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The impact of schizophrenia on frontal perfusion parameters: a DSC-MRI study

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Abstract We performed a dynamic susceptibility contrast magnetic resonance imaging (DSC-MRI) analysis to study the role of the demographic/clinical information on perfusion parameters between patients with schizophrenia and normal control subjects. 39 schizophrenia patients and 27 normal controls were studied with a Siemens 1.5T magnet. PWI images were obtained following intravenous injection of paramagnetic contrast agent (gadolinium-DTPA). For each perfusion parameter, i.e. relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), mean transit time (MTT) and time-to-peak (TTP), the best predictor model was computed in left and right frontal cortex following a stepwise strategy. First of all, a linear model, including all the sociodemographic information and clinical variables as predictors was computed. At each step, the least significant predictor was excluded and a new linear model was evaluated until all predictors were excluded. Then, the best predictor model was selected based on the F statistic value and on the p value. The models for the rCBF and the rCBV both in the left and right frontal cortex were estimated independently from each other, and the best models contained the same predictors, i.e. clinical state, age, and length of illness. No significant models were obtained for the MTT and the TTP. This study showed a decrease in rCBF and rCBV frontal cortex values in subject affected by schizophrenia. Future DSC-MRI studies should further investigate the role of cerebral perfusion for the pathophysiology of the disease by recruiting first-episode patients and by considering cerebellar, parietal and temporal regions.

Keywords Cerebral blood flow · Cerebral blood volume · Frontal cortex · Perfusion imaging · Mean transit time · Time-to-peak

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Introduction

Dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI) was developed to study disorders of blood flow and has increasingly been used for the measurement of cerebral perfusion in humans (Inao et al. 1986; Kaneoke et al. 1989; Moseley et al. 1990; Strich et al. 1985). The standard DSC-MRI acquisition protocol is composed by the injection of a bolus of contrast agent and the fast acquisition of several MR images to monitor the signal variations during the passage of the contrast agent. Usually, gadolinium is employed as contrast agent because it is a paramagnetic and intravascular element. During its passage, the gadolinium causes a signal loss in the

T2-weighted MR images proportional to the contrast agent concentration (Østergaard et al. 1996a, b). The analysis of DSC-MRI data is based on the indicator dilution theory (Zierler 1962, 1965), which allows to quantify several perfusion parameters, such as relative cerebral blood flow (rCBF), relative cerebral blood volume (rCBV), mean transit time (MTT), and time-to-peak (TTP).

Even if DSC-MRI is widely used to study the cerebral perfusion, the quantification process still present several open issues, such as the deconvolution operation that has to be performed to compute the rCBF and the arterial input function (AIF) (Calamante et al. 2002; Grandin 2003; Kiselev 2001). The most used methods to perform the deconvolution operation in DSC-MRI are the singular value decomposition (SVD) (Østergaard et al. 1996a, b) and its evolution, the block-circulant SVD (cSVD) (Wu et al. 2003). Several other deconvolution methods have been proposed in literature to analyze DSC-MRI data (Andersen et al. 2002; Vonken et al. 1999; Wirestam et al. 2000), but SVD and cSVD are still the most used ones. The AIF represents the amount of contrast agent entering in the voxel during the experiment and it is necessary to quantify the perfusion parameters. It is determined by selecting a group of voxels that are representative of the signal intensity change in a major brain feeding artery. This process is usually performed manually and requires detailed anatomical knowledge, as well as a good understanding of large vessel flow and susceptibility artifacts (Calamante et al. 1999). Several automatic methods to select the arterial voxels have been proposed in literature (Carroll et al. 2003, Calamante et al. 2004, Mouridsen et al. 2006), but a standard method has not been achieved yet.

It is important to remark that the perfusion parameters obtained by using DSC-MRI reflect the cerebral hemodynamic at a capillary level. CBF, CBV, MTT and TTP alterations may occur when hemodynamic organization is altered, such as in brain vascular diseases or in psychiatric disorders such as schizophrenia (Renshaw et al. 1997; Brambilla and Tansella 2007; Bellani et al. 2009).

Interestingly, with regard to schizophrenia, cerebral hemodynamic alterations may represent the vascular basis potentially accompanying structural brain abnormalities, particularly in the frontal lobes (Wright et al. 2000; Brambilla et al. 2007a; Bellani et al. 2010), being blood supply crucial in sustaining neural integrity, energy, and activation (Hanson and Gottesman 2005; Brambilla et al. 2007). However, the effects of sociodemographical and clinical variables on the cerebral vasculature are still under investigated. Indeed, they may have an impact on both normal and schizophrenia brain, in particular age, gender, education, alcohol, smoke, chronicity and psychopathology. In our study, we performed a DSC-MRI analysis to study the role of the demographic and clinical information in the detected between-subject variability of the estimated parameter values in patients with schizophrenia and normal control subjects.

Materials and methods

Subjects

Thirty-nine patients with DSM-IV schizophrenia (mean age ± SD 37.10 ± 11.54 years; 25 males, 14 females; all Caucasians, 31 right-handed) and 27 normal controls (mean age ± SD 45.37 ± 10.48 years; 11 males, 16 females; all Caucasians, 24 right handed) were studied (Table 1). Patients were recruited from the South-Verona Psychiatric Care Register (PCR) (Tansella et al. 2006; Amaddeo and Tansella 2009), a community-based mental health register, after reaching clinical consensus diagnoses of schizophrenia by two staff psychiatrists. Subsequently, the clinical diagnosis of schizophrenia for each patient was confirmed using the IGC-SCAN Item Group Checklist of the Schedule for Clinical Assessment in Neuropsychiatry (IGC-SCAN) (World Health, 1992), as previously described (Andreone et al. 2007). Patients with comorbid psychiatric disorders, alcohol or substance abuse within the 6 months preceding the study, history of traumatic head injury with loss of consciousness, epilepsy or other neurological or medical diseases, including hypertension and diabetes, were excluded from the study. None of our patients had history of ECT treatment. All patients were receiving antipsychotic medications and none of them was on any cardiovascular drugs at the time of imaging, including β-blockers or nitrates. Specifically, 16 patients were on olanzapine (mean dose ± SD = 15.94 ± 6.12 mg/day), 6 on clozapine (mean dose ± SD = 341.67 ± 177.25 mg/day), 3 on risperidone (mean dose ± SD = 6.5 ± 0.71 mg/day), 9 on haloperidol (mean dose ± SD = 2.35 ± 1.53 mg/day), 3 on fluphenazine (mean dose ± SD = 1.15 ± 0.55 mg/day) and the remaining 2 on other antipsychotics, such as quetiapine ($N = 1$), zuclopenthixol ($N = 1$). In addition, 16 patients were on benzodiazepines and 1 was on valproate. Regarding the clinical status, 7 patients were experiencing an acute psychotic episode, whereas the remaining ones were clinically stable at the time of MR investigation. Patients' clinical information was retrieved from psychiatric interviews, the attending psychiatrist, and medical charts and clinical symptoms were characterized using the Brief Psychiatric Rating Scale (BPRS 24-item version) (Ventura et al. 2000). Symptom ratings were assessed with the BPRS by two trained research clinical psychologists and the reliability was established and monitored utilizing similar procedures as to the IGC-SCAN, as mentioned elsewhere (Baiano et al.

Table 1 Demographic and clinical variables for normal controls and patients with schizophrenia

	Normal subjects ($N = 27$)	Schizophrenia patients ($N = 39$)	Statistics
Age (years)	45.37 ± 10.48	37.10 ± 11.54	$t = 2.97$, $p = 0.04$
Males/females	11/16	25/14	$\chi^2 = 3.51$ p = 0.06
Race	Caucasian	Caucasian	
Right-handed/non right-handed	24/3	31/8	$\chi^2 = 1.02$ $p = 0.31$
Age at onset (years)	–	24.74 ± 7.14	
Smokers/non smokers	3/24	19/20	$\chi^2 = 10.15$ $p < 0.01$
Alcoholic abuse	–	1	
Drug abuse	–	4	
School attendance (A, B, C, D)	8/8/5/4	4/23/11/1	
Length of illness (years)	–	12.32 ± 10.23	
Number of hospitalizations	–	2.69 ± 2.96	
Lifetime AP treatment (years)	–	10.19 ± 9.57	
BPRS total score	–	48.29 ± 17.03	
Negative symptom score	–	12.03 ± 4.36	
Positive symptom score	–	13.11 ± 6.41	
Chlorpromazine-equivalent dose (mg)	–	245.94 ± 170.56	

AP antipsychotic, *BPRS* Brief Psychiatric Rating Scale, *A* primary school, *B* middle school, *C* high school, *D* bachelor degree or professional school

2008). Handedness was determined by the Oldfield handedness questionnaire (Oldfield 1971).

Control individuals were recruited from the same catchment area and had no DSM-IV axis I disorders, as determined by a brief interview modified from the SCID-IV non-patient version (SCID-NP), no history of psychiatric disorders among first-degree relatives, no history of alcohol or substance abuse, and no current major neurological or medical illness, including hypertension and diabetes. No evidence of central nervous system abnormalities on the serial conventional MR images and on the pre- and post-contrast MR acquisitions were detected by the neuroradiologist. None of them was on medication at the time of participation in the study, including drugs for nausea or vertigo.

This research study was approved by the Biomedical Ethics Committee of the Azienda Ospedaliera di Verona. All subjects provided signed informed consent after having understood all issues involved in study participation.

MRI procedure

Magnetic resonance imaging scans were acquired with a 1.5T Siemens Magnetom Symphony Maestro Class, Syngo MR 2002B. A standard head coil was used for RF transmission and reception of the MR signal and restraining foam pads were utilized for minimizing head motion. T1-weighted images were first obtained to verify subject's head position and image quality (TR 450 ms, TE 14 ms, flip angle 90°, FOV 230 × 230, 18 slices, slice thickness 5 mm, matrix size 384 × 512, NEX 2). PD/T2-weighted images were then acquired (TR 2.5 s, TE 24/121 ms, flip angle 180°, FOV 230 × 230, 20 slices, slice thickness 5 mm, matrix size 410 × 512, NEX 2), according to an axial plane parallel to the anterior–posterior commissure (AC–PC), for clinical neurodiagnostic evaluations (exclusion of focal lesions). A coronal 3D MPR sequence covering the entire brain was also acquired (TR 2.06 s, TE 3.9 ms, flip angle 15°, FOV 176 × 235, slice thickness 1.25 mm, matrix size 384 × 512). Subsequently, perfusion-weighted acquisitions, consisting of echo-planar imaging of T2-weighted sequence, were acquired in the axial plane parallel to the AC–PC line (20 sequential images for 60 repetitions, TR 2.16 s, TE 47 ms, FOV 230 × 230, slice thickness 5 mm, matrix size 256 × 256 interpolated, NEX 1, EPI factor 128) immediately before, during, and after injection of a bolus of gadopentetate dimeglumine-dietilen-tetra-penta-acetic acid (Gd-DTPA), a paramagnetic agent with intravascular space distribution. Contrast material (0.1 mmol/kg) administration was started after 4 s by power injector (Medrad Spectris MR injector) through an 18 or 20-gauge angiocatheter through the right antecubital vein at a rate of approximately 2.5 mL/s, followed immediately by 25 mL of continuous saline flush. The same neuroradiologist controlled timing and accuracy of gadolinium administration for all patients and controls. Finally, post-contrast spin-echo T1-weighted images were obtained in the axial plane to exclude for possible focal lesions (TR 0.448 s, TE 14 ms, flip angle 90°, FOV 230 × 230, slice thickness 5 mm, matrix size 384 × 512 interpolated, NEX 2). Normal controls and patients with schizophrenia completed the MRI session without any apparent hyperventilation due to anxiety reaction. Indeed, to minimize any possible anxiety symptoms, fellows from our research

group carefully provided full information on MRI and personally accompanied subjects at the MR center, waiting for them until the end of the session.

Post-processing and image analysis

Raw echo-planar data of the images were first transferred to a commercial workstation and semi-automatically processed using in-house software written in MATLab developed by our engineers (version 7; The Mathworks Inc., Natick, MA). Regions of interests (ROIs) were traced in the left and right frontal lobes (Fig. 1). The ROIs were hand-drawn by a trained rater who was blind to the diagnosis and identity of the subjects. The intra-class correlation coefficients (ICCs), which were calculated by having two independent raters trace 10 scans, were higher than 0.90. Two slices containing the frontal cortex were selected for each subject and a total of four ROIs have been manually drawn (i.e. 2 ROIs in each slice, 1 in the left hemisphere and 1 in the right one). Every ROI was also delimited by the frontal sulcus, by the inter-hemispheric scissure and by the cerebral external border. Figure 1 shows an example of the ROI drawn on the frontal cortex. For each ROI, the mean MR signal was computed to quantify the ROI perfusion parameters. Then, the rCBF, rCBV, MTT and TTP assessed on the mean signal were assumed to characterize the whole ROI.

AIF was also determined in each subject by averaging the MR signal of few voxels placed in the middle cerebral artery (MCA). A physician manually selected the arterial voxels in the MCA branch supplying the frontal cortex.

Perfusion parameters were calculated based on the principles of tracer kinetics for nondiffusible tracers (Zierler 1962, 1965). First of all, the concentration curve was obtained from the MR signal $S(t)$ following the relation:

$$c(t) = -\frac{1}{\mathrm{TE}} \ln\left(\frac{S(t)}{S_0}\right)$$

where S_0 was computed by averaging the signal samples before the tracer injection (Østergaard et al. 1996a). Subsequently, a fit with a gamma-variate function was computed to eliminate the recirculation as reported in Benner et al. (1997), Østergaard et al. (1996a, b), Porkka et al. (1991)).

rCBV values were computed as the ratio between the voxel area under the curve (AUC) and the arterial AUC, as reported in Østergaard et al. (1996a):

$$\mathrm{rCBV} = \frac{\int C_{\mathrm{ROI}}(t)\mathrm{d}t}{\int C_{\mathrm{AIF}}(t)\mathrm{d}t}$$

rCBF values were computed using block-circulant singular value decomposition (cSVD) method as reported in (Wu et al. 2003), then MTT values were computed as the ratio between CBV and CBF (Østergaard et al. 1996a).

A parameter accounting for the concentration raise time was also considered and called TTP, defined as the time interval from the tracer arrival time to the moment of the maximum concentration.

Statistical analyses

All analyses were conducted using the R Project for Statistical Computing for Windows platforms, version 2.7.1, and the two-tailed statistical significance level was set at $p < 0.05$. Before the experiments, additional information about the subjects was collected, with the purpose of investigating which physiological characteristics were

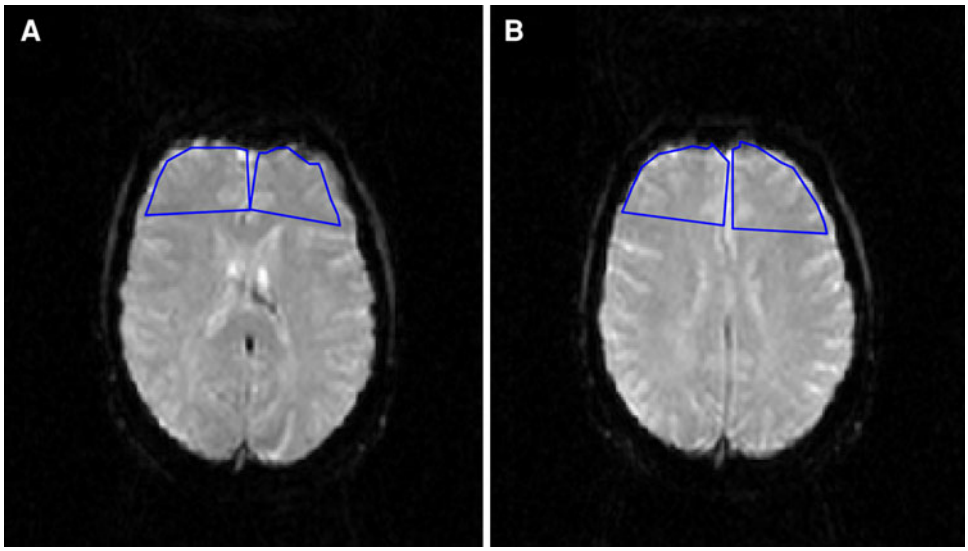

Fig. 1 Example of the regions of interest (ROI) placed in *right* and *left* frontal lobe. Two slices (**a**, **b**) are selected and a ROI containing the frontal cortex is manually drawn in each slice and hemisphere. Every ROI is delimited by the frontal sulcus, the inter-hemispheric scissure and the cerebral external border

significant predictors of the perfusion parameters. For each perfusion parameters (rCBV, rCBF, MTT, TTP), the best predictor model was computed in each ROI (left/right frontal cortex) following a stepwise strategy. First of all, a linear model including all the predictors was computed (GROUP, AGE, GENDER, HANDEDNESS, SMOKE, ALCHOHOLIC ABUSE, DRUG ABUSE, SCHOOL ATTENDANCE, LENGTH OF ILLNESS, BPRS NEGATIVE, POSITIVE SYMPTOMS and CHLORPROMAZINE EQUIVALENT DOSE).

At each step, the least significant predictor was excluded and a new linear model was evaluated until all predictors were excluded. Then, the best predictor model was selected on the basis of the F statistic value and on the p value.

Results

None of the subjects reported any adverse reaction to rapid power injection of the contrast material and susceptibility artifacts inherent in echo-planar imaging did not interfere with imaging or post-processing. All perfusion parameters were successfully computed in each subject.

Left and right rCBF, rCBV, MTT and TTP values were compared between the two groups (e.g. patient left rCBF vs control left rCBF) and within the two groups (e.g. patient left rCBF vs. patient right rCBF) using the Student's t test to evaluate possible asymmetric distribution due to schizophrenia (paired sample t test). No significant differences were found for both analyses ($p > 0.05$) (Table 2).

Stepwise procedure was performed to estimate the best linear predictor model for each perfusion parameter in each ROI. During model estimation procedure, the two populations were merged and GROUP was also considered as predictor. Table 3 shows an example of the exclusion procedure in the estimate of the best linear model for the rCBF in the left ROI. The best model contains the predictors LENGTH OF ILLNESS, GROUP, AGE ($F = 2.56, p = 0.06$).

The predictors of the best model in the different ROI were calculated for each perfusion parameter independently from each other. The models for the rCBF and the rCBV, bilaterally, contain the same predictors (i.e. LENGTH OF ILLNESS, GROUP and AGE) (Table 4). In contrast, no significant models were obtained for the MTT and the TTP (i.e. the best predictor model does not contain any predictor), meaning that the best predictor model is represented by the mean parameter value in the population. Table 4 shows the best models obtained for the rCBF and rCBV in the left and in the right ROIs. For example, the best model obtained for the right rCBF contains the predictors GROUP, AGE, LENGTH OF ILLNESS. An F test was used to compare this model to the model containing no predictors (i.e. the model using only the mean value rCBF in the right ROI). The F value obtained by this model is 2.09 ($p = 0.11$), that is, the best result obtained among the models with different combinations of the predictors. A coefficient had been estimated for each predictor and for the intercept. The intercept coefficient (0.29 ± 0.05) represents the amount of rCBF that it is not predictable using the other predictors. AGE and LENGTH OF ILLNESS are numeric predictors and this means that their coefficient must be multiplied by the value of the predictors. For example, the coefficient of AGE in the right rCBF is -0.002 ± 0.001, so the impact on the right rCBF prediction for a 50-year-old subject is -0.1 ($=-0.002 \times 50$). Because the control subjects are not affected by the illness, their LENGTH OF ILLNESS is set to 0 (zero). Therefore, the LENGTH OF ILLNESS coefficient does not influence the perfusion parameter prediction for an healthy subject, because it is multiplied by 0 (zero). On the other hand, GROUP is a class-based predictor and its coefficient (e.g. -0.07 ± 0.03) represents the impact of the secondary class on the rCBF prediction with respect to the primary class. In our study, the primary class for GROUP includes the normal subjects, whereas the secondary class contains the patients. Therefore, if the subject is a patient, then the right

Table 2 Comparison of the perfusion parameters within and between the two groups

Left vs. right ROI within each group	rCBV	rCBF	MTT	TTP
Normal controls	$t = -0.47, p = 0.64$	$t = -0.24, p = 0.81$	$t = -0.23, p = 0.82$	$t = 0.15, p = 0.88$
Schizophrenia patients	$t = 0.40, p = 0.69$	$t = 0.27, p = 0.79$	$t = 0.34, p = 0.74$	$t = 0.14, p = 0.89$
Comparison between patients and controls	rCBV	rCBF	MTT	TTP
Right ROI	$t = 1.17, p = 0.25$	$t = 0.35, p = 0.73$	$t = 1.74, p = 0.09$	$t = 0.11, p = 0.91$
Left ROI	$t = 1.04, p = 0.30$	$t = 0.34, p = 0.73$	$t = 1.67, p = 0.10$	$t = 0.38, p = 0.71$

All the comparisons have been performed using paired sample t test for within-group analysis and Student's t test for between group analysis

The significance level was set to $p < 0.05$

ROI region of interest (i.e. left and right frontal lobes), *rCBF* relative cerebral blood flow, *rCBV* relative cerebral blood volume, *MTT* mean transit time, *TTP* time-to-peak

Table 3 Example of the stepwise procedure in the evaluation of the best linear model for the left relative cerebral blood flow (rCBF)

rCBF Predictors (left ROI)	*F* value	*p* value
YOP GRP AGE ALC ECD HND SMK DRG GENDER SNEG BPRS SPOS SCH	1.18	0.32
YOP GRP AGE ALC ECD HND SMK DRG GENDER SNEG BPRS SPOS	1.09	0.39
YOP GRP AGE ALC ECD HND SMK DRG GENDER SNEG BPRS	1.19	0.32
YOP GRP AGE ALC ECD HND SMK DRG GENDER SNEG	1.31	0.25
YOP GRP AGE ALC ECD HND SMK DRG GENDER	1.53	0.16
YOP GRP AGE ALC ECD HND SMK DRG	1.66	0.13
YOP GRP AGE ALC ECD HND SMK	1.85	0.10
YOP GRP AGE ALC ECD HND	1.95	0.09
YOP GRP AGE ALC ECD	2.23	0.06
YOP GRP AGE ALC	2.36	0.06
YOP GRP AGE	**2.56**	**0.06**
YOP GRP	1.63	0.20
YOP	1.87	0.18

Each row in the table represents a step in the stepwise procedure. The first column reports the demographic and clinical variables used as predictors in each step. The second and the third columns report the *F* value and the *p* value scored by the prediction model. At each step, the least significant demographic or clinical variable is excluded and a new model is evaluated. Finally, the best combination between *F* and *p* values is used to select the best prediction model (highlighted in bold)

ROI region of interest, *YOP* years of pathology, *GRP* GROUP, *AGE* AGE, *ALC* ALCHOLIC ABUSE, *ECD* EQUIVALENT CHLORPROMAZINE DOSE, *HND* HANDEDNESS, *SMK* SMOKERS, *DRG* DRUG ABUSE, *GENDER* GENDER, *SNEG* BPRS negative symptoms, *SPOS* BPRS positive symptoms, *SCH* school attendance

rCBF prediction is lower of 0.07 with respect to a normal subject one.

AGE and GROUP are characterized by a negative coefficient in all models. This means that the subject's age and clinical state have an impact on the perfusion parameters, reducing both rCBF and rCBV. On the other hand, length of illness shows a positive coefficient in all models, thus increasing rCBF and rCBV.

Finally, for each predictor, a Student's *t* test was performed to compare the performance of the predictor model with and without the predictor and the results are also reported in Table 4. Noticeably, predictor AGE appears to be not significant predictor for rCBV, bilaterally (i.e. $p = 0.08$ for the left rCBV and $p = 0.12$ for the right rCBV). However, the models estimated without the predictor age performed worse than the models containing it.

Discussion

The study showed that (1) schizophrenia does not influence the perfusion parameters TTP and MTT, (2) the models for the rCBF and the rCBV, bilaterally, were estimated independently from each other, with the best models containing the same predictors for these variables (i.e. LENGTH OF ILLNESS, GROUP, AGE); (3) rCBF was significantly predicted by GROUP, AGE and by LENGTH OF ILLNESS and (4) rCBV by GROUP and by LENGTH OF ILLNESS and (5) the coefficient estimates (mean and SD) were comparable when considering the left and the right regions.

In particular, no significant models were obtained for MTT and TTP, i.e. none of the considered demographic and clinical variables significantly influence MTT or TTP, thus the best prediction we can make on MTT and TTP is their average values. However, these are not surprising results because compensatory mechanisms might act on CBF and CBV to preserve a physiological MTT. Moreover, TTP alterations are expected to reflect mostly macroscopic hemodynamic variations, due for example to a stroke, than the small variations.

Differences (i.e. between-subject variability) in rCBF and rCBV were partially explained by a difference in the age of the subjects and/or by a difference in the healthy condition of the subjects. In particular, negative coefficients for covariate AGE (Table 4) indicated that rCBF decrease when age increases, in accordance to previous studies (Koshimoto et al. 1999; Helenius et al. 2003; Bertscha et al. 2009). Interestingly, a recent study showed that total cerebral blood flow correlates with parenchymal volume (van Es et al. 2010). In this perspective, it would be important to investigate the correlation between perfusion and brain size in schizophrenia. Moreover, the covariate GROUP presented negative coefficients in the models, thus suggesting that a perfusion and a blood volume decrease is present in patients with respect to control subjects. The positive model coefficients for the LENGTH OF ILLNESS covariate suggested a partial recovery from

Table 4 Estimate of the prediction model parameters computed for the relative cerebral blood flow (rCBF) and the relative cerebral blood volume (rCBV)

Model statistics	Left rCBF		Right rCBF		Left rCBV		Right rCBV	
	$F = 2.56,\ p = 0.06$		$F = 2.09,\ p = 0.11$		$F = 2.75,\ p = 0.05$		$F = 2.04,\ p = 0.11$	
	Estimate ± SD	*t* value (*p* value)	Estimate ± SD	*t* value (*p* value)	Estimate ± SD	*t* value (*p* value)	Estimate ± SD	*t* value (*p* value)
Predictor								
Intercept	0.29 ± 0.05	6.01 (<0.01)	0.29 ± 0.05	5.77 (<0.01)	0.982 ± 0.16	6.16 (<0.01)	1.002 ± 0.17	5.90 (<0.01)
GROUP	−0.07 ± 0.03	−2.25 (0.02)	−0.07 ± 0.03	−2.10 (0.04)	−0.262 ± 0.10	−2.67 (<0.01)	−0.256 ± 0.11	−2.4 (0.02)
AGE	−0.002 ± 0.0010	−2.06 (0.04)	−0.002 ± 0.0011	−1.88 (0.05)	−0.006 ± 0.003	−1.74 (0.08)	−0.006 ± 0.004	−1.6 (0.12)
LENGTH OF ILLNESS	0.004 ± 0.0014	2.73 (<0.01)	0.004 ± 0.0015	2.46 (0.02)	0.013 ± 0.005	2.69 (<0.01)	0.011 ± 0.005	2.13 (0.03)

In the second row, the statistics describing the model (i.e. *F* value and *p* value) is reported; for each model the *F* value reported is the best value achieved in the stepwise procedure. Then, the predictors in the best model, their coefficient estimate (mean and SD) and their statistics (*t* and *p* values) are shown. The intercept represents the amount of the perfusion parameter that is not predictable using the other predictors. The best model for each perfusion parameter and ROI were calculated independently from each other

the pathological perfusion deficit as the length of the illness increases. This may indicate that the CBF and CBV age-induced decrease is less evident in patients than in control subjects. Alternatively, since all patients were under treatment, antipsychotic treatment may in part reduce the perfusion deficit in schizophrenia. The CHLORPROMAZINE EQUIVALENT DOSE was also included as treatment predictor in this study, but it did not result in any best model, suggesting that antipsychotic treatment does not significantly affect cerebral perfusion parameters in schizophrenia. Noticeably, LENGTH OF ILLNESS coefficients are very small when compared with GROUP ones, thus the recovery in perfusion parameters is small when compared with the decrease due to the pathology. It should be considered that the two groups differed for age and number of smokers; this may partially limit the generalization of the findings.

In conclusion, this study showed that a relationship does exists between schizophrenia and cerebral hemodynamic. Specifically, a decrease in rCBF and rCBV frontal cortex values is expected when the subject is affected by schizophrenia. Future DSC-MRI studies longitudinally investigating first-episode drug-naïve patients and considering different cerebral regions, such as the cerebellum and the temporal and parietal cortex, will be crucial to elucidate the role of cerebral perfusion for the pathophysiology of schizophrenia.

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