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Research Article

Association of Cerebral Hemodynamics and Anemia on Processing Speed in Adults with Sickle Cell Disease

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Abstract

Background and Purpose: Compared to healthy controls, adult patients with Sickle Cell Disease (SCD) are anemic, and therefore have higher cardiac output and Cerebral Blood Flow (CBF) to maintain brain oxygenation. They also demonstrate comparatively more cognitive deficits due to either overt strokes or silent cerebral ischemia. However, there are few correlative studies between CBF and cognitive deficits, specifically processing speed in SCD. Such studies are important to develop biomarkers of central brain processing and ischemia for diagnosis, prognosis, and evaluating the effectiveness of potential interventions. This pilot cross-sectional study tested the hypotheses that adults with SCD and elevated CBF demonstrate lower central brain processing speed than controls on average and that CBF is inversely correlated with processing speed. **Methods:** We conducted a pilot cross-sectional study to assess the relation-ships between CBF, central brain processing speed, and hemoglobin levels in asymptomatic adults with SCD and controls from an urban academic medical center. MRI acquisitions at 3T consisted of 2D phase-contrast quantitative arteriograms (Qflow) of the bilateral internal carotid and vertebral arteries and 3D pseudo-continuous arterial spin labeling (pCASL) of the brain. Participants were patients with SCD (hemoglobin [Hb]SS, [Hb] SBetaThal°, or [Hb]SC) aged 22-52 years of African American descent (N=7) or community controls (Hb AA) (n=3). Processing speed was assessed as an in-direct functional marker of ischemia using a recommended test from the NIH Toolbox for Assessment of Neurological and Behavioral Function, the Pattern Comparison Processing Speed Test. t-tests were used to compare means of CBF, hemoglobin, and cognition between SCD patients and healthy controls. Among SCD patients only multivariate correla-tions were used to evaluate relationships between brain perfusion in specific brain regions vs. processing speed and CBF. The significance level was set at $p \leq 0.05$. **Results:** Adults with SCD reported higher CBF compared to healthy con-trols (72.15±28.90 vs. 47.23±12.30 ml/min/100g, p=0.04), and lower hemoglobin concentration (8.64±2.33 vs. 13.33±0.58, p=0.001). Heart rate in SCD patients was higher than in controls (86.29±1.37 vs. 74.00±2.10, p=0.04). Patients with SCD demonstrated lower processing speed (96.14±21.04 vs.123±13.74, p=0.02) than controls. Among adult patients with SCD, perfusion in specific regions of the brain showed an inverse relationship with processing speed, as did whole-brain CBF (p=0.0325). **Conclusion:** These findings, although from a small sample, lend a degree of validity to the claim that processing speed is slower in people with SCD than in controls and that CBF is significantly higher in SCD patients com-pared to controls. The results also lend credence to the finding that the degree of processing speed deficiencies among adults with SCD is correlated with the degree of elevated CBF, which is known to correspond with the degree of anemia associated with SCD.

Keywords: Hemodynamic; Arterial Spin Labelling; Cerebral Blood Flow; Processing Speed; Sickle Cell Disease

Introduction

Sickle Cell Disease (SCD) is a rare hemoglobinopathy consisting of various mutations in the beta- globin (HBB) gene associated with various expressions of morbidity and mortality. In SCD, the sickle hemoglobin (HbS) polymerizes under deoxygenated conditions. This results in sickle-shaped erythrocytes and causes vaso-occlusion and hemolytic anemia, which underlie the clinical complications of SCD. Homozygous HbSS is classically the most severe phenotype with the most severe anemia, whereas doubly heterozygous Hb S Beta+ Thalassemia is classically the least severe phenotype [1,2]. An estimated 70,000-100,000 people in the United States live with SCD [3]. One of its most devastating complications is overt ischemic stroke, occurring at a median age of five years [4]. The incidence of the first stroke is 500-1280 per 100,000 person-years in adults with HbSS and 360-1160 for all adults with SCD, compared with 12 per 100,000 person-years in African– Americans less than 35 years of age and 202 in those 35 to 54 years of age [5]. Related to brain ischemia, it is well-known that cognitive deficiencies associated with SCD is related to a decrement in general intellectual abilities, and poorer academic achievement [6,7], though the specific mechanisms contributing to these deficits are not fully understood.

The mechanism of brain ischemia in SCD is that of chronic vaso-occlusion and hemolytic anemia, which reduces brain oxygen delivery. Fewer, faulty erythrocytes result in impaired oxygen delivery to all tissues. Sensing hypoxia, the heart responds with chronic, reflex elevation of cardiac output. This elevation includes an elevation of cerebral blood flow (CBF). In children with SCD, the degree of elevation of CBF, measured using transcranial Doppler velocity, is one of the strongest predictors of stroke [8]. Thus, SCD brain ischemia produces cerebral autoregulation to deliver sufficient oxygen at rest by compensatory hyperemia as described above. In SCD, at-rest anemia and attempts at compensation may reach capacity, and oxygen demand may still outstrip supply [9]. The limit on the brain's ability to further compensate acutely in response to acute ischemic stress means pathological brain ischemia, either symptomatic or silent [10]. Cerebral infarcts associated with SCD most commonly occur in the frontal, temporal, and parietal lobes. Although elevations in CBF in SCD are well studied, the adequacy of compensatory hyperemia has never been assessed or compared to patients with anemias from other etiologies [11]. In fact, there is little to no data exploring CBF in African Americans, despite their twofold risk of cerebrovascular accidents [12]. Similarly, little work exists to relate CBF in SCD to the known deficits and cognitive deficits observed in patients with SCD.

Arterial spin labeling (ASL) is a magnetic resonance imaging technique for measuring tissue perfusion using a freely diffusible intrinsic tracer. Its noninvasive nature and ability to quantitatively measure tissue perfusion make ASL ideal for research and clinical studies looking to quantify CBF, which has been shown to be globally increased in children and adults with SCD. One limitation of ASL in SCD is that labeling efficiency would be expected to be reduced with elevated CBF. Cervical phase contrast angiography has been used to determine labeling efficiency in adults with SCD to correct for elevated blood velocities [13].

Lesions in the brain areas most prone to ischemia are associated with cognitive deficits in executive functioning, processing speed, working memory, and attention [14,15]. These measures are associated with abilities to organize one's health care, succeed in school, and maintain a job [16,17] These cognitive deficits exist with or without a history of cerebral infarcts in patients with SCD. In a study assessing the Wechsler Adult Intelligence Scale, third edition (WAIS-III) Performance IQ Index, the mean WAIS-III Performance IQ score of patients with SCA was significantly lower than that of controls adjusted mean, 86.69 for patients with SCA vs 95.19 for controls [18]. However, there is little data exploring potential mechanistic variables contributing to these cognitive deficits, including CBF.

We fielded a pilot cross-sectional study to test two hypotheses among adults with SCD compared to African American control adults. First, we hypothesized SCD subjects would have higher CBF, and lower central brain processing speed compared to healthy control subjects. Second, we hypothesized that higher CBFs would be associated with lower processing speed—the two would be inversely correlated among all studied subjects. We conducted our study by measuring CBF, central brain processing speed, and hemoglobin levels in asymptomatic adults with SCD and controls in an urban academic medical center. Additional hypotheses were that hemoglobin concentration would be inversely correlated with CBF and positively correlated with processing speed, and that patients with SCD with genotypes (HbSC and SBeta+ Thal) associated with higher hemoglobin concentration would have higher processing speed and lower CBF than patients with genotypes associated with lower hemoglobin concentration (HbSS and HBSBetaoThal). This study represented an initial pilot study to investigate correlational patterns that may have implications for larger investigations into CBF and cognitive performance among patients with SCD.

Methods

Participants

Participants with SCD (hemoglobin [Hb]SS, [Hb] SBetaThal°, or [Hb]SC) aged 22-52 years and of African American descent (N=9) and community controls (Hb AA) (N=3) were recruited

from an urban academic med-ical center in Central Virginia. Participants were provided information regarding the study during a scheduled clinic visit. Participants that expressed interest in the study were provided with an Institutional Review Board-approved consent for review and signature. Once consented, participants underwent the study procedure at a dedicated research facility on dedicated research MRI scanner. Participants were provided with monetary compensation for their time. Two SCD patients were excluded from analysis because of brain damage noticed during MRI readout resulting in a final sample of N=7 patients with SCD with the following genotypes HbSS (N=5), HbSC (N=1), and HbSβ0 (N=1). Data collection included: hemoglobin level, heart rate, CBF, genotype, and cognitive function (executive function, cognitive flexibility, and processing speed).

Hemodynamic Imaging

MRI acquisitions used a Philips Ingenia 3T scanner with 32 channel head coil and consisted of 2D phase contrast quantitative arteriograms (Qflow) of the bilateral internal carotid and vertebral arteries and 3D pseudo-continuous arterial spin labeling (pCASL) of the brain.

The 2D phase contrast quantitative arteriogram is an MRI technique used to visualize moving fluid. The basic principle behind this technique is based on the use of bipolar gradients that create phase shifts of moving spins proportional to their velocity. Arterial spin labeling (ASL) is a magnetic resonance imaging technique for measuring tissue perfusion using a freely diffusible intrinsic tracer. Compared with other perfusion techniques, ASL offers several advantages and is now available for routine clinical practice in many institutions. Its noninvasive nature and ability to quantitatively measure tissue perfusion make ASL ideal for research and clinical studies. ASL generates an image by magnetically "labeling" water hydrogen protons as an endogenous tracer. A selective radiofrequency pulse inverts the magnetization of arterial blood water protons in the region or plane to which it is applied, usually in the neck for brain perfusion, and a downstream measurement is taken as labeled water molecules are exchanged into the brain. Labeled image are subtracted from control (unlabeled) images to estimate CBF. One limitation of ASL in SCD is that labeling efficiency would be expected to be reduced with elevated CBF [19]. To address this, cervical phase contrast angiography is used to determine labeling efficiency in adults with SCD and correct for elevated blood velocities [13]. The 2D phase contrast quantitative arteriograms were acquired using parameters: Slice thickness = 5 mm, slices were placed perpendicular to the internal carotid and vertebral arteries just superior to the bifurcation of the carotid artery, Flip angle (deg) = 8.1, TR/TE (ms) =16 / 9.3, heart phases = 15, Phase Contrast velocity (cm/s) = 100, Total scan duration = 1:48 minutes, ACQ matrix = 300 x 300; acquisition voxel size (mm) = 0.60 x0.60 x 5.00; reconstruction voxel size (mm) = 0.45 x 0.45 x 5.00. The 3D pCASL images were acquired using the following parameters: FOV (mm) = 240 x 240, acquisition voxel size (mm) = 3.75 x 3.75 x 6, reconstruction voxel size (mm) = 3 x 3 x 6, slices= 20, slice orientation = transverse, acquisition mode =cartesian, Fast Imaging mode =GraSE, TSE factor = 6, EPI factor = 31, Flip angle (deg) = 90, TR/TE (ms) = 6000 / 20, label type = parallel slab, label distance (mm) = 100, label duration (ms) =1800, post label delay (ms) =1800, Total scan duration =15:00 minutes.

Cognitive assessment

Cognitive flexibility was assessed using the NIH Toolbox Dimensional Change Card Sort Test (DCCS) [20]. In this test, the patient is presented with two pictures that can vary based on shape or color. These pictures are known as "target pictures". Participants are subsequently asked to match a series of bi-dimensional test pictures (e.g., yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g., color) and then, after several trials, according to the other dimension (e.g., shape). After some time, "Shift" trials will be introduced; where the participant must be able to swiftly change the dimension being matched, thus requiring the cognitive flexibility to quickly choose the correct stimulus. This test takes approximately four minutes to ad-minister, is recommended for ages 3-85, and is scored based on a combination of accuracy and reaction time. This combination is then converted to a normative score.

Executive function was measured using the NIH Toolbox Flanker Inhibitory Control and Attention Test [20]. This test is used to measure the participant's attention and inhibitory control and requires the participant's ability to focus on a given stimulus while inhibiting attention to other stimuli. In this case, a set of arrows pointing in one direction and one arrow pointing either in the same direction or in a different direction. This measure of executive function measures the participant's inhibitory control and attention abilities and is recommended for ages 3-85. Similar to the DCCS test, the FLANKER test score is a combination of accuracy and reaction time converted to a normative score.

Processing speed was assessed as an indirect functional marker of ischemia using a test recommended by The NIH Toolbox for Assessment of Neurological and Behavioral Function, the Pattern Comparison Processing Speed Test [20]. This test measures processing speed by asking participants to discern, as quickly as possible, whether two side-by-side pictures are the same or not. The items are presented one pair at a time on the iPad screen, and the participant is given 85 seconds of response time (excluding any time needed for the given iPad to "load" the items) to respond to as many items as possible (up to a maximum of 130) [20].

Statistical analysis

Students' unpaired t-tests were used to evaluate hemoglobin, CBF, heart rate, and cognition differences between SCD patients and healthy controls. ANOVA was performed to test if amongst patients with SCD, genotype affected hemoglobin level, CBF, processing speed, or response time. Relationships between regional per-fusion in the centers of the brain associated with cognitive functioning and processing speed as well as whole brain CBF were analyzed by Pearson correlations. The significance level was set at $p \leq 0.05$.

Data Sharing Statement

For original data, please contact daniel.sop@vcuhealth.org

Results

Table 1 t-test results indicated that adults with SCD had significantly higher CBF compared to controls. In contrast, SCD patients had significantly lower Hgb than controls. They had higher heart rates than controls. And, although not statistically significant, compared to healthy controls, patients with SCD demonstrated lower cognitive flexibility and lower executive function. SCD adults had significantly lower processing speed than controls.

Biomarker (Mean±Std)	SCD Patient	Healthy Control	*P*-Value
Hemoglobin (g/dl)	8.64±2.33	13.33±0.58	0.001**
Heart Rate (bpm)	86.29±1.37	74.00±2.10	0.04**
CBF (ml/min/100g)	72.15±28.9	47.23±12.30	0.04**
Cognition Flexibility	97.57±5.43	115.33±8.29	0.29
Executive Function	79.71±7.10	119.33±10.71	0.12
Processing Speed	96.14±7.36	123.00±11.25	0.02**
**Indicates significance.			

Table 1: Biomarkers Comparison between SCD Patients and Healthy Adults.

Further, within SCD patients, processing speed was found to be significantly correlated to CBF (R-Square=0.63, P=0.0325) as seen in figure 1. Processing speed decreased as CBF increased.

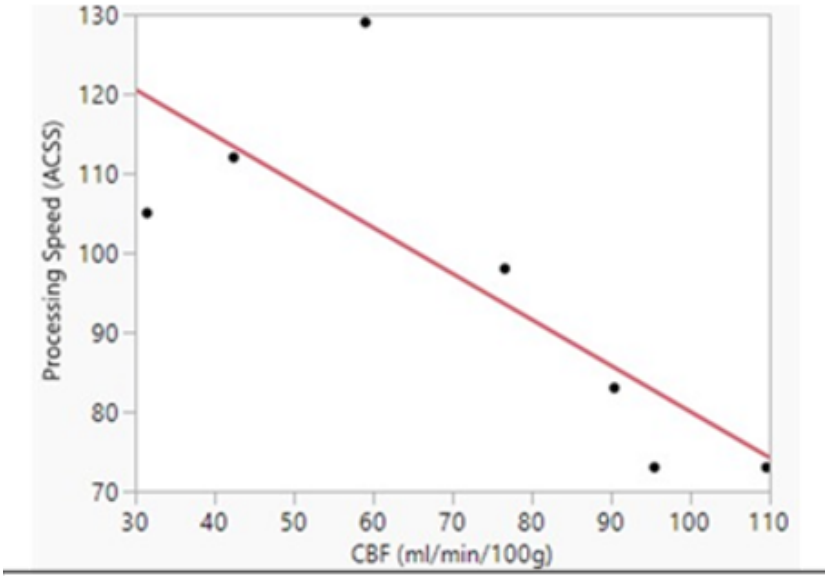

Figure 1: Processing Speed and CBF in SCD Patients.

When comparing hemoglobin levels between different genotypes and healthy controls, the most significant difference was seen between healthy controls and patients with the SS genotype (R- Square=0.78, P =0.02) as shown in figure 2. ANOVA tests also indicated that although CBF was lower and processing speed higher in healthy controls when compared to SCD, the differences in CBF and processing speed among each SCD genotype were not statistically significant (all P- values>0.05, Figures 3 and 4).

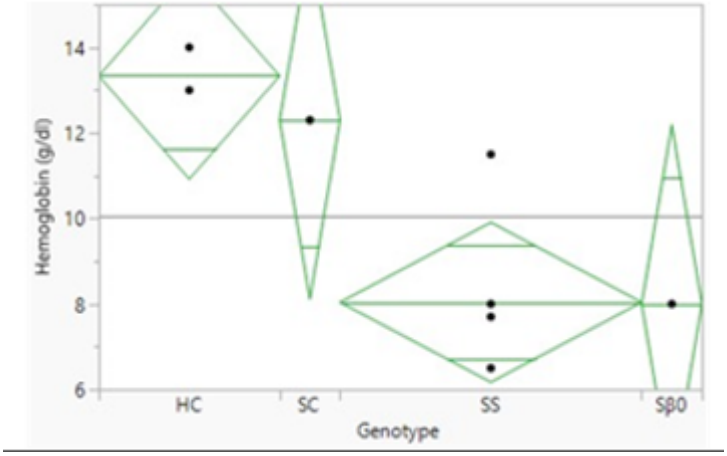

Figure 2: Analysis of Hemoglobin by Genotype.

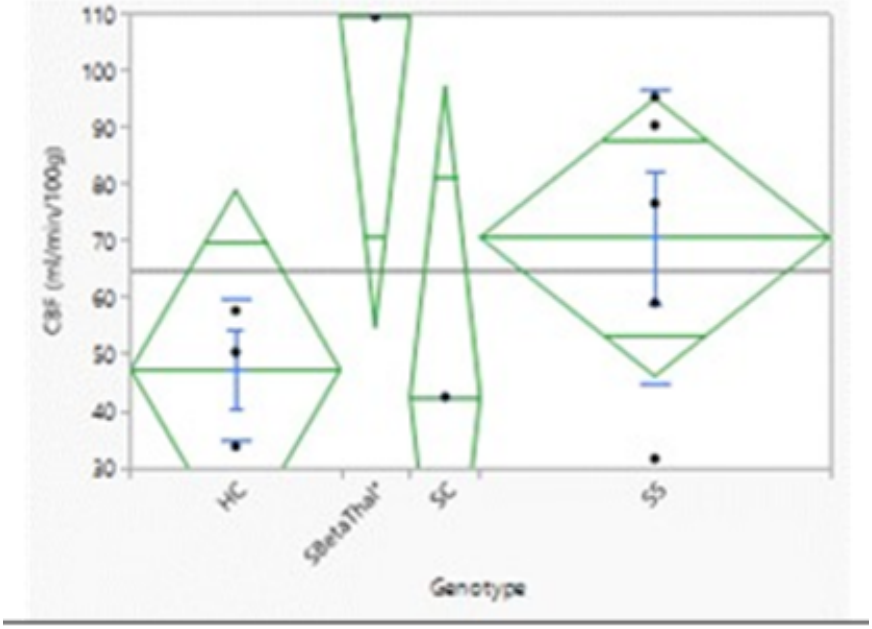

Figure 3: Analysis of CBF (ml/min/100g) by Genotype.

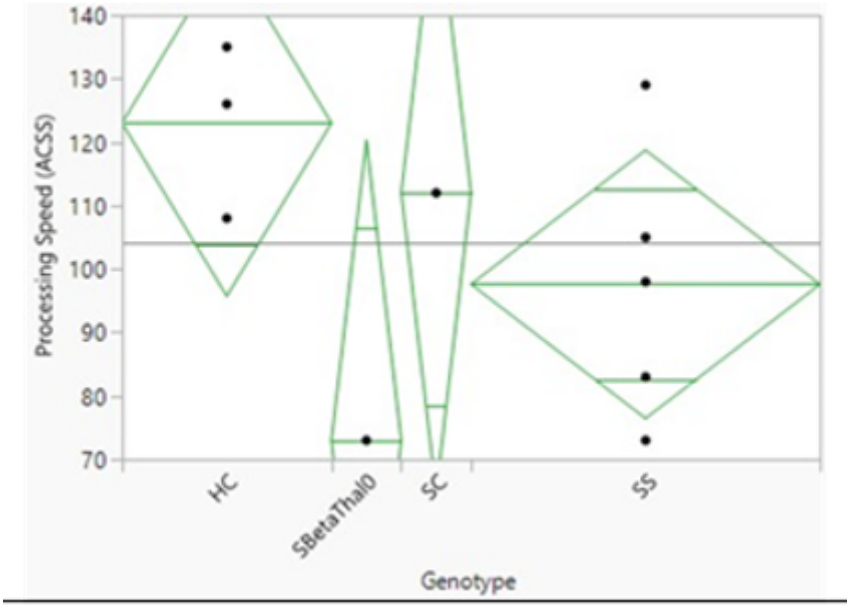

Figure 4: Analysis of Processing Speed by Genotype.

When assessing the relationships between regional perfusion in the centers of the brain associated with cognitive functioning and processing speed, significant correlations were noted between processing speed and blood flow to the Middle Frontal Gyrus (R = -0.9, P=0.005), Precuneus Cortex (R= -0.77, P=0.04), Frontal Orbital Cortex (R = -0.79, P=0.03), Parietal Operculum Cortex (R = -0.8, P=0.02), Temporal Fusiform Cortex (R = -0.76, P=0.04), Left Cerebral Cortex (R = -0.82, P=0.02), Left Pallidum (R = -0.77, P=0.04), and Right Pallidum (R = -0.78, P=0.03) . All these regions of the brain have been identified previously as being part of the cognitive processing centers of the brain. (21) Additionally, whole brain CBF was also positively correlated to blood flow to the Middle Frontal Gyrus (R = 0.76, P=0.04) and Inferior Frontal Gyrus, pars triangularis (R = 0.77, P=0.04) indicating that changes in CBF may have a greater effect in these brain regions. (Table 2).

	Processing Speed		**CBF**	
	Correlation (R)	***P*-Value**	**Correlation (R)**	***P*-Value**
Frontal Lobe (Cognitive processing centers)				
Frontal Pole	-0.72	.0707	0.67	.10
Superior Frontal Gyrus	-0.61	.1450	0.71	.07
Middle Frontal Gyrus	-0.90	.005**	0.76	.04**
Inferior Frontal Gyrus, pars triangularis	-0.63	.1259	0.77	.04**
Inferior Frontal Gyrus, pars opercularis	-0.66	.1038	0.73	.06
Frontal Medial Cortex	-0.71	.0718	0.50	.25
Paracingulate Gyrus	-0.54	.2126	0.73	.06
Cingulate Gyrus, anterior division	-0.54	.2098	0.47	.28
Cingulate Gyrus, posterior division	-0.75	.0515	0.62	.14
Precuneus Cortex	-0.77	.043**	0.56	.18

Frontal Orbital Cortex	-0.79	.035**	0.59	.16
Frontal Operculum Cortex	-0.48	.2726	0.15	.75
Central Opercular Cortex	-0.29	.5251	0.07	.88
Parietal Operculum Cortex	-0.80	.029**	0.68	.08
Temporal Lobe (Memory/Auditory)				
Temporal Pole	-0.66	.1089	0.68	.09
Superior Temporal Gyrus, anterior division	-0.34	.4533	0.60	.15
Superior Temporal Gyrus, posterior division	-0.44	.3252	0.71	.07
Middle Temporal Gyrus, anterior division	NA	NA	NA	NA
Middle Temporal Gyrus, posterior division	-0.50	.2579	0.68	.09
Middle Temporal Gyrus, temporooccipital part	NA	NA	NA	NA
Inferior Temporal Gyrus, anterior division	-0.42	.3493	0.54	.21
Inferior Temporal Gyrus, posterior division	-0.60	.1528	0.73	.062
Inferior Temporal Gyrus, temporooccipital part	NA	NA	NA	NA
Temporal Fusiform Cortex, anterior division	-0.55	.2040	0.34	.45
Temporal Fusiform Cortex, posterior division	-0.76	.045**	0.40	.37
Temporal Occipital Fusiform Cortex	NA	NA	NA	NA
Grey Matter				
Left Cerebral Cortex	-0.82	.024**	0.54	.20
Left Putamen	-0.75	.0514	0.29	.52
Left Pallidum	-0.77	.042**	0.62	.13
Right Cerebral Cortex	NA	NA	NA	NA
Right Putamen	-0.68	.0959	0.25	.58
Right Pallidum	-0.78	.038**	0.69	.085
*NA indicates lacking data ** Indicates significance.				

Table 2: Correlation between regional Grey matter perfusion and processing speed and whole brain CBF in adult patients with SCD.

Table 3 shows that, when looking at response time, results indicated that adults with SCD generally took more time to complete the cognitive assessment compared to healthy controls (P<0.0001). There were also significant differences in response time between SCD genotypes. Patients with Sβ0 genotypes needed more time to complete the assessment than patients with SC and SS genotypes. Also, patients with SS genotypes were found to need more time than patients with SC genotypes. No statistical significance was found between patients with SC genotypes and healthy controls.

Genotype Compared	Mean Difference (Std Err Dif)	*P*-Value
Sβ° - HC	0.75 (0.08)	<.0001**
Sβ° - SC	0.68 (0.10)	<.0001**
Sβ° - SS	0.43 (0.08)	<.0001**
SS - HC	0.32 (0.05)	<.0001**
SS - SC	0.25 (0.07)	0.002**
SC – HC	0.07 (0.07)	0.7529
**Indicates significance		

Table 3. Response Time Comparison by Patient Group.

Discussion

We found that compared to healthy controls, a small sample of adults with SCD had higher CBF, and lower hemoglobin levels and demonstrated lower processing speed than healthy controls. Additionally, we found that in adult patients with SCD, processing speed was inversely correlated with CBF, suggesting that CBF could be a mechanistic variable mediating cognitive functioning. These findings confirmed and extended previous work regarding the relationship among Hemoglobin, cardiac output, and CBF in patients with SCD. Findings further support the potential presence of silent ischemia which may manifest as deficits in central brain processing speed. Findings also support the utility of processing speed as a marker for silent ischemia in adults, showing correlations between the degree of apparent ischemia, and the degree of anemia and elevation in CBF.

While the transcranial Doppler has been used to screen children for overt stroke, and a cutoff of 200 m/sec [22] is used to start prophylactic transfusions to prevent a first stroke, no such screener exists for adults [23]. It is true that overt cerebral infarction is far less prevalent in adults than in children. But our results and that of other studies show that cerebral ischemia is no less important in adults than in children [24]. It is simply less clinically obvious. Subtle differences in processing speed may occur gradually, and prior publications suggest that patients adapt to these losses by compensating over time [25,26]. Nonetheless, tests such as the Wechsler demonstrate severe deficits that may limit employment or school performance in adults with SCD just as much as for children [27]. Our results suggest more screening for these deficits is clinically warranted, via neuropsychological testing. While testing and screening although appropriate might not be within reach for some providers, a more practical approach for reducing the burden of education and/or employment would be to allow a little more time for adults with SCD to process the information provided to them.

Perhaps for the first time in adults with SCD, our results demonstrated strong inverse relationships be-tween processing speed and regional blood flow in specific areas of the brain associated with cognitive processing. We found individual correlations between regional brain blood flow and processing speed in: the middle frontal gyrus, which serves as a circuit-breaker to interrupt ongoing endogenous attentional processes in the dorsal network and reorient attention to an exogenous stimulus [28]; the precuneus cortex which is often implicated in the sense of self and agency, autobiographical memory, spatial function, and navigation [29,30]; the frontal orbital cortex, which is a hub for sensory integration, the modulation of autonomic reactions, and participation in learning, prediction, and decision making for emotional and reward-related behaviors [31]; the parietal operculum cortex, with functions that include sensory, motor, autonomic and cognitive processing [32], and; the temporal fusiform cortex, which plays a role in processing the printed forms of words [33]. Corroborating these findings was our finding of a positive correlation between whole brain CBF and blood flow to the Middle Frontal Gyrus, Inferior Frontal Gyrus, and pars triangularis. These findings suggest that altered blood flow patterns especially in these regions should be associated with attentional processes in adult SCD patients. The majority of these regions are located in the frontal and temporal regions of the brain. In children with SCD, these regions have been linked to executive functions, attention, and working memory, and processing speed which are crucial for high-level cognitive processes [34,35].

Our findings raise the hypothesis of regional cerebral blood flow autoregulation. They imply that overuse of certain regions of the brain in SCD patients, in order to process information similarly to controls, is necessary, is possibly even a strain on cardiac output, and, like high-output heart failure, may cause fatigue.

Our findings could be translated into clinical practice via patient-provider encounters in the healthcare system. Historically, healthcare providers have always been encouraged to increase their turn-around time when interacting with patients to increase their clinical productivity, but perhaps our results could be an indication that providers need to slow down to allow enough time for patients to process the information provided to them. This is very important given that in the United States, on average 88% of all adults have limited healthcare literacy [36]. This is exacerbated in chronic diseases. Our results further validate these findings. Our results are also consistent with the recommendations of The American Society of Hematology for screening MRIs for adults with SCD. Future guidelines may consider adding screening neuropsychological testing to screen for cognitive deficits and obtain help for those needing social program assistance.

Perhaps more importantly, our results suggest that both cerebral blood flow measured by arterial spin labeling, and cognitive function measured by processing speed tests could be potential biomarkers useful to measure whether new drugs intended to improve hemoglobin in SCD such as voxelotor [37] improve organ function. We are a long way off in making such

claims of organ preservation, but the success of hydroxyurea in reducing mortality in the non-randomized MSH Follow-up study [38] suggests hope for long-term improvements in organ function by eradicating or ameliorating the anemia of SCD. These improvements could include improvements in cerebral ischemia, which may not all be permanent, but possibly reversible.

Limitations

Our study was limited by a small sample size. Larger studies are needed to replicate and expand these findings. Further, to truly evaluate processing speed testing in the SCD population, a direct comparison with well-validated neuropsychological measures would be needed. Finally, with the NIH Toolbox test series and administration, we were unable to determine whether cognitive processing or motor speed was the primary contributor to the observed cognitive impairment. Despite these limitations, we were successfully able to replicate data showing an association between whole-brain CBF and processing speed in adults with SCD.

Conclusion

Early diagnosis of cognitive difficulties in adults with SCD may be beneficial in clinical care. Our study implies such an evaluation should include an objective measurement of baseline cognitive function, an analysis of brain blood flow and ischemia in specific regions, and a determination of the relationships between the two measures, thereby possibly enhancing clinical care and improving quality of life and survival.

Author Contributions

D.S. Research design, implementation, data analysis, statistical analysis, and manuscript writing. J.S. Provided Neuro imaging expertise in study design and paper review. J.J. Provided MRI expertise and paper review. T.C. Provided Psychological expertise and insight and paper review. Y.Z. Assisted with statistical analysis and paper critique. W.S. Provided project oversight and paper review.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of the Virginia Commonwealth University (protocol code HM20019011 approved on 7/12/2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy.

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Conflicts of Interest

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