White Matter Integrity and Processing Speed in Sickle Cell Anemia

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Abstract

Objective: The purpose of this retrospective cross-sectional study was to investigate whether changes in white matter integrity are related to slower processing speed in Sickle Cell Anemia (SCA).

Method: 37 patients with silent cerebral infarction (SCI), 46 patients with normal MRI, and 32 sibling controls (age range 8-37 years), underwent cognitive assessment using the Wechsler scales and 3T MRI. Tract-based spatial-statistics analyses of diffusion tensor (DTI) and neurite orientation dispersion and density imaging parameters (NODDI) were performed.

Findings: Processing speed index (PSI) was lower in patients than controls by 9.34 points (95% CI: 4.635-14.855, \( p=0.0003 \)). FSIQ was lower by 4.14 scaled points (95% CI: -1.066-9.551, \( p=0.1 \)), but this difference was abolished when PSI was included as a covariate (\( p=0.18 \)). There were no differences in cognition between patients with and without SCI, and both groups had lower PSI than controls (both \( p<0.001 \)). In patients, arterial oxygen content, socio-economic status, age, and male sex were identified as predictors of PSI, and correlations were found between PSI and DTI scalars (fractional anisotropy \( r=0.614, p<0.00001 \); \( r=-0.457, p<0.00001 \); mean diffusivity \( r=-0.341, p=0.0016 \); radial diffusivity \( r=-0.457, p<0.00001 \)) and NODDI parameters (intracellular volume fraction \( r=0.364, p=0.0007 \)) in widespread regions.

Conclusion: Our results extend previous reports of impairment that is independent of presence infarction and may worsen with age. We identify processing speed as a vulnerable domain, with deficits potentially mediating difficulties across other domains, and provide
evidence that reduced processing speed is related to the integrity of normal-appearing white matter using microstructure parameters from DTI and NODDI.

Glossary

Analyses of covariance (ANCOVA)
Axial Diffusivity (AD)
Daytime oxygen saturation (SpO₂)
Diffusion Tensor Imaging (DTI)
Fluid-attenuated inversion recovery (FLAIR)
Fractional Anisotropy (FA)
Full-scale Intelligence-Quotient (FSIQ)
Intracellular Volume Fraction (ICVF)
Mean Diffusivity (MD)
Neurite Orientation Dispersion and Density Imaging (NODDI)
Orientation Dispersion Index (ODI)
Prevention of Morbidity in SCA study (POMS)
Processing Speed Index (PSI)
Radial Diffusivity
Sickle Cell Anemia (SCA)
Silent Cerebral Infarction (SCI)
Sleep Asthma Cohort follow-up study (SAC)
Socio-economic status (SES)
Introduction

Even in the absence of silent cerebral infarction (SCI), patients with sickle cell anemia (SCA) are at risk of cognitive impairment that may worsen with age\textsuperscript{1,2} and affect quality of life.\textsuperscript{3} Reduced processing speed is the most prominent impairment,\textsuperscript{4} and may mediate difficulties across other domains,\textsuperscript{5} but the etiology is not well understood, and there are no models of risk factors.

MRI studies have revealed hemodynamic\textsuperscript{6–11} and structural abnormalities\textsuperscript{12–14} that may underlie cognitive impairment. Diffusion tensor imaging (DTI) studies have reported widespread reductions in fractional anisotropy (FA) and increases in radial diffusivity (RD).\textsuperscript{15–17} Diffusion changes have been associated with oxygen desaturation and anemia,\textsuperscript{15} and may relate to reduced processing speed, but functional consequences have yet to be investigated.

A limitation of DTI is that the parameters are not specific to particular microstructural elements of white matter. Neurite orientation dispersion and density imaging (NODDI)\textsuperscript{18} may offer more sensitivity and specificity as it models changes in fiber dispersion (orientation dispersion index; ODI) as well as density of the tissue microstructure (intracellular volume fraction; ICVF). NODDI has been successfully applied in studies of typical development,\textsuperscript{19,20} and clinical populations,\textsuperscript{21} but not yet in SCA.

In the present study, we aimed to (1) investigate differences in processing speed between patients with SCA, grouped by presence of SCI, and controls; (2) explore the effect of processing speed on general intelligence and potential risk factors for deficits; and (3)
examine the relationship between DTI and NODDI-derived indices of white matter microstructure and processing speed.

Methods

Patients

Patients were aged 8-38 years and enrolled on two studies at UCL: the Sleep Asthma Cohort follow-up study (SAC-III)\textsuperscript{22} and Prevention of Morbidity in SCA 2b (POMS)\textsuperscript{23} baseline investigation. Controls were healthy siblings of patients recruited to either study with no history of neurological or psychiatric conditions. Participants were recruited and assessed between 2015-2016. Patients were ineligible for SAC and POMS study participation if they were receiving nocturnal respiratory support at the time of enrolment, participating in a clinical trial evaluating blood transfusion or oxygen therapy, or had chronic lung disease (other than Asthma) or existing respiratory failure. Additional exclusion criteria for the POMS study were hospital admissions for acute sickle complications within one month of enrolment, more than six hospital admissions for acute sickle complications within 12 months of enrolment, overnight oximetry showing mean overnight saturation of less than 90\% for more than 30\% of total sleep time, severe sleep apnea defined by 4\% oxygen desaturation index $>15$/hour, and chronic blood transfusion or transfusion within 3 months of enrolment. For the SAC study, patients were enrolled without regard to past sickle- or sleep-related morbidity or transfusion status.

Standard protocol approvals, registrations, and patient consents
Ethical approval was granted by West London and South Yorkshire Research Ethics Committees, respectively. Full informed consent and assent according to the Declaration of Helsinki was obtained from participants and for children from their parent/guardian.

Cognitive Variables

Full-scale IQ was measured using the Wechsler Abbreviated Scale of Intelligence (WASI 2-subscale IQ; POMS Patients), Wechsler Intelligence Scale for Children (WISC-IV; SAC Patients & Controls <16 years), or the Wechsler Adult Intelligence Scale (WAIS-IV; SAC Patients & Controls >16 years). Processing speed index (PSI) was derived from the WISC-IV or the WAIS-IV using the coding and symbol search subtests. Strong correlations have been demonstrated between editions (WASI/WAIS/WISC) and between the child and adult versions (WISC/WAIS), justifying their inclusion in the same analyses. Assessments were double-scored by trained assessors (JMK, MK, HS, PB) that were blind to disease status. In the event of disagreement or ambiguity, the opinion of a third assessor was sought.

Socio-economic Variables

Education decile was obtained from UK postcode to provide an index of socio-economic status (SES). This scale captures attainment and skills in local areas based on several indicators: average scores for pupils in state-funded schools at ages 7-11 and 14-16 years, absence from state-funded secondary schools, proportion of people staying on in education/training post 16 years, entry to higher education, proportion of working adults with no/low qualifications and language proficiency. Total scores are ranked from one to ten, with one representing the most deprived.
Hematological Variables

Steady-state hemoglobin was recorded from patient medical records using the closest available full blood within six months of the day of cognitive testing. Arterial oxygen content (CaO$_2$) was calculated using:

\[
CaO_2 = 1.34 \times \text{Hemoglobin} \times \text{Oxygen Saturation} + 0.003 \times pO_2
\]

where oxygen saturation (SpO$_2$) was estimated by pulse oximetry on the day of cognitive testing (SAC) or the baseline clinic visit (POMS), and pO$_2$, the partial pressure of oxygen, was assumed to be 100 Torr in room air.

MRI Acquisition

Imaging was conducted within two weeks of cognitive assessment on a 3T Siemens Prisma (Erlangen, Germany) with 80 mT/m gradients and a 64-channel receive headcoil. The MRI protocol included axial T2-weighted (TR=8420ms, TE=68ms, voxel size=0.51x0.51x5.6mm), fluid-attenuated inversion recovery (FLAIR; TR=5000ms, TE=395ms, voxel size=0.65x1x0.65mm), and diffusion-weighted (TR=3050ms, TE=60ms, 2 shells at b=1000s/mm$^2$ & b=2200s/mm$^2$ with 13 interleaved b=0 images, voxel size=2x2x2mm) sequences. A neuroradiologist (DS), blind to disease status, read each participant’s MRI and classified SCI according to the criteria of a hyperintensity on FLAIR of more than 3mm in diameter and present on two planes, as for the Silent Infarction Transfusion trial$^{27}$.

MRI Processing

The diffusion images were pre-processed using TractoR 3.0.7$^{28}$ and FSL 5.0.1.$^{29}$ Images were visually screened for motion, and corrected for susceptibility-induced distortions and eddy current artefact using FSL. Maps for each of the DTI parameters were generated in FSL by
fitting a diffusion tensor model to each voxel using a weighted least squares method. ODI and ICVF maps were generated using the NODDI Matlab Toolbox. DTI and NODDI parameters were analyzed using whole-brain voxel-wise tract-base spatial statistics (TBSS). The specifics of this approach have been described elsewhere. Briefly, each participant’s FA map was aligned with every other FA map, and the most representative map was used as the target. The target was affine-aligned to Montreal Neurological Institute standard-space. All FA maps underwent non-linear transformation to the target and affine transformation to standard-space. FA maps were merged, and voxels with the highest FA at the core of main white matter tracts (threshold: FA=0.2) were used to create a mean FA skeleton. Each participant’s FA map was projected onto the mean FA skeleton, enabling voxel-wise statistical analyses. The maps for the remaining parameters were similarly projected onto the skeleton for analyses. Reference was made to the JHU DTI white-matter atlas to describe the locations of significant voxels.

Statistical Analysis
Analyses were performed in RStudio Desktop 1.0.153 using the companion to applied regression and global validation of linear models packages. Prior to statistical analysis, neurocognitive variables were assessed for normality and equality of variance using the Shapiro-Wilk and Levene’s tests, respectively. For all analyses, results were considered significant at p<0.05. FSIQ and PSI were compared between patient and sibling control groups using type II analyses of covariance (ANCOVA) including education deciles as covariates. The effect of PSI on other domains of cognition was explored by including PSI as a covariate in comparisons between patients and controls in FSIQ. An exploratory multiple linear regression analysis was performed to predict PSI from previously implicated and potentially confounding variables: presence of SCI (SCI+/-), CaO₂, education decile, age,
sex, hydroxyurea use, and transfusion status. Influential measures were assessed by calculating the standardized difference of the beta for each model variable, difference in fits, covariance ratios, Cook's distances and the diagonal elements of the hat matrix. For all patients, inter-subject voxel-wise correlation was performed between DTI and NODDI parameters and PSI, while treating age, sex, and postcode-based education deciles as covariates. Threshold-free cluster enhancement was used to correct for multiple comparisons.

Data Availability
Full anonymised data will be shared at the request from any qualified investigator. Interactive maps from imaging analyses will be uploaded on neurovault where results can be explored and downloaded (https://neurovault.org/collections/3510/).

Results
Patient Characteristics
There were no differences between groups in age or sex (Table 1). Of 83 patients (82 HbSS, 1 Hb S/β0-Thalassemia), 37 (45%) without neurological signs were identified with SCI (SCI+). Lesions were right-sided in eight patients, left-sided in six, and bilateral in twenty-three. Thirteen patients had lesions in more than one region; 35 had frontal lesions, twelve had parietal lesions, two had temporal lesions, and three had occipital lesions. Lesions were most commonly located in the border zones between arterial distributions in the deep frontal white matter. Twenty-nine patients were on hydroxyurea (16 SCI-), five were on chronic transfusions (3 SCI-), and nine had undergone a transfusion within six months of assessment (6 SCI-). Mean hemoglobin, SpO2 and CaO2 were lower than reference norms (Table 1). Eighteen patients (22%, 8 SCI-) were desaturated with SpO2<96%. Mean hemoglobin and
CaO₂ were lower in patients with SCI, but there were no differences in saturation (Fig. 1). This pattern remained when transfused patients were excluded.

Neurocognitive Variables

The data met the ANCOVA and multiple linear regression assumptions. After controlling for the effect of education deciles, mean PSI was lower in patients than controls by 9.34 scaled points (95% CI: 4.635-14.855, \( p=0.0003 \)). FSIQ was lower by 4.14 scaled points (95% CI: -1.066-9.551, \( p=0.1 \)), but this difference was abolished when PSI was included as a covariate (\( p=0.18 \)). There were no differences in cognition between patients with and without SCI, and both groups had lower PSI (Table 1; \( p<0.001 \)), but not FSIQ, compared to controls (Fig. 1). This pattern remained when analyses were repeated in children and adults separately (\( p<0.05 \)).

Multiple linear regression was conducted to predict PSI from previously implicated variables. Of all the predictors, only male sex, CaO₂, and education decile (SES) had zero-order correlations with PSI (Fig 2). However, in the full model, all predictors apart from SCI and chronic transfusion, had partial effects (Table 2). The seven-predictor model was able to account for 25% of the variance in PSI (\( F_8, \; \gamma_4=3.042, \; p=0.005, \; \text{multiple } R^2=0.25 \)). All predictors remained when eleven influential cases, including all five patients on chronic transfusion, were removed from the analysis (\( F_7,\gamma_4=3.404, \; p=0.004, \; \text{multiple } R^2=0.27 \)).

Neuroimaging Metrics

In patients, PSI was correlated with FA, MD, RD, and ICVF (Fig. 3). Specifically, decreases in PSI were associated with decreases in FA across the internal capsule and corpus callosum (\( r_{81}=0.614, \; p<0.00001, \; 30492 \) voxels), and with decreases in ICVF in more widespread regions covering much of the white matter skeleton, with clusters extending throughout the
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corpus callosum, corona radiata, and superior and inferior longitudinal fasciculi \( r_{81}=0.364, p=0.0007, 70659 \) voxels). In addition, decreases in PSI were associated with increases in MD \( r_{81}=-0.341, p=0.0016, 82663 \) voxels) and RD, also in widespread regions, with many clusters located posteriorly, including the posterior corona radiata, and splenium of the corpus callosum, respectively \( r_{81}=-0.457, p<0.00001, 67296 \) voxels). Statistical maps can be viewed and explored interactively at https://neurovault.org/collections/3510/. These correlations remained when examined in SCI+ and SCI- groups separately. There were no relationships between PSI and AD or ODI.

Discussion

This study provides evidence for a relationship between reductions in processing speed and changes in DTI and NODDI parameters in SCA and models risk factors. Patients with SCA showed processing speed deficits, irrespective of presence of SCI. The results suggest that the degree of slower processing speed is related to loss of white matter integrity, and that lower \( \text{CaO}_2 \) and SES may be independent risk factors for deficit.

PSI was lower in patients than controls by nine scaled points. FSIQ was numerically lower by four scaled points, but this difference did not reach significance. Differences in PSI were greater than the often-cited seven-point (one-half of a standard deviation) threshold for clinically meaningful differences\(^{34}\). Moreover, although mean PSI in the patient group fell in the low-average range, 28% of patients had PSI scores that fell in the borderline to extremely-low ranges \( i.e. \) scores of <80) compared to 6% of controls. Taken together, these results suggest that although there is variability within the SCA population, patients with SCA are at risk of clinically significant cognitive difficulties. Controlling for PSI abolished a
numerical difference between patients and controls in FSIQ. These findings extend those of studies with adults\textsuperscript{5} to children with SCA, and are consistent with the notion that slower processing may contribute to other cognitive difficulties. Research on ageing in the general population has similarly highlighted that fast and efficient information processing may be a pre-requisite for higher-order cognitive abilities.\textsuperscript{35}

Although cognitive performance was scaled for age, age was a negative predictor of PSI in our regression model. PSI has yet to be examined longitudinally in SCA, but this finding is in agreement with previous reports and may suggest worsening cognitive function with age in SCA.\textsuperscript{1,4,36} Whilst processing speed has been shown to predict academic attainment in typical development,\textsuperscript{37} further work is required to examine the developmental trajectory of PSI in SCA, and to investigate the effect of deficits on abilities potentially important for life outcomes.

In patients, after correcting for the effects of age and gender, strong correlations were found between PSI and multiple diffusion-derived indices of white matter microstructure. Correlated regions were widespread, and only partially overlapped with lesions, suggesting that slower processing speed is related to the integrity of normal-appearing white matter in SCA. These results provide evidence that cognitive impairment in SCA is related to white-matter integrity using quantitative microstructure parameters from multi-shell diffusion MRI, and highlight the utility of novel diffusion imaging methods in identifying functionally relevant white matter changes that may not be visible on conventional clinical MRI. The results are in agreement with the notion that processing speed is a domain-general cognitive
ability, and may suggest that fast and efficient neural processing is dependent upon the integrity of many tracts simultaneously.

Our findings extend previous reports of white-matter injury in SCA\textsuperscript{16,17} by highlighting possible functional consequences of such injury, and may reflect links between widespread axonal damage, demyelination and/or disorganization of fibers and slower processing speed. It has been suggested that demyelination can be represented in DTI parameters by decreases in FA and increases in RD with no change in AD\textsuperscript{38}, and in NODDI parameters by decreases in ICVF with no change in ODI\textsuperscript{18,39,40}. Our findings are consistent with this pattern. However, MD appeared to be the most sensitive metric, with more than double the number of voxels correlating with PSI than FA. In this sample, therefore, NODDI did not appear to offer improved sensitivity to functionally relevant microstructural changes. Rather, NODDI and DTI metrics were similarly sensitive.

Of note, the histopathological processes that drive changes in imaging parameters are not well established, and although NODDI overcomes certain specificity issues in DTI, regions with crossing fibers remain problematic. Moreover, NODDI fixes intrinsic diffusivity to an a priori value, and there is scope to further optimize the choice of this value in the model. Before diffusion changes can confidently be referred to as markers of specific microstructural changes, further work comparing diffusion metrics not only to each other, but also to histology measures, is required.

In this sample, 44\% of patients were identified with SCI. Lesions were most commonly bilateral, and located in the borderzones between arterial distributions in the frontal white matter. These findings are consistent with previous studies employing similar MRI protocols
and criteria for SCI\textsuperscript{41}. Hemoglobin was lower in patients with SCI than in patients reported radiologically as normal, but SpO\textsubscript{2} was not. Differences in hemoglobin remained after patients on transfusion were removed from the analysis, suggesting more severe anemia in patients with SCI.

However, there were no differences in FSIQ or PSI as a function of SCI, irrespective of age. Similarly, there were no differences between patients with and without SCI in relationships between white matter microstructure parameters and processing speed, and correlated regions only partially overlapped with lesions, confirming the contribution of loss of integrity in normal-appearing white matter to reduced processing speed. These findings accord with recent studies\textsuperscript{4,15} and, taken together, suggest that neither white matter abnormalities nor cognitive deficits are explicable solely by presence of SCI; other factors, whether psychosocial or disease-related, are likely to be involved.

In patients, education-decile was associated with PSI, an indication that this postcode-based index was able to capture some of the variance in SES that may affect cognition. Previous research has similarly highlighted that lower maternal educational may be a risk factor for slower processing speed in SCA.\textsuperscript{36} Moreover, in our regression model, education decile was identified as an independent predictor of PSI, further suggesting that socio-economic and educational deprivation may be risk factors for slower processing speed in SCA patients.

However, any effects of education decile were controlled for in our comparisons between patients and controls in cognition, and the control group in this sample were siblings; therefore, SES differences are unlikely to have had a major effect on the difference in PSI reported in the present study. Moreover, in our exploratory model, CaO\textsubscript{2}, age, and male sex were also identified as predictors of PSI, suggesting that there may be multiple causal
pathways to cognitive deficits in SCA, in which disease and socio-economic factors may interact.

One explanation for this pattern of results may be that SCI is associated with acute anemic events, where inadequate perfusion within the watershed distribution leads to infarction in brain tissue. Acute anemic events are more common in patients with lower steady-state hemoglobin, perhaps accounting for the relationship between anemia severity and SCI observed here. By contrast, white matter damage that is below the resolution of clinical MRI may be the result of less severe, but sustained, exposure to hypoxia secondary to compensatory increases in CBF accompanied by reduced cerebrovascular reserve and increased oxygen extraction fraction. This damage may be more diffuse and therefore more functionally significant, potentially explaining the presence of relationships between PSI and diffusion metrics, the absence of relationships with SCI, and the links between both types of damage and anemia severity. The additional identified predictors of PSI are not inconsistent with this explanation, as hydroxyurea-use and recent crisis-related transfusion both increase hemoglobin and SpO₂, and are prescribed more often in patients with greater disease burden, and there is evidence that males have more severe disease courses. These findings may explain previous discrepancies in the literature, and underscore the need for researchers and clinicians to consider the interplay among risk factors, as well as potential confounding effects of treatment.

The identification of CaO₂ as an independent predictor of PSI is consistent with previous reports of relationships between lower SpO₂ and cognitive impairment and white matter damage in SCA, and with reports of processing speed deficits in the general pediatric population with iron-deficiency anemia and sleep-disordered breathing as well as in those living at altitude. Taken together, these results may suggest improvement of deficits
following interventions that target hypoxemic exposure. Overnight respiratory support appears to be safe and viable in children with SCA, and is a treatment option that may hold promise.23

The study utilized medical records, and there was significant between-patient variation, with time between steady-state full blood count and SpO2 measurement to cognitive assessment varying from 1 day to 6 months. There are few data on the stability of these measures over time. Although low SpO2 predicts neurological complications in SCA,48 in patients with hemoglobinopathies, right-shift of the oxygen dissociation curve and the presence of carboxyhemoglobin and methemoglobin, may lead to over-estimation.49 Daytime and nocturnal SpO2 are not necessarily correlated in SCA, with a greater proportion of patients experiencing desaturation at night.50 Further, we used postcode rather than direct measures of socio-economic status (SES), which were unavailable for the majority. Due to these limitations, we were not able to comprehensively model specific disease and socio-economic risk factors for slower processing speed.

Further work is required not only to determine risk factors for and mechanisms of white matter injury and cognitive impairment in SCA, but also to establish whether the underlying pathology is preventable or reversible. To this end, future work will need to disentangle the effects of SCA pathology, and to separate them from the effects of psychosocial factors. As this will require regression and potentially more advanced statistical modelling, future quantitative MRI studies are warranted.

This study provides evidence that reduced processing speed is correlated with widespread white matter abnormalities using quantitative microstructure parameters from multi-shell diffusion MRI. Although lesion status is commonly used as a proxy of disease severity, the results from this study indicate cognitive difficulties in the absence of SCI and highlight the
consequences of possible damage to normal-appearing white matter. Clinicians should therefore assess for cognitive difficulties irrespective of presence of SCI, and future research should employ diffusion MRI as a tool to further investigate potential mechanisms of cognitive impairment in SCA, as well as to monitor therapies designed to ameliorate cognitive dysfunction. This study adds to a growing body of evidence indicating imaging abnormalities and cognitive impairment that may worsen with age in SCA, which together highlight the need to investigate the effect of early treatment delivery.

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### Sample Demographics and Cognitive Performance

|                           | Controls (n=32) | SCI- (n=46) | SCI+ (n=37) |
|---------------------------|----------------|-------------|------------|
| **Median Age**            | 15·26 (8-30y)  | 14·62 (8-37y) | 16·34 (8-36y) |
| **Sex**                   | 14M (43%)      | 23M (50%)   | 20M (54%)  |
| **Socio-Economic Status (SES)** | 4·94 (2·26) | 5·370 (2·26) | 5·11 (1·97) |
| **Full-scale IQ (FSIQ)**  | 96·50 (11·62)  | 93·72 (12·99) | 90·68 (13·52) |
| **Processing Speed Index (PSI)** | 97·81 (11·32) | 90·07 (14·28) | 86·49 (11·26) |
| **Haemoglobin (g/L)**     | -              | 90·96 (13·66) | 84·54 (12·92) |
| **Oxygen saturation (SpO₂)** | -             | 97·37 (1·95) | 96·46 (3·08) |
| **Oxygen Content (CaO₂, mL/dL)** | -              | 12·17 (1·79) | 11·25 (1·87) |

| Inferential Statistics | Post-Hoc |
|------------------------|----------|
| $F_{2,112}=0·398$, $p=0·6723$ | NS       |
| $F_{2,111}=1·799$, $p=0·1702$ | NS       |
| $F_{2,111}=7·876$, $p=0·0006^*$ | a, b     |
| $t_{78·839}=2·192$, $p=0·0313^*$ | -        |
| $t_{58·096}=1·564$, $p=0·1233^-$ | -        |

**Table 1.** Tabled values are summary and test-statistics. SCI-; patients without silent cerebral infarction, SCI+; patients with cerebral infarction. Post-Hoc: a. Controls > SCI+; b. Controls > SCI-; c. SCI- > SCI+, NS; not significant
## Regression Coefficients for variables predicting Processing Speed Index

| Variable      | β    | b     |
|---------------|------|-------|
| SCI           | -0.009 | -0.229 |
| Age           | -0.301** | -0.649 |
| Male Sex      | -0.278** | -7.228 |
| CaO₂          | 0.311** | 2.172 |
| SES           | 0.283*  | 1.734 |
| Hydroxurea    | -0.211^  | -5.760 |
| Tx. Crisis    | -0.190^  | -7.955 |
| Tx. Chronic   | -0.020   | -1.092 |

### Table 2.
Tabled values are standardised regression coefficients ($β$), and unstandardised regression coefficients (b) from the exploratory multiple linear regression analysis.

SCI; Silent Cerebral Infarction, SES: Socio-economic Status. Tx; Transfusion.

^p<0.1, *p<0.5, **p<0.01
Figure Legends

**Figure 1.** Neurocognitive and hematological variables.
Top: Differences in Hemoglobin (Hgb; Left), Arterial Oxygen Content (CaO₂; Middle), and Oxygen Saturation (SpO₂), between patients with (SCI+) and without (SCI-) silent cerebral infarction. Bottom: Differences in processing speed index (PSI) between healthy controls, and patients (SCI-, SCI+). *p <0.05; ** p<0.01 (after Bonferroni correction for multiple comparisons). Horizontal line represents mean PSI in the normative population.

**Figure 2.** Correlations between predictors of processing speed
Correlogram visualizing relationships between variables included in the exploratory regression analysis. Values are zero-order Pearson correlation coefficients. Shaded areas represent significant relationships. Blue colors represent positive relationships, whereas red colors represent negative relationships. Intensity signifies the strength of relationships.

**Figure 3.** Correlations between diffusion metrics and processing speed
Left: Blue voxels indicate areas in which fractional anisotropy correlated with PSI (34392 voxels, p<0.05). Red voxels indicate areas in which intracellular volume fraction correlated with PSI (70659 voxels, p<0.05). Right: Yellow voxels indicate areas in which radial diffusivity correlated with PSI (67296 voxels, p<0.05). Purple voxels indicate areas in which mean diffusivity correlated with PSI (82663 voxels, p<0.05). Results were age, sex, education decile (SES), and threshold-free cluster enhancement corrected and overlaid on the group white matter skeleton (green) and the study-specific mean fractional anisotropy template.
