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# Relation between white matter integrity, perfusion, and processing speed in early-stage schizophrenia

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A B S T R A C T

*Objective:* Cerebral blood flow (CBF) plays a critical role in the maintenance of neuronal integrity, and CBF alterations have been linked to deleterious white matter changes. Several studies report CBF and white matter structural alterations individually. However, whether and how these pathological changes relate to each other remains elusive. By using our cohort of individuals with early-stage schizophrenia, we investigated the relationship between CBF and white matter structure.

*Method:* We studied 51 early-stage schizophrenia patients and age- and sex-matched healthy controls. We investigated the relationship among tissue structure (assessed with diffusion weighted imaging), perfusion (accessed by pseudo-continuous arterial labeling imaging), and neuropsychological indices (focusing on processing speed). We focused on the corpus callosum, due to its major role in associative functions and directness on revealing the architecture of a major white matter bundle. We performed mediation analysis to identify the possible mechanism underlay the relationship among cognition and white matter integrity and perfusion.

*Results:* The CBF and the fractional anisotropy (FA) were inversely correlated in the corpus callosum of early-stage schizophrenia patients. While CBF negatively correlated with processing speed, FA correlated positively with this cognitive measure. These results were not observed in controls. Mediation analysis revealed that the effect of FA on processing speed was mediated via the CBF.

*Conclusions:* We provide evidence of a relationship between brain perfusion and white matter integrity in the corpus callosum in early-stage schizophrenia. These findings may shed the light on underlying metabolic support for structural changes with cognitive impact in schizophrenia.

## 1. Introduction

There is plentiful evidence supporting that psychotic disorders, schizophrenia in particular, are likely linked to abnormal interactions among brain regions, rather than regional pathology per se (Nath et al., 2021). These interactions include abnormal synchronies on blood fluctuations among remote brain areas (the "functional networks"), and abnormal physical communication mediated by white matter connections (Prasad et al., 2022; Kraguljac et al., 2021; Maximo et al., 2021; Rashid and Calhoun, 2020; Chien et al., 2022). Others and we had found that both types of abnormalities are detectable since early stages of psychosis (Faria et al., 2021; Shim et al., 2010; Brüne et al., 2011), and that several abnormalities show clear relationship with social and cognitive domains (Faria et al., 2021; Fusar-Poli et al., 2007; Metzak et al., 2021).

The corpus callosum, the main associative bundle for interhemispheric communication, has been a central area for investigating these relationships (Berkovitch et al., 2021; Kelly et al., 2021; Lee et al., 2022; Keshavan et al., 2002; Pol et al., 2004; Arnone et al., 2008; Alba-Ferrara and de Erausquin, 2013). By the preponderant unidirectional organization of axonal bundles, the corpus callosum is less affected by the "crossing fiber" issue; metrics extracted from clinical diffusion weighted MRIs (DWI) in corpus callosum reflect the microscopic tissue properties more directly than in other peripheral white matter areas. Given these biological and technical particularities, it is not surprising that previous studies focused at corpus callosum to access the relationship between speed of information processing and white matter fractional anisotropy (FA) (Kochunov et al., 2017; Tyburski et al., 2021). This relationship exists and is stronger in populations that present a broad range of performance and deficits in processing speed, such as patients with

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schizophrenia (Haining et al., 2020). Furthermore, diffusion abnormalities in corpus callosum were also related to positive symptoms (Fitzsimmons et al., 2020; Carletti et al., 2012).

Questions remain about the mechanism and extent that diffusion abnormality may influence axonal transmission velocities and eventually result in "connectivity" deficit. An inverse correlation between cerebral blood flow (CBF) in the white matter and the anisotropy of water diffusion has been observed (Aslan and Lu, 2010).The CBF plays a critical role in the maintenance of neuronal integrity, is one of the potential biomarkers of cognitive performance (De Vis et al., 2018), and is correlated to schizophrenia symptoms (du Sert et al., 2022). Studies using 18FDG PET hypothesized that the observed increased metabolic rates in the white matter of patients with schizophrenia may be related to inefficient and more energy consuming information-processing in the brain (Buchsbaum et al., 2007).

Although speculative, the hypothesis that the energy demand (and, consequently, the blood supply) is inversely correlated with myelin sheath and its density, has found support in several conditions. The white matter CBF is higher and the FA is lower in older people compared to younger people (Lu et al., 2011; Salat et al., 2005). Pathology severity (e.g., in multiple sclerosis) has been associated to increased CBF in normal-appearing white matter (Zhou et al., 2022). Patients at clinical high risk for psychosis exhibit increased striatal CBF (Hubl et al., 2018), and those with schizophrenia show a mismatch in white/gray matter blood perfusion associated to reduced white matter integrity (Wright et al., 2015).

In terms of cognition, a reduced speed of processing information in patients with schizophrenia is often attributed to diminished myelination (Bruce et al., 2017). As myelination increases the velocity of signal and reduces the metabolic burden, a poor myelinated bundle would require more energy and slow the performance of a given task. If this is true: 1) white matter integrity measures, such as FA, and energy consumption indices, such as relative cerebral blood flow (rCBF), should be inversely related; 2) processing speed should be directly related to FA, while 3) inversely related to rCBF.

We investigated these hypotheses in individuals with early-stage schizophrenia. Looking at early stages of disease minimizes, although does not exclude, the confounding effects of chronicity and medication. We focused on the corpus callosum because of its major role as association bundle and its directness in reflecting the tissue structure in DWI. Using conventional imaging acquisitions for DWI and CBF, and an automated and accessible method for post-processing, we increased the reproducibility of this study, as our findings are easily testable and extensible to other cohorts. We tested the population-specificity of your findings by analyzing a matched group of healthy controls. Finally, we tested for mediation among white matter integrity, perfusion and cognition.

## 2. Materials and methods

### 2.1. Participants

This study was approved and conducted using guidelines established by the Johns Hopkins School of Medicine Institutional Review Board. Individuals with early-stage schizophrenia and healthy controls were recruited to the Johns Hopkins Schizophrenia Center. Recruitment was limited to individuals between 15 and 35 years of age with the onset of psychosis within 24 months of the study. The diagnosis of schizophrenia was determined according to the DSM-IV. Participants with an estimated intellect below 70 on the Hopkins Adult Reading Test (Schretlen et al., 2009) were excluded. Individuals with active substance abuse or urine drug screen positive for illicit substance use, except marijuana, were excluded from participation. Individuals were also excluded if they were pregnant or taking anti-inflammatory agents. Healthy controls were additionally screened and excluded for a family history of schizophrenia or schizophrenia-spectrum disorder.

Neuropsychological assessments were conducted for all the participants according to a methodology published by our group (Kamath et al., 2019; Ishizuka et al., 2010; Schretlen et al., 2007). Briefly, there were 24 individual scores from 11 neurocognitive tests grouped into six domains:

1) processing speed (calculated from the combined scores of the Grooved Pegboard test and the Salthouse test);
2) attention/working memory (Digit Span and Brief Attention Memory test);
3) verbal learning and memory (Hopkins Verbal Learning test);
4) visual learning and memory (Brief Visuospatial Memory test);
5) ideational fluency (Ideational Fluency assessment for Word Fluency and Acceptable Designs); and
6) executive functioning (Modified Wisconsin Card Sorting test). "Adjusted" scores were calculated after adjusting for age, sex, and race.

We included individuals with complete neuropsychological and imaging evaluation, with at least the following MRI modalities (detailed bellow): T1-WI, ASL, DWI; comprising the final sample of 51 patients and 51 age and sex matched controls. As some of the patients may experience exacerbation of the symptoms within this initial period of time (24 months after the onset of schizophrenia), we will use the term "early-stage schizophrenia" rather than "first episode psychosis". Patients were screened in a remission of the disease. The symptoms were evaluated through the Scale for the Assessment of Negative Symptoms (SANS) and the Assessment of Positive Symptoms (SAPS) (Andreasen, 1990). These indices are calculated by the sum of global ratings in each symptom category. At the time of study visit, 5 patients were treated with first generation of antipsychotics (APs), 38 were on second generation of APs, and 5 were on third generation of APs; 3 patients were unmedicated.

### 2.2. Image analysis

The MRI was obtained in the same day as the neuropsychological evaluation, on a Philips 3T scanner. The T1-MPRAGE image was acquired for anatomical reference and spatial normalization, in sagittal orientation, with voxel size $1 \times 1 \times 1.2$ mm$^3$, TR/TE/TI 2700/3.1/900 ms. Pseudo-continuous ASL (pCASL) was then used to obtain estimates of rCBF. Thirty control and label pairs of images were acquired with the following parameters: labeling duration = 1650 ms, post-labeling delay = 1525 ms, TR/TE = 4000/12 ms, flip angle = 90°, matrix size = $80 \times 80$, voxel size = $3 \times 3 \times 5$ mm (Kraguljac et al., 2021), 35 slices, no gap, duration = 5 min. The DWI had axial orientation, TR/TE = 2000/30 ms, 32 gradients, b-factor = 1000, reconstructed voxel size = $0.8281 \times 0.8281 \times 2.2$ mm, and 70 slices.

MRI analysis was performed using a public web-based service for multi-contrast imaging segmentation and quantification, the MRICloud (Mori et al., 2016; Li et al., 2019). The tensor reconstruction and quality control of diffusion tensor images (DTI) in MRICloud is done as in DtiStudio (www.MRIStudio.org). Both DTI and pCASL were automatically post-processed and segmented in MRICloud as reported in our previous publications (Li et al., 2019; Zhang et al., 2010). Regions of interest (ROIs), generated from the T1-based brain segmentation, were applied to yield structure-based CBF values and DTI indices (FA; mean diffusivity, MD; radial diffusivity, RD; and

axial diffusivity AD). To minimize the influences of physiological factors that affect the CBF globally (Aslan and Lu, 2010), such as breathing pattern and consumption of caffeine, we calculated the "relative" CBF (rCBF), which corresponds to the CBF normalized by the whole brain CBF.

### 2.3. Statistical analysis

We used Spearman correlations and general linear models to investigate the association between neurocognition, diffusion metrics (FA, MD, RD, AD), and rCBF in the corpus callosum, both adjusting and not adjusting for confounding factors (age, gender, race, duration of illness (DOI), and AP medication dosages, converted to chlorpromazine equivalents (CPZ) using published reference tables (Woods and Equiv, 2005)). We also tested the association between perfusion (rCBF) and diffusion metrics. Mediation analysis (Chén et al., 2018; Chen et al., 2022) aimed to identify the possible mechanism underlay the relationship among processing speed, rCBF and FA. The significance of indirect effects was measured using bootstrapping procedures. Unstandardized indirect effects were computed for each of 1000 bootstrapped samples (Fritz et al., 2012; MacKinnon et al., 2002; Preacher and Hayes, 2008; Steffener, 2021), and the 95% confidence interval was computed by determining the indirect effects at the 2.5th and 97.5th percentiles. The statistical analysis was performed in R3.5.1. The mediation analysis was performed with the R package "mediation"

## 3. Results

Basic demographic and clinical profiles are presented in Table 1. Male were predominant in the early-stage schizophrenia group (84%), reflecting the disease prevalence. The early-stage schizophrenia and healthy control groups did not differ with respect to age, sex, and race, since they were matched as much as possible in such characteristics. Although controls had more years of education, the groups did not differ with regard to parental education, an estimate of potential that minimizes the confound of illness (Goldberg et al., 1990; Resnick, 1992). The early-stage schizophrenia group had significant lower processing speed compared to controls.

According to previous mechanistic hypothesis (Bruce et al., 2017), diminished myelination would increase metabolic burden and decrease the speed of information processing in patients with schizophrenia. Experimentally, this would reflect in an inverse relation between white matter integrity (as measured by FA) and metabolic/perfusion indices (as measured by rCBF), and by the relation of such indices with processing speed (positive with FA, negative with rCBF).

In fact, the rCBF negatively correlated with FA in the corpus callosum in the early-stage schizophrenia group (rho = −0.37, p-value = 0.0078) but not in controls, as shown in Fig. 1. Although an inverse relationship was observed in other brain regions, it achieved significant level (p-value<0.05) only in the corpus callosum (Table 3). The subsegments of the corpus callosum (genu, body, splenium) (Djamanakova et al., 2014) showed such negative relationship between rCBF and FA, although none was significant at p-value<0.05. This is likely due to the increase of noise that happens by looking to small regions of interest. On the other hand, it indicates that this relationship is widespread in the corpus callosum, although of small effect size. The genu showed stronger relationship between FA and rCBF (rho = −0.18, p-value = 0.07), compared to the body (rho = −0.12, p-value = 0.28) and the splenium (rho = −0.15, p-value = 0.39). Note that the genu is primarily composed by transversal commissural fibers connecting the frontal lobes, associated to cognitive functions.

The processing speed negatively correlated with rCBF ($R^2 = 0.15$, p-value = 0.002) and positively correlated with FA ($R^2 = 0.07$, p-value = 0.003), in early-stage schizophrenia but not in controls (p-values 0.89 for rCBF and 0.98 for FA) (Fig. 1). These correlations remained significant after adding age, sex, race, DOI, and antipsychotic medication dosage as covariates (p-value for rCBF = 0.007; p-value for FA = 0.033). None of these covariates show significant independent correlation with processing speed. The mediation analysis showed that the effect of FA on processing speed was mediated via the rCBF. The indirect effect was 0.51 (-0.85 (effect of rCBV in processing speed) * −0.7 (effect of rCBV in FA)); 95% confidence interval ranged from 0.07 to 1.2, p-value = 0.018.

**Table 1**
Demographic and neuropsychologic profile. Race is defined here according to the Revisions to the Standards for the Classification of Federal Data on Race and Ethnicity (Classification of federal data on, 1997). By this classification, "white" is a person having origins in any of the original peoples of Europe, the Middle East, or North Africa and "black or African American" is a person having origins in any of the Black racial groups of Africa. CPZ stands for chlorpromazine equivalent dose. The CPZ calculation excluded 14 patients that were not medicated at the time of the evaluation. * for categorical variables, differences between groups were evaluated with Fisher exact test and the "t-statistics" is actually the odds ratio.

| | early stage schiz. (n = 51) | controls (n = 51) | t-statistics | P-value |
|---|---|---|---|---|
| Age | 22.4 ± 4.2 | 232.9 ± 3.4 | −0.75 | 0.45 |
| Sex (male/female) | 43/8 | 41/10 | 1.3* | 0.8 |
| Race (black/white) | 28/23 | 31/20 | 0.78* | 0.68 |
| Parents education level (years) | 15.4 ± 2.7 | 15.0 ± 2.6 | 1.06 | 0.289 |
| Subjects education level (years) | 12.2 ± 2.5 | 13.9 ± 2.6 | −4.06 | <0.0001 |
| Age at onset (years) | 21.3 ± 4.1 | N.A. | N.A. | N.A. |
| Duration of illness (years) | 1.04 ± 0.8 | N.A. | N.A. | N.A. |
| Medication (CPZ) | 334.6 ± 247.3 | N.A. | N.A. | N.A. |
| SANS | 8.61 ± 3.76 | N.A. | N.A. | N.A. |
| SAPS | 3.8 ± 2.6 | N.A. | N.A. | N.A. |
| **Neurocognitive function** | | | | |
| Processing speed | 100.55 ± 13.41 | 114.51 ± 8.21 | −6.33 | <0.0001 |
| Processing speed adjusted | 85.86 ± 19.92 | 109.88 ± 12.91 | −7.22 | <0.0001 |
| Attention/working memory | 89.7 ± 14.86 | 105.14 ± 11.59 | −5.85 | <0.0001 |
| Attention/working memory adjusted | 83.84 ± 18.27 | 105.62 ± 14.58 | −6.65 | <0.0001 |
| Verbal memory | 91.37 ± 15.09 | 106.71 ± 12.35 | −5.61 | <0.0001 |
| Verbal memory adjusted | 86.39 ± 16.83 | 105.09 ± 14.55 | −6.00 | <0.0001 |
| Visual memory | 100.73 ± 12.22 | 112.99 ± 10.5 | −5.43 | <0.0001 |
| Visual memory adjusted | 86.64 ± 15.63 | 104.11 ± 14.04 | −5.93 | <0.0001 |
| Ideational fluency | 91.6 ± 12.91 | 108.79 ± 9.44 | −7.67 | <0.0001 |
| Ideational fluency adjusted | 92.19 ± 16.12 | 115.39 ± 10.6 | −8.58 | <0.0001 |
| Executive functioning | 91.12 ± 12.67 | 101.56 ± 10.4 | −4.54 | <0.0001 |
| Executive functioning adjusted | 86.23 ± 17.7 | 101.76 ± 14.58 | −4.83 | <0.0001 |
| **MRI indices in corpus callosum** | | | | |
| rCBF | 0.44 ± 0.6 | 0.45 ± 0.6 | −0.73 | 0.46 |
| FA | 0.55 ± 0.03 | 0.58 ± 0.03 | −3.72 | 0.0003 |
| MD | 0.92 ± 0.04 | 0.92 ± 0.03 | −0.46 | 0.99 |
| RD | 0.59 ± 0.04 | 0.58 ± 0.03 | −0.89 | 0.39 |
| AD | 1.59 ± 0.05 | 1.61 ± 0.04 | −1.22 | 0.13 |

The verbal memory also negatively correlated with rCBF ($R^2 = 0.19$, p-value = 0.0008) and positively correlated with FA ($R^2 = 0.07$, p-value = 0.03), in early-stage schizophrenia but not in controls (p-values 0.08 for rCBF and 0.37 for FA) (Fig. 1). Again, these correlations remained significant after adding age, sex, race, DOI, and antipsychotic medication dosage as covariates (p-value for rCBF = 0.001; p-value for FA = 0.018). None of these covariates show significant independent correlation with verbal memory. The mediation analysis showed that the effect of FA on verbal memory was mediated via the rCBF. The indirect effect was 0.49 (-0.7 (effect of rCBV in processing speed) * −0.7 (effect of rCBV in FA)); 95% confidence interval ranged from 0.08 to 1.3, p-value = 0.015.

The other diffusivity indices (MD, RD, AD) did not show significant correlation either to neurocognitive indices (Table 2) or to rCBF (p-

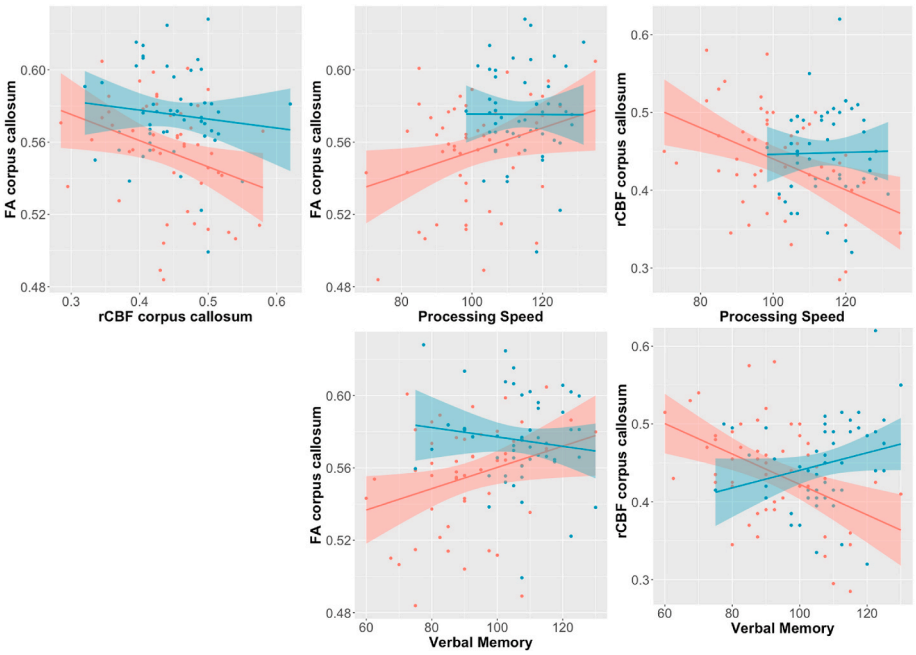


**Fig. 1.** The relations between rCBF and FA, and of these indices with processing speed and with verbal memory, in the corpus callosum. These relationships were significant in early stage schizophrenia patients (red) but not in controls (blue).

**Table 2**
Correlation of neurocognitive indices with diffusion indices and with rCBF.

| | rCBF | | FA | | MD | | RD | | ADC | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $R^2$ | p-value | $_R2$ | p-value | $R^2$ | p-value | $R^2$ | p-value | $R^2$ | p-value |
| **Processing Speed** | **−0.41** | **0.003** | **0.30** | **0.03** | 0.02 | 0.87 | −0.03 | 0.86 | 0.11 | 0.46 |
| **Attention/Working Memory** | −0.20 | 0.16 | **0.30** | **0.03** | −0.07 | 0.62 | −0.09 | 0.55 | −0.02 | 0.87 |
| **Verbal Memory** | **−0.45** | **0.001** | **0.30** | **0.03** | −0.07 | 0.61 | −0.04 | 0.76 | −0.10 | 0.46 |
| **Visual Memory** | −0.16 | 0.27 | 0.22 | 0.13 | 0.02 | 0.88 | −0.01 | 0.92 | 0.08 | 0.58 |
| **Ideation Fluency** | −0.26 | 0.06 | 0.19 | 0.19 | −0.03 | 0.82 | −0.11 | 0.46 | 0.11 | 0.44 |
| **Executive Memory** | −0.23 | 0.10 | 0.27 | 0.06 | −0.04 | 0.76 | −0.16 | 0.27 | 0.17 | 0.22 |

**Table 3**
Correlation between FA and rCBF in the white matter.

| | rho (rCBF vs. FA) | p-value |
|---|---|---|
| **deep white matter** | | |
| projection fibers | 0.15 | 0.20 |
| posterior thalamic radiation | 0.11 | 0.44 |
| anterior corona radiata | 0.04 | 0.77 |
| superior corona radiata | 0.10 | 0.47 |
| posterior corona radiata | 0.20 | 0.16 |
| superior longitudinal fasciculus | 0.14 | 0.31 |
| sagittal stratum | −0.16 | 0.27 |
| **peripheral white matter (beneath gyri)** | | |
| superior frontal | 0.07 | 0.63 |
| middle frontal | −0.03 | 0.83 |
| inferior forntal | −0.13 | 0.36 |
| precentral area | −0.08 | 0.58 |
| postcentral area | −0.07 | 0.64 |
| superior parietal | 0.18 | 0.21 |
| cingulate | 0.05 | 0.74 |
| anguar | 0.07 | 0.63 |
| pre-cuneus | 0.03 | 0.81 |
| cuneus | −0.21 | 0.14 |
| lingual | 0.11 | 0.44 |
| fusifrm | −0.09 | 0.55 |
| superior occipital | 0.26 | 0.07 |
| inferior occipital | 0.21 | 0.13 |
| middle occipital | 0.02 | 0.91 |
| superior temporal | −0.14 | 0.31 |
| inferior temporal | −0.02 | 0.90 |
| middle temporal | −0.19 | 0.19 |

values = 0.9, 0.6, 0.4 for MD, RD, AD, respectively). Neither negative nor positive symptoms (SANS or SAPS) at the time of the scan significantly correlated to diffusivity indices or to rCBF (Table 4). There was a marginally significant correlation between SANS and processing speed.

## 4. Discussion

This study showed an inverse relationship between white matter integrity (represented by FA, from DWI) and brain perfusion (represented by rCBF, from pCASL) in the corpus callosum of early-stage schizophrenia patients. Processing speed and verbal memory

**Table 4**
Relationship of negative and positive symptoms (measured by the Scale for the Assessment of Negative Symptoms, SANS, and the Assessment of Positive Symptoms, SAPS) at scan time, with neurocognitive indices, with FA, and with rCBF.

| | SANS | | SAPS | |
|---|---|---|---|---|
| | rho | p value | rho | p value |
| FA | −0.21 | 0.14 | 0.01 | 0.94 |
| rCBF | 0.27 | 0.057 | 0.21 | 0.15 |
| Processing Speed | −0.29 | 0.04 | 0.18 | 0.22 |
| Attention/Working Memory | −0.05 | 0.74 | −0.05 | 0.73 |
| Verbal Memory | −0.12 | 0.41 | −0.05 | 0.74 |
| Visual Memory | −0.18 | 0.22 | 0.02 | 0.88 |
| Ideational Fluency | −0.27 | 0.06 | 0.09 | 0.55 |
| Executive Functioning | 0.05 | 0.74 | −0.22 | 0.14 |

correlated positively with FA and negatively with rCBF. The effect of FA on processing speed and verbal memory was mediated via the rCBF. From the mechanistic point-of-view, the mediation effects observed and the inverse relationship between CBF and FA in early-stage schizophrenia support the hypothesis of an increased metabolic demand for corpus callosum that has an abnormal microstructural organization and is less efficient. In analogy to a bare electric wire, a poor myelinated (or "insulated") bundle (low FA) would require more energy (high rCBF) and would be less efficient in a given task.

Aligned with this hypothesis, Wright et al. (2015) showed that processing speed deficits in patients with schizophrenia are explained by reduced whole brain white matter integrity, mediated by a mismatch in white-gray matter blood perfusion (Wright et al., 2015). Similarly to Wright's, but focusing in corpus callosum due to its role in processing speed, we found association between cerebral perfusion, white matter integrity, and neurocognitive indices (processing speed and verbal memory). We did not find such significant relationship in other white matter regions. However, this can result from the fact that the diffusion tensor models are highly sensitive to crossing fibers, which is particularly important in the sub cortical associative areas. Therefore, we cannot exclude the hypothesis that the coupling between metabolism (CBF) and white matter structure (FA) is a more general phenomenum. By studying early-stage schizophrenia patients and minimizing the effects of chronicity and medication, our research supports the idea that the structural and perfusion changes observed in schizophrenia conform to an endophenotype of the psychosis, rather than to confounding effects.

The cognitive deficits in schizophrenia are general phenomena, more strongly correlated with functional outcomes than symptoms (Green et al., 2004). There is evidence that the process mediating these impairments is part of the neurodevelopmental risk for schizophrenia (Khandaker et al., 2011). Processing speed is disproportionately impaired in patients with schizophrenia (Leeson et al., 2010; Dickinson et al., 2007), being one of fundamental causes of cognitive deficits (Joyce, 2013; Dickinson et al., 2011). Although we found similar relation between all the neuropsychological factors and the imaging indices in corpus callosum (i.e. positive for FA and negative for rCBF), this relation achieved significant level (at p-value $<0.05$) for processing speed and verbal memory only (Table 2). While this can be partially attributed to the small sample used, it also points to disproportional deficits in these domains. Relatedly, the fact that processing speed is linked to the integrity of myelinated axons (Kochunov et al., 2017; Tyburski et al., 2021; Alloza et al., 2016; Faria et al., 2019; Roalf et al., 2015), which can now be studied by computational neuroscience, makes the basis of this deficit potentially more easily tractable. From the practical point-of-view, this may lead to insights into the causative abnormal mechanisms of schizophrenia as well as may guide methods for symptoms remediation (Wykes et al., 2011). For example, it could be speculated that metabolism may be an important predictor of function and that the maintenance of vascular health is a critical point of intervention in the prevention of cognitive impairments, especially at the early stage.

The relatively small sample is the most obvious limitation of this study. A post-hoc power analysis shows that with our sample of 51 early schizophrenia individuals, our power to detect correlations at $R^2$ of 0.3 and 0.4 was 0.7 and 0.8, respectively. Samples of 67 and 92 individuals would be needed to detect correlations at $R^2$ of 0.3 with power of 0.8 and 0.9, respectively. Samples of 153 and 211 individuals would be needed to detect correlations at $R^2$ of 0.2 with power of 0.8 and 0.9, respectively. Furthermore, in this cross-sectional study, we cannot establish a causal direction among the effects of CBF and FA on cognition. Finally, the "ecological validity" (Chaytor and Schmitter-Edgecombe, 2003) of the neuropsychological tests is variable. In other words, the scores do not necessarily represent behaviors outside the test environment, or real impairments in everyday life, therefore being imperfect (although useful) models of brain function.

Although these limitations, we provide evidence that CBF relates to processing speed and verbal memory, and to changes in white matter FA in the corpus callosum, specifically in early-stage schizophrenia patients. Future studies are needed to further elucidate the time course of these dynamic relationships and consequently indicate the neural basis of cognitive impairment. This will be useful not only to improve our understanding about the pathology as well as to potentially inform the prognosis and treatment in patients with schizophrenia.

## Author statement

Feng Chen: Data curation; Formal analysis; Writing - original draft, Marina Mihaljevic: Data curation; Writing - review & editing, Zhipeng Hou: Methodology; Software, Yang Li: Formal analysis, Hanzhang Lu: Methodology; Software; Writing - review & editing, Susumu Mori: Methodology; Software, Akira Sawa: Data curation; Funding acquisition; Writing - review & editing, Andreia Faria: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Supervision; Validation; Writing - original draft, review & editing.

## Data availability

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

## Declaration of competing interest

The authors declare no conflict of interest.

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