signal at rest that are temporally associated with functionally related regions of the brain and have been described as resting-state functional networks (RSNs, see **Table 1**).[85–88] These functional networks have been examined at rest and during the administration of cognitive tasks to define the associated neurocognitive function for each RSN. The default mode network (DMN), comprised of the posterior cingulate, precuneus, ventromedial prefrontal cortex, and the inferior-lateral parietal cortices, is one of the most widely studied RSNs.[88,89] The DMN represents a baseline or "default" mode of brain function that is activated during internally focused tasks and deactivated during externally focused task-oriented behaviors.[88,90] In addition to the DMN, there are primary RSNs associated with neurocognitive functions, such as sensation and movement, vision, hearing, memory, attention, and executive function.[88,91] Disrupted functional connectivity of these networks has been implicated in altered cognition in other disease entities,[92,93] and can potentially be utilized as a biomarker for the neurocognitive complications of SCD.

Children and adults with SCD have alterations in functional connectivity compared with healthy controls.[94–101] Whole-brain analysis of the amplitude of low frequency fluctuations (ALFF) in BOLD signaling has demonstrated that SCD patients have significant differences in the insula, precuneus, anterior cingulate cortex, and medial superior frontal gyrus in comparison to healthy age and race-matched controls.[98] The impact of SCD on functional connectivity within the DMN remains unclear, with some finding diminished connectivity,[94,96,97] unchanged connectivity[101] and increased connectivity[94,95,97] in children with SCD compared with healthy controls. Additional large-scale RSNs have been reported to be impacted by SCD, including the sensory motor,[97,101] auditory,[101] executive control,[94] and salience networks.[94,97,101] While these studies report differences, there can be discrepant findings. For example, Case and colleagues reported increased connectivity within parts of the salience networks[94] while Fields and colleagues reported diminished connectivity[101] within this specific RSN. Such differences are most likely secondary to discrepancies between study samples and analysis techniques. Lastly, some investigators have focused on connectivity involving specific brain regions versus large-scale networks, as evidenced by Bhatt and colleagues reporting greater connectivity between the left locus coeruleus and the left dorsolateral prefrontal cortex in patients with SCD,[99] and Karafin and colleagues reporting changes in connectivity involving the peraqueductal gray.[100]

Several recent studies have aimed to examine the implications of physiologic parameters on functional connectivity in patients with SCD.[95,96,98,102] Hemoglobin was associated with similarity in resting connectivity patterns between patients with SCD and healthy controls as assessed with a graphical lasso model[102] and significantly modulated activation of the DMN in SCD.[96] Alterations in functional connectivity as measured by ALFF persisted after accounting for the degree of anemia.[98] Additionally, diminished functional connectivity is associated with increased metabolic stress, as demonstrated in Fields and colleagues' report that nodes included within large-scaled RSNs with diminished connectivity in participants with SCD co-localized with regions of elevated white matter OEF.[101]

Importantly, recent investigations have shown associations between altered functional connectivity and neurocognitive abilities in patients with SCD (see **Table 2**). In examining regional intensities of spontaneous fluctuations, decreased ALFF within the frontal lobe correlated with reduced verbal fluency.[98] Attenuated activation of the

DMN was appreciated in a pediatric SCD cohort with significantly lower scores in measures of executive function, auditory attention, and working memory in comparison to healthy age, ethnicity, and background-matched controls.[96] Conversely, increased activity within the posterior precuneus of the DMN has been observed in SCD patients with decreased IQ, which the authors hypothesized to represent DMN recruitment as a compensatory strategy in the setting of mild cognitive impairment.[95] Disrupted functional connectivity is present before the onset of significant changes in IQ,[96,101] suggesting the use of fcMRI as an early neuroimaging biomarker for cognitive decline.

CONCLUSION

Patients with SCD suffer from a host of neurologic complications of their disease, including cognitive dysfunction in the absence of concomitant stroke. While the pathophysiology of these cognitive deficits requires further investigation, recent studies utilizing MRI to evaluate metabolism, structure, and function of the brain have provided insight into the impact of this disease on brain development. Patients with SCD experience cerebral hemodynamic adaptations to compensate for severe anemia, which are associated with microstructural and functional alterations in the brain. Future investigations will be required to explore the relationship between these different imaging biomarkers and to determine if these metabolic, structural, and functional changes in the brains of patients with SCD are related to long-term cognitive outcomes.

DISCLOSURE

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POTENTIAL CONFLICTS OF INTEREST

M.E. Fields declares equity ownership in Proclara Biociences, a biopharmaceutical company developing therapies for Alzheimer's Disease. M.E. Fields received one-time compensation for scientific advisory board participation with Bluebird Bio, who is developing gene therapy trials for sickle cell disease. M.E. Fields works as a consultant for Global Blood Therapeutics, a company manufacturing Oxbryta for sickle cell disease.

REFERENCES

1. Becklake MR, Griffiths SB, Mc GM, et al. Oxygen dissociation curves in sickle cell anemia and in subjects with the sickle cell trait. J Clin Invest 1955;34(5):751–5.
2. Ware RE, de Montalembert M, Tshilolo L, et al. Sickle cell disease. Lancet 2017;390(10091):311–23.
3. Schatz J, Finke RL, Kellett JM, et al. Cognitive functioning in children with sickle cell disease: a meta-analysis. J Pediatr Psychol 2002;27(8):739–48.
4. Steen RG, Fineberg-Buchner C, Hankins G, et al. Cognitive deficits in children with sickle cell disease. J Child Neurol 2005;20(2):102–7.
5. Vichinsky EP, Neumayr LD, Gold JI, et al. Neuropsychological dysfunction and neuroimaging abnormalities in neurologically intact adults with sickle cell anemia. JAMA 2010;303(18):1823–31.

6. Thompson RJ Jr, Gustafson KE, Bonner MJ, et al. Neurocognitive development of young children with sickle cell disease through three years of age. J Pediatr Psychol 2002;27(3):235–44.
7. Hogan AM, Kirkham FJ, Prengler M, et al. An exploratory study of physiological correlates of neurodevelopmental delay in infants with sickle cell anaemia. Br J Haematol 2006;132(1):99–107.
8. Hogan AM, Telfer PT, Kirkham FJ, et al. Precursors of executive function in infants with sickle cell anemia. J Child Neurol 2013;28(10):1197–202.
9. Glass P, Brennan T, Wang J, et al. Neurodevelopmental Deficits Among Infants and Toddlers with Sickle Cell Disease. J Dev Behav Pediatr 2013;34(6):399–405.
10. Wang W, Enos L, Gallagher D, et al. Neuropsychologic performance in school-aged children with sickle cell disease: A report from the Cooperative Study of Sickle Cell Disease. J Pediatr 2001;139(3):391–7.
11. Armstrong FD, Elkin TD, Brown RC, Baby Hug Investigators, et al. Pediatrics 2013;131(2):e406–14.
12. King AA, Strouse JJ, Rodeghier MJ, et al. Parent education and biologic factors influence on cognition in sickle cell anemia. Am J Hematol 2014;89(2):162–7.
13. Powars DR, Conti PS, Wong WY, et al. Cerebral vasculopathy in sickle cell anemia: diagnostic contribution of positron emission tomography. Blood 1999; 93(1):71–9.
14. Balkaran MB, Char MG, Morris JS, et al. Stroke in a cohort of patients with homozygous sickle cell disease. J Pediatr 1992;120(3):360–6.
15. Bernaudin F, Verlhac S, Freard F, et al. Multicenter prospective study of children with sickle cell disease: radiographic and psychometric correlation. J Child Neurol 2000;15(5):333–43.
16. Adams R, McKie V, Nichols F, et al. The use of transcranial ultrasonography to predict stroke in sickle cell disease. N Engl J Med 1992;326(9):605–10.
17. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. N Engl J Med 1998;339(1):5–11.
18. Bernaudin F, Verlhac S, Arnaud C, et al. Impact of early transcranial Doppler screening and intensive therapy on cerebral vasculopathy outcome in a newborn sickle cell anemia cohort. Blood 2011;117(4):1130–40 ; quiz 1436.
19. Wang WC, Gallagher DM, Pegelow CH, et al. Multicenter comparison of magnetic resonance imaging and transcranial Doppler ultrasonography in the evaluation of the central nervous system in children with sickle cell disease. J Pediatr Hematol Oncol 2000;22(4):335–9.
20. Kwiatkowski JL, Zimmerman RA, Pollock AN, et al. Silent infarcts in young children with sickle cell disease. Br J Haematol 2009;146(3):300–5.
21. Wang WC, Pavlakis SG, Helton KJ, et al. MRI abnormalities of the brain in one-year-old children with sickle cell anemia. Pediatr Blood Cancer 2008;51(5): 643–6.
22. Bernaudin F, Verlhac S, Arnaud C, et al. Chronic and acute anemia and extracranial internal carotid stenosis are risk factors for silent cerebral infarcts in sickle cell anemia. Blood 2015;125(10):1653–61.
23. Kassim A, Pruthi S, MAtthew Daym, et al. Blood. Blood 2016;127(16):2038–40.
24. Armstrong FD, Thompson RJ Jr, Wang W, et al. Cognitive functioning and brain magnetic resonance imaging in children with sickle Cell disease. Neuropsychology Committee of the Cooperative Study of Sickle Cell Disease. Pediatrics 1996;97(6 Pt 1):864–70.

25. Schatz J, Brown RT, Pascual JM, et al. Poor school and cognitive functioning with silent cerebral infarcts and sickle cell disease. Neurology 2001;56(8):1109–11.
26. Prussien Kv, Jordan LC, Debaun MR, et al. cognitive function in sickle cell disease across domains, cerebral infarct status, and the lifespan: a meta-analysis. J Pediatr Psychol 2019;44(8):948–58.
27. Hogan A, Cate IMP, Vargha-Khadem F, et al. Physiological correlates of intellectual function in children with sickle cell disease: hypoxaemia, hyperaemia and brain infarction. Developmental Sci 2006;9(4):379–87.
28. Watkins KE, Hewes D, Connelly A, et al. Cognitive deficits associated with frontal-lobe infarction in children with sickle cell disease. Developmental Med Child Neurol 1998;40:536–43.
29. Debaun M, Schatz J, Siegel M, et al. Cognitive screening examinations for silent cerebral infarcts in sickle cell disease. Neurology 1998;50(6):1678–82.
30. DeBaun MR, Jordan LC, King AA, et al. American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults. Blood Adv 2020;4(8):1554–88.
31. DeBaun MR, Gordon M, McKinstry RC, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med 2014;371(8):699–710.
32. Kuwabara Y, Sasaki M, Hirakata H, et al. Cerebral blood flow and vasodilatory capacity in anemia secondary to chronic renal failure. Kidney Int 2002;61:564–9.
33. Floyd TF, McGarvey M, Ochroch EA, et al. Perioperative Changes in Cerebral Blood Flow after Cardiac Surgery: Influence of Anemia and Aging. Ann Thorac Surg 2003;76(6):2037–42.
34. Bush AM, Borzage MT, Choi S, et al. Determinants of resting cerebral blood flow in sickle cell disease. Am J Hematol 2016;91(9):912–7.
35. Dhar R, Zazulia AR, Derdeyn CP, et al. RBC Transfusion Improves Cerebral Oxygen Delivery in Subarachnoid Hemorrhage. Crit Care Med 2017;45(4):653–9.
36. Zheng G, Lu H, Yu W, et al. Severity-specific alterations in CBF, OEF and CMRO2 in cirrhotic patients with hepatic encephalopathy. Eur Radiol 2017;27(11):4699–709.
37. Neunhoeffer F, Hofbeck M, Schuhmann MU, et al. Cerebral oxygen metabolism before and after RBC transfusion in infants following major surgical procedures. Pediatr Crit Care Med 2018;19(4):318–27.
38. Bush A, Chai Y, Choi SY, et al. Pseudo continuous arterial spin labeling quantification in anemic subjects with hyperemic cerebral blood flow. Magn Reson Imaging 2018;47:137–46.
39. Afzali-Hashemi L, Baas KPA, Schrantee A, et al. Impairment of Cerebrovascular Hemodynamics in Patients With Severe and Milder Forms of Sickle Cell Disease. Front Physiol 2021;12:1–11.
40. Gevers S, Nederveen AJ, Fijnvandraat K, et al. Arterial spin labeling measurement of cerebral perfusion in children with sickle cell disease. J Magn Reson Imaging 2012;35(4):779–87.
41. Croal PL, Leung J, Kosinski P, et al. Assessment of cerebral blood flow with magnetic resonance imaging in children with sickle cell disease: A quantitative comparison with transcranial Doppler ultrasonography. Brain Behav 2017;7(11):e00811.
42. Kosinski PD, Croal PL, Leung J, et al. The severity of anaemia depletes cerebrovascular dilatory reserve in children with sickle cell disease: a quantitative magnetic resonance imaging study. Br J Haematol 2017;176(2):280–7.

43. Kawadler JM, Hales PW, Barker S, et al. Cerebral perfusion characteristics show differences in younger versus older children with sickle cell anaemia: Results from a multiple-inflow-time arterial spin labelling study. NMR Biomed 2018; 31(6):e3915.
44. Fields ME, Guilliams KP, Ragan DK, et al. Regional oxygen extraction predicts border zone vulnerability to stroke in sickle cell disease. Neurology 2018; 90(13):e1134–42.
45. Václavů L, Meynart BN, Mutsaerts HJMM, et al. Hemodynamic provocation with acetazolamide shows impaired cerebrovascular reserve in adults with sickle cell disease. Haematologica 2019;104(4):690–9.
46. Ikwuanusi I, Jordan LC, Lee CA, et al. Cerebral hemodynamics and metabolism are similar in sickle cell disease patients with hemoglobin SS and Sβ0 thalassemia phenotypes. Am J Hematol 2020;95(3):E66–8.
47. Kawadler JM, Clark CA, McKinstry RC, et al. Brain atrophy in paediatric sickle cell anaemia: findings from the silent infarct transfusion (SIT) trial. Br J Haematol 2017;177(1):151–3.
48. Vaclavu L, Petr J, Petersen ET, et al. Cerebral oxygen metabolism in adults with sickle cell disease. Am J Hematol 2019;95(4):401–12.
49. Kim JA, Leung J, Lerch JP, et al. Reduced cerebrovascular reserve is regionally associated with cortical thickness reductions in children with sickle cell disease. Brain Res 2016;1642:263–9.
50. Ford AL, Ragan DK, Fellah S, et al. Silent infarcts in sickle cell anemia occur in the borderzone region and are associated with low cerebral blood flow. Blood 2018;132(16):1714–23.
51. Chai Y, Bush AM, Coloigner J, et al. White matter has impaired resting oxygen delivery in sickle cell patients. Am J Hematol 2019;94(4):467–74.
52. Prussien Kv, Compas BE, Siciliano RE, et al. Cerebral hemodynamics and executive function in sickle cell anemia. Stroke 2021;52(5):1830–4.
53. Vaclavu L, van der Land V, Heijtel DF, et al. In Vivo T1 of blood measurements in children with sickle cell disease improve cerebral blood flow quantification from arterial spin-labeling MRI. AJNR Am J Neuroradiol 2016;37(9):1727–32.
54. Bush AM, Coates TD, Wood JC. Diminished cerebral oxygen extraction and metabolic rate in sickle cell disease using T2 relaxation under spin tagging MRI. Magn Reson Med 2018;80(1):294–303.
55. Juttukonda MR, Jordan LC, Gindville MC, et al. Cerebral hemodynamics and pseudo-continuous arterial spin labeling considerations in adults with sickle cell anemia. NMR Biomed 2017;30(2):e3681.
56. Powers WJ, Grubb RL Jr, Darriet D, et al. Cerebral blood flow and cerebral metabolic rate of oxygen requirements for cerebral function and viability in humans. J Cereb Blood Flow Metab 1985;5(4):600–8.
57. Giffard C, Young AR, Kerrouche N, et al. Outcome of acutely ischemic brain tissue in prolonged middle cerebral artery occlusion: a serial positron emission tomography investigation in the baboon. J Cereb Blood Flow Metab 2004;24(5): 495–508.
58. Derdeyn CP, Videen TO, Yundt KD, et al. Variability of cerebral blood volume and oxygen extraction: stages of cerebral haemodynamic impairment revisited. Brain 2002;125(Pt 3):595–607.
59. Heiss WD, Huber M, Fink GR, et al. Progressive derangement of periinfarct viable tissue in ischemic stroke. J Cereb Blood Flow Metab 1992;12(2):193–203.

60. An H, Lin W, Celik A, et al. Quantitative measurements of cerebral metabolic rate of oxygen utilization using MRI: a volunteer study. NMR Biomed 2001;14(7–8):441–7.
61. An H, Liu Q, Chen Y, et al. Evaluation of MR-derived cerebral oxygen metabolic index in experimental hyperoxic hypercapnia, hypoxia, and ischemia. Stroke 2009;40(6):2165–72.
62. Lu H, Ge Y. Quantitative evaluation of oxygenation in venous vessels using T2-relaxation-under-spin-tagging MRI. Magn Reson Med 2008;60(2):357–63.
63. Jordan LC, Gindville MC, Scott AO, et al. Non-invasive imaging of oxygen extraction fraction in adults with sickle cell anaemia. Brain 2016;139(Pt 3):738–50.
64. Guilliams KP, Fields ME, Ragan DK, et al. Red cell exchange transfusions lower cerebral blood flow and oxygen extraction fraction in pediatric sickle cell anemia. Blood 2018;131(9):1012–21.
65. Watchmaker JM, Juttukonda MR, Davis LT, et al. Hemodynamic mechanisms underlying elevated oxygen extraction fraction (OEF) in moyamoya and sickle cell anemia patients. J Cereb Blood Flow Metab 2018;38(9):1618–30.
66. Wang Y, Fellah S, Fields ME, et al. Cerebral Oxygen Metabolic Stress, Microstructural Injury, and Infarction in Adults With Sickle Cell Disease. Neurology 2021;97(9):e902–12.
67. Fields ME, Mirro AE, Binkley MM, et al. Cerebral oxygen metabolic stress is increased in children with sickle cell anemia compared to anemic controls. Am J Hematol 2022;97(6):682–90.
68. Vu C, Bush A, Choi S, et al. Reduced global cerebral oxygen metabolic rate in sickle cell disease and chronic anemias. Am J Hematol 2021;96(8):901–13.
69. Li W, Xu X, Liu P, et al. Quantification of whole-brain oxygenation extraction fraction and cerebral metabolic rate of oxygen consumption in adults with sickle cell anemia using individual T2-based oxygenation calibrations. Magn Reson Med 2020;83(3):1066–80.
70. Østergaard L, Jespersen SN, Engedahl T, et al. Capillary Dysfunction: Its Detection and Causative Role in Dementias and Stroke. Curr Neurol Neurosci Rep 2015;15(6):37.
71. Juttukonda MR, Lee CA, Patel NJ, et al. Differential cerebral hemometabolic responses to blood transfusions in adults and children with sickle cell anemia. J Magn Reson Imaging 2019;49(2):466–77.
72. Hood AM, King AA, Fields ME, et al. Higher executive abilities following a blood transfusion in children and young adults with sickle cell disease. Pediatr Blood Cancer 2019;66(10):e27899.
73. Beaulieu C, Allen PS. Determinants of Anisotropic Water Diffusion in Nerves. Magn Reson Med 1994;31(4):394–400.
74. Beaulieu C. The basis of anisotropic water diffusion in the nervous system - A technical review. NMR Biomed 2002;15(7–8):435–55.
75. Basser PJ. New histological and physiological stains derived from diffusion-tensor MR images. Ann N Y Acad Sci 1997;30:123–38.
76. Scantlebury N, Mabbott D, Janzen L, et al. White matter integrity and core cognitive function in children diagnosed with sickle cell disease. J Pediatr Hematol Oncol 2011;33(3):163–71.
77. Balci A, Karazincir S, Beyoglu Y, et al. Quantitative brain diffusion-tensor MRI findings in patients with sickle cell disease. AJR Am J Roentgenol 2012;198(5):1167–74.

78. Sun B, Brown RC, Hayes L, et al. White matter damage in asymptomatic patients with sickle cell anemia: screening with diffusion tensor imaging. AJNR Am J Neuroradiol 2012;33(11):2043–9.
79. Kawadler JM, Kirkham FJ, Clayden JD, et al. White Matter Damage Relates to Oxygen Saturation in Children With Sickle Cell Anemia Without Silent Cerebral Infarcts. Stroke 2015;46(7):1793–9.
80. Kapustin D, Leung J, Odame I, et al. Hydroxycarbamide treatment in children with Sickle Cell Anaemia is associated with more intact white matter integrity: a quantitative MRI study. Br J Haematol 2019;187(2):238–45.
81. Chai Y, Ji C, Coloigner J, et al. Tract-specific analysis and neurocognitive functioning in sickle cell patients without history of overt stroke. Brain Behav 2021; 11(3):e01978.
82. Costa TC de M, Chiari-Correia R, Salmon CEG, et al. Hematopoietic stem cell transplantation reverses white matter injury measured by diffusion-tensor imaging (DTI) in sickle cell disease patients. Bone Marrow Transplant 2021;56(11): 2705–13.
83. Jacob M, Stotesbury H, Kawadler JM, et al. White Matter Integrity in Tanzanian Children With Sickle Cell Anemia: A Diffusion Tensor Imaging Study. Stroke 2020;51(4):1166–73.
84. Stotesbury H, Kirkham FJ, Kolbel M, et al. White matter integrity and processing speed in sickle cell anemia. Neurology 2018;90(23):e2042–50.
85. Biswal B, Yetkin FZ, Haughton VM, et al. Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. Magn Reson Med 1995; 34(4):537–41.
86. Fox MD, Raichle ME. Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. Nat Rev Neurosci 2007;8(9):700–11.
87. Fox MD, Snyder AZ, Vincent JL, et al. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc Natl Acad Sci U S A 2005; 102(27):9673–8.
88. Smith SM, Fox PT, Miller KL, et al. Correspondence of the brain's functional architecture during activation and rest. Proc Natl Acad Sci U S A 2009;106(31): 13040–5.
89. Raichle ME. The brain's default mode network. Annu Rev Neurosci 2015;38: 433–47.
90. Buckner RL, Andrews-Hanna JR, Schacter DL. The brain's default network: Anatomy, function, and relevance to disease. Ann N Y Acad Sci 2008; 1124:1–38.
91. Power JD, Cohen AL, Nelson SM, et al. Functional network organization of the human brain. Neuron 2011;72(4):665–78.
92. Li R, Wu X, Fleisher AS, et al. Attention-related networks in Alzheimer's disease: A resting functional MRI study. Hum Brain Mapp 2012;33(5):1076–88.
93. Orliac F, Naveau M, Joliot M, et al. Links among resting-state default-mode network, salience network, and symptomatology in schizophrenia. Schizophr Res 2013;148(1–3):74–80.
94. Case M, Zhang H, Mundahl J, et al. Characterization of functional brain activity and connectivity using EEG and fMRI in patients with sickle cell disease. Neuroimage Clin 2017;14:1–17.
95. Colombatti R, Lucchetta M, Montanaro M, et al. Cognition and the default mode network in children with sickle cell disease: a resting state functional MRI study. PLoS One 2016;11(6):e0157090.

96. Sun B, Brown RC, Burns TG, et al. Differences in activation and deactivation in children with sickle cell disease compared with demographically matched controls. AJNR Am J Neuroradiol 2017;38(6):1242–7.
97. Zempsky WT, Stevens MC, Santanelli JP, et al. Altered functional connectivity in sickle cell disease exists at rest and during acute pain challenge. Clin J Pain 2017;33(12):1060–70.
98. Coloigner J, Kim Y, Bush A, et al. Contrasting resting-state fMRI abnormalities from sickle and non-sickle anemia. PLoS One 2017;12(10):e0184860.
99. Bhatt RR, Zeltzer LK, Coloigner J, et al. Patients with sickle-cell disease exhibit greater functional connectivity and centrality in the locus coeruleus compared to anemic controls. NeuroImage: Clin 2019;21:101686.
100. Karafin MS, Chen G, Wandersee NJ, et al. Chronic pain in adults with sickle cell disease is associated with alterations in functional connectivity of the brain. PLoS One 2019;14(5):e0216994.
101. Fields ME, Mirro AE, Guilliams KP, et al. Functional connectivity decreases with metabolic stress in sickle cell disease. Ann Neurol 2020;88(5):995–1008.
102. Coloigner J, Phlypo R, Coates TD, et al. graph lasso-based test for evaluating functional brain connectivity in sickle cell disease. Brain Connect 2017;7(7):443–53.