

# Cerebral blood flow in striatal regions is associated with apathy in patients with schizophrenia

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**Background:** Striatal dysfunction has been proposed as a pathomechanism for negative symptoms in schizophrenia. There is consensus that negative symptoms can be grouped into 2 dimensions: apathy and diminished expression. Recent studies suggest that different neural mechanisms underlie these dimensions, but the relationship between regional resting-state cerebral blood flow (rCBF) and negative symptom dimensions has not been investigated. **Methods:** This study included 29 patients with schizophrenia and 20 healthy controls. We measured rCBF in the striatum using arterial spin labelling (ASL) MRI. We assessed negative symptoms using the Brief Negative Symptom Scale. **Results:** In the ventral and dorsal striatum, rCBF was not different between patients with schizophrenia and controls. However, we did find a positive association between the severity of apathy and increased rCBF in the ventral and dorsal striatum in patients with schizophrenia. This effect was not present for diminished expression. **Limitations:** All patients were taking atypical antipsychotics, so an effect of antipsychotic medication on rCBF could not be excluded, although we did not find a significant association between rCBF and chlorpromazine equivalents. **Conclusion:** The main finding of this study was a specific association between increased striatal rCBF and the negative symptom dimension of apathy. Our results further support the separate assessment of apathy and diminished expression when investigating the neural basis of negative symptoms. The ASL technique can provide a direct and quantitative approach to investigating the role of rCBF changes in the pathophysiology of negative symptoms.

## Introduction

For decades, it has been hypothesized that striatal dysfunction is a fundamental mechanism underlying symptoms of schizophrenia.<sup>1</sup> Robust findings in the literature have shown increased striatal dopamine synthesis in schizophrenia as measured by positron emission tomography (PET) and single-photon emission computed tomography (SPECT).<sup>2,3</sup> Studies using functional MRI (fMRI) to assess striatal response to rewards have shown a decreased signal in unmedicated patients with schizophrenia.<sup>4-6</sup> Results in medicated patients have been heterogeneous,<sup>7-9</sup> indicating a complex relationship between dopamine dysregulation and fMRI findings.

More recently, it has been suggested that an increase in dopamine turnover could be accompanied by an increased perfusion of striatal areas.<sup>10,11</sup> Arterial spin labelling (ASL) imaging allows for an absolute measure of regional cerebral blood flow (rCBF). Previous studies have suggested an increase in striatal

rCBF in patients with schizophrenia<sup>11-14</sup> and at a high risk for psychosis,<sup>15</sup> but these findings were not fully consistent;<sup>11,16-18</sup> further research is clearly needed.

Schizophrenia is a disorder with heterogeneous symptom expression along its course, and negative symptoms have a strong effect on long-term morbidity and poor functional outcome.<sup>19,20</sup> There is now consensus that negative symptoms can be divided into 2 dimensions:<sup>21-23</sup> apathy, which consists of anhedonia, avolition and asociality, and diminished expression, which combines the symptoms of blunted affect and alogia. In fMRI studies, an association between ventral striatal hypoactivation and negative symptoms (in particular, apathy) has repeatedly been reported.<sup>8,24-26</sup> A recent study also found dorsal striatal hypoactivation in response to reward and apathy.<sup>27</sup>

These fMRI results do not reflect absolute hypoactivation in the striatum; rather, they represent a decreased signal difference between rewarding and nonrewarding stimuli.

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Therefore, the absolute measure of rCBF provided by ASL can offer additional information about the neural basis of symptoms. Most studies investigating ASL have not focused specifically on the striatum; they have used whole-brain analysis.<sup>12,14,28</sup> Nevertheless, a few have reported associations between striatal rCBF and symptoms. Kindler and colleagues<sup>11</sup> showed a positive correlation between striatal rCBF and positive symptoms in patients with treatment-resistant auditory hallucinations. Zhuo and colleagues<sup>16</sup> found increased rCBF in striatal and auditory areas in patients with auditory verbal hallucinations.

In addition to these ASL studies on rCBF in the striatum, earlier PET studies have reported an association between negative symptoms and reduced rCBF at rest and during an attentional task in frontal and parietal regions.<sup>29–31</sup> However, these studies did not address the distinction between apathy and diminished expression. Liemburg and colleagues<sup>32</sup> found apathy to be related to abnormal activation in parietal and thalamic regions during a planning task, but did not specifically investigate striatal rCBF. Overall, negative symptoms seem to be associated with reduced rCBF, particularly in frontal regions, but regional specificity has yet to be determined.

The main goal of this study was to investigate the association between striatal rCBF and negative symptoms. There is evidence that apathy and diminished expression show different associations with behavioural<sup>33,34</sup> and neurobiological correlates, suggesting differences in pathophysiology. Therefore, this distinction is of high relevance when investigating striatal rCBF. The paucity of reported associations between striatal rCBF and negative symptoms could result from the fact that until now apathy and diminished expression have not been addressed separately, even though the striatum might play very different roles in their pathophysiology.

Based on the extant (albeit limited) evidence for increased striatal resting-state rCBF in patients with schizophrenia,<sup>24,26</sup> our first hypothesis was that these patients would show increased rCBF in the ventral and dorsal striatum compared with controls. Our second and main hypothesis was that apathy would be associated with altered rCBF in the ventral and dorsal striatum. Because no study has previously reported striatal rCBF in relation to specific dimensions of negative symptoms, we could not make predictions about the directionality of the effects.

## Methods

### *Participants*

Twenty-nine patients with schizophrenia and 20 healthy controls, matched at a group level for age and sex, were included in the present study. We recruited patients from outpatient and inpatient units of the Psychiatric Hospital of the University of Zurich and affiliated institutions. We recruited healthy controls from the community via advertisement.

We conducted the Mini-International Neuropsychiatric Interview to confirm diagnosis.<sup>35</sup> Patients were clinically stable and had been on a stable dose of medication for at least

2 weeks before testing. Inpatients were at the end of their hospitalization, engaging in a multimodal therapy program and activities outside the hospital. The average duration of hospitalization for patients with schizophrenia in Switzerland is longer than in most other countries, so the majority of patients would have been treated as outpatients in other health care systems.

Exclusion criteria for patients were any other DSM-IV axis I disorder; acute psychotic symptoms (i.e., scores higher than 4 on the positive subscale of the Positive and Negative Syndrome Scale [PANSS]<sup>36</sup>); extrapyramidal adverse effects (i.e., a total score higher than 2 on the Modified Simpson–Angus Scale [MSAS]<sup>37</sup>); and lorazepam dosage higher than 1 mg/d. If patients met the criteria for cannabis abuse or dependency, they were also excluded from the study. Participants were excluded if they had any alcohol use disorder based on lifetime criteria. Smoking was not an exclusion criterion, but participants did not smoke for 2 hours before the ASL scans. Controls were excluded if any neuropsychiatric diagnosis was present in the structured Mini-International Neuropsychiatric Interview.<sup>35</sup> Any participants with a neurologic disorder were excluded.

The Ethics Committee of the Canton of Zurich approved the project, and participants gave written informed consent to participate in the study. The ability of each participant with schizophrenia to provide informed consent was evaluated by the treating psychiatrist.

### *Clinical and neuropsychological assessment*

We assessed negative symptoms using the Brief Negative Symptom Scale.<sup>38</sup> We calculated the 2 dimensions of negative symptoms as follows: the apathy dimension consisted of the anhedonia, avolition and asociality items; the diminished expression dimension included the blunted affect and alolia items.<sup>39</sup> Other assessment instruments used were the PANSS,<sup>36</sup> the Calgary Depression Scale for Schizophrenia,<sup>40</sup> the Global Assessment of Functioning scale<sup>41</sup> and the Personal and Social Performance scale.<sup>42</sup> We assessed cognition using a brief neurocognitive test battery (see our previous studies<sup>33,34</sup> for details) to compute a composite cognitive ability score for each participant. The following domains were included in the battery: verbal learning, verbal and visual short-term and working memory, processing speed, planning, and semantic and phonemic fluency.

### *MRI data acquisition*

We acquired MRI data on a Philips Achieva 3.0 T whole-body scanner (Best). We employed resting-state pseudo-continuous ASL (pCASL) perfusion-weighted scans. Due to superior signal-to-noise ratio, pCASL is considered to be a more reliable method than other ASL sequences.<sup>43,44</sup> We based the imaging parameters for pCASL on the sequence developed by Dai and colleagues.<sup>45</sup> The plane was positioned parallel to the imaging volume, with a 20 mm labelling gap between the imaging volume and the labelling volume. The ASL parameters for the single-shot, gradient-echo,

echo planar imaging sequence were as follows: repetition time 4400 ms, echo time 20 ms, flip angle 90°, field of view 240 × 161 × 240 mm, spacing 3 mm, matrix size 80 × 80, 23 slices with a slice thickness of 7 mm and no gap, SENSE 2.5, postlabelling delay 1525 ms, label duration 1650 ms, number of dynamics 75 (duration 667.9 s). One dynamic consisted of a control and a labelled image. We also acquired high-resolution anatomic images (repetition time 8.1 ms, echo time 3.7 ms, field of view 240 × 240 mm<sup>2</sup>, voxel size 1 × 1 × 1 mm) using a standard T<sub>1</sub>-weighted 3D magnetization-prepared rapid gradient echo sequence.

#### Calculation of cerebral blood flow

We performed image data processing and analysis using the ASLtoolbox<sup>46</sup> running in MATLAB (MathWorks, Inc.) and compatible with SPM12 statistical parametric mapping software (Wellcome Trust Centre for Neuroimaging, implemented in MATLAB). For each participant, we conducted image preprocessing, including independent realignment for labelled and unlabelled images, spatial smoothing (6 × 6 × 14 mm kernel), perfusion-weighted image construction and calculation, and normalization to the Montreal Neurological Institute template (for ASL data, rCBF calculations should be performed before spatial normalization<sup>46</sup>). We recorded equilibrium brain tissue magnetization (M<sub>0</sub>) images in a separate run for each participant using the same parameters as for the pCASL sequence, apart from repetition time (10 s). Next, we calculated unique cerebral spinal fluid M<sub>0</sub> values per participant for each session (corrected for T<sub>2</sub><sup>\*</sup> decay using a T<sub>2</sub><sup>\*</sup> value of 74.9 ms); we took the relevant H<sub>2</sub>O partition coefficient from the literature<sup>47</sup> and considered it in the calculation of each perfusion-weighted image. We generated perfusion-weighted image series by simple subtraction of the label and control images, and then conversion to absolute mean rCBF image series.

#### Region-of-interest image analysis

We derived predefined regions of interest (ROIs) for the ventral and dorsal striatum from previous key publications that used fMRI (Fig. 1). Yip and colleagues<sup>48</sup> defined ROI coordinates (Montreal Neurological Institute) for the ventral striatum according to a meta-analysis by Knutson and Greer<sup>49</sup> (left:  $x = -12, y = 10, z = -2$ ; right:  $x = 10, y = 8, z = 0$ ; both 9 mm spheres); we have also used these coordinates in previous studies.<sup>25,50</sup> We also adopted coordinates for the dorsal striatum ROI from Yip and colleagues<sup>48</sup> (left:  $x = -9, y = 3, z = 15$ ; right:  $x = 9, y = 3, z = 15$ ; both 9 mm spheres). We generated the ROIs using the Wake Forest University Toolbox.<sup>51</sup> For each ROI (ventral or dorsal striatum) we extracted mean rCBF using the MarsBaR toolbox (<http://marsbar.sourceforge.net>).

To compare the mean cortical (grey matter masked) cerebral blood flow (CBF) between groups, we extracted the mean CBF for each group from 90 cortical brain regions (AAL atlas, [http://neuro.imm.dtu.dk/wiki/Automated\\_Anatomical\\_Labeling](http://neuro.imm.dtu.dk/wiki/Automated_Anatomical_Labeling)) and applied an unpaired 2-tailed *t*-test.

#### Statistical analysis

We conducted statistical analyses using IBM SPSS Statistics version 22. We tested demographic comparisons using a  $\chi^2$  test, *t* tests and Mann–Whitney *U* tests if the criterion of normal distribution was not met. To test our first hypothesis, we calculated *t* tests for group comparisons of rCBF between patients and controls for each ROI (ventral and dorsal striatum). We confirmed normal distribution with a Shapiro–Wilk test, and tested homogeneity of variance using a Levene test. Both assumptions were met in the current sample. We also calculated analyses of covariance to control for potential sociodemographic differences between the patient and control groups.

To test the main hypothesis, we calculated Spearman correlation coefficients ( $r_s$ ) between negative symptoms (apathy and diminished expression) and rCBF in the ventral and dorsal striatum. We used a Steiger *z* test to calculate the difference between the 2 negative symptom dimensions as dependent variables and rCBF as the common independent variable.

To address potentially confounding factors in the patient group, we calculated Spearman correlation coefficients between rCBF in the ventral and dorsal striatum and age, positive symptoms, chlorpromazine equivalents, depressive symptoms and cognitive impairments via the composite cognitive ability score. Only age showed a significant association with rCBF, as well as apathy. Therefore, we calculated non-parametric partial correlations to account for the effects of age on the correlation between negative symptoms and rCBF.

All primary analyses described above related to bilateral striatal regions; we had no a priori hypotheses about differences between the left and right striatum.

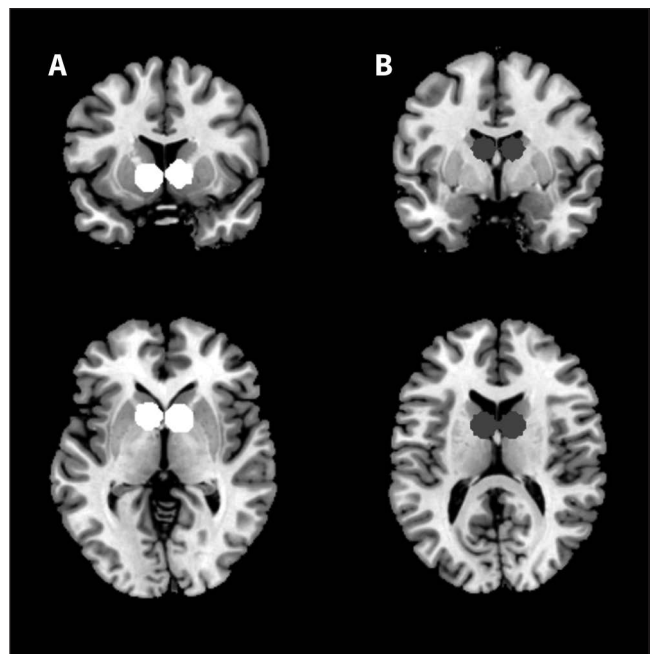


Fig. 1: Regions of interest of the (A) ventral and (B) dorsal striatum.

## Results

### Demographic and clinical characteristics

Demographic and clinical characteristics are summarized in Table 1. The groups showed no significant differences with respect to age or sex. Controls had a higher educational level and higher cognitive scores.

Patients took the following antipsychotic monotherapies: clozapine (2 patients), olanzapine (1 patient), quetiapine (2 patients), amisulpride (2 patients), risperidone (7 patients), paliperidone (2 patients) and aripiprazole (2 patients). Several patients took a combination of antipsychotic medications: clozapine and aripiprazole (1 patient), clozapine and amisulpride (1 patient), olanzapine and aripiprazole (1 patient), olanzapine and quetiapine (1 patient), olanzapine and risperidone (1 patient), amisulpride and quetiapine (1 patient), risperidone and quetiapine (3 patients), risperidone and aripiprazole (1 patient), and aripiprazole and quetiapine (1 patient).

### CBF differences between groups

To test our first hypothesis, we compared rCBF in the ventral and dorsal striatum between groups and found that patients and controls did not differ significantly (Table 2). Thus, we could not confirm our hypothesis that patients with schizophrenia would show altered rCBF in the striatum.

After we controlled for educational level and cognitive score, patients with schizophrenia showed a trend toward higher rCBF in the ventral striatum ( $F_{1,45} = 3.37$ ,  $p = 0.07$ ), but not in the dorsal striatum ( $F_{1,45} = 1.89$ ,  $p = 0.18$ ).

To control for differences in total grey matter CBF between patients (mean  $\pm$  SD 41.4  $\pm$  8.8 mL/100 mg/min) and controls (mean  $\pm$  SD 41.7  $\pm$  8.7 mL/100 mg/min) we used a  $t$  test, which showed no significant differences between groups ( $t_{47} = 0.11$ ,  $p = 0.91$ ). We also addressed potential differences in total grey matter volume between patients (mean  $\pm$  SD 671.8  $\pm$  51.4 mm<sup>3</sup>) and controls (mean  $\pm$  SD 677.7  $\pm$  46.23 mm<sup>3</sup>), and found no significant differences between groups ( $t_{47} = 0.41$ ,  $p = 0.68$ ).

**Table 1: Demographic, psychopathological and clinical characteristics of study participants**

Characteristic	Patients, mean $\pm$ SD* <i>n</i> = 29 <sup>†</sup>	Healthy controls, mean $\pm$ SD* <i>n</i> = 20	Statistical test <sup>‡</sup>	<i>p</i> value
Age, yr	27.7 $\pm$ 7.2	30.6 $\pm$ 6.6	$t_{47} = 1.45$	0.15
Sex, female:male	7:22	6:14	$\chi^2_1 = 0.21$	0.65
Education, yr	11.4 $\pm$ 2.8	14.2 $\pm$ 2.5	$U = 101.5$	$\leq 0.001$
Smoking, pack-years	5.7 $\pm$ 13.7	2.4 $\pm$ 4.8	$U = 239.5$	0.25
Duration of illness, yr	7.2 $\pm$ 7.1	—	—	—
Age of onset, yr	21.0 $\pm$ 4.8	—	—	—
Chlorpromazine equivalents, mg/d	497.7 $\pm$ 407.4	—	—	—
BNSS score				
Apathy (motivation and pleasure)	15.5 $\pm$ 6.9	—	—	—
Diminished expression	8.6 $\pm$ 7.0	—	—	—
SANS score <sup>§</sup>				
Apathy	11.9 $\pm$ 5.6	—	—	—
Diminished expression	10.4 $\pm$ 9.6	—	—	—
PANSS score <sup>¶</sup>				
Positive	6.4 $\pm$ 2.5	—	—	—
Negative	12.0 $\pm$ 5.2	—	—	—
Disorganized	4.7 $\pm$ 2.0	—	—	—
Excited	4.5 $\pm$ 0.7	—	—	—
Depressed	5.4 $\pm$ 2.4	—	—	—
Total	47.7 $\pm$ 10.2	—	—	—
CDSS total score	2.1 $\pm$ 2.5	—	—	—
GAF score	58.1 $\pm$ 9.6	—	—	—
PSP total score	58.2 $\pm$ 9.1	—	—	—
Cognition (composite cognitive ability)**	-0.85 $\pm$ 0.80	0 $\pm$ 0.58	$t_{47} = 4.07$	$\leq 0.001$
MWT IQ	24.5 $\pm$ 6.0	28.7 $\pm$ 2.8	$t_{47} = 2.89$	0.006

BNSS = Brief Negative Symptom Scale; CDSS = Calgary Depression Scale for Schizophrenia; GAF = Global Assessment of Functioning; MWT IQ = Multiple Word Test Intelligence Quotient; PANSS = Positive and Negative Syndrome Scale; PSP = Personal and Social Performance scale; SANS = Scale for the Assessment of Negative Symptoms; SD = standard deviation.

\*Unless otherwise indicated.

<sup>†</sup>All patients were receiving atypical antipsychotics at the time of testing.

<sup>‡</sup>We investigated potential group differences using 2-sample  $t$  tests for continuous data and  $\chi^2$  tests for categorical data. For data with non-normal distribution, we applied Mann-Whitney  $U$  tests.

<sup>§</sup>Apathy includes avolition/apathy and anhedonia/asociality; diminished expression includes affective flattening or blunting and alopecia.

<sup>¶</sup>Positive factor = P1, P3, P5, P9; negative factor = N1, N2, N3, N4, N6, G7; disorganized factor = P2, G5, N11; excited factor = P4, P7, G8, G14; depressed factor = G2, G3, G6.

\*\*Cognition data have been z-transformed based on the data of the control group for each test separately. The composite cognitive ability score was computed as the mean of the z-transformed test scores at the participant level.

No participants were excluded because of excessive motion. Patients and controls did not differ significantly with respect to motion parameters.

### Correlation between CBF and negative symptoms

To test our main hypothesis, we calculated Spearman correlations between rCBF in the striatum and the 2 negative symptom dimensions in the patient group (Table 3). We found a significant positive correlation between ventral striatal rCBF and apathy (Fig. 2a and Table 3), and between dorsal striatal rCBF and apathy (Fig. 2b and Table 3). This finding provides evidence that patients with more apathy show higher rCBF in the striatum. We found no significant correlation between ventral striatal rCBF and diminished expression (Fig. 2c and Table 3) or between dorsal striatal rCBF and diminished expression (Fig. 2d and Table 3). The results of the Steiger  $z$  test were nearly significant (ventral striatum:  $z = 1.88$ ,  $p = 0.06$ ; dorsal striatum:  $z = 1.73$ ,  $p = 0.08$ ). In other words, the correlation between rCBF and apathy was stronger than that between rCBF and diminished expression. For the Brief Negative Symptom Scale total score, we observed a trend-level correlation with rCBF in the dorsal striatum ( $r_{27} = 0.34$ ,  $p = 0.07$ ), but not in the ventral striatum ( $r_{27} = 0.20$ ,  $p = 0.29$ ).

We found that rCBF did not correlate significantly with the following potentially confounding variables: PANSS positive factor, Calgary Depression Scale for Schizophrenia for depressive symptoms, chlorpromazine equivalents and composite cognitive ability score (Table 4). However, we did find significant positive correlations between age and rCBF of the ventral and dorsal striatum. Therefore, we calculated non-parametric partial correlations to control for the effects of age on the correlation of rCBF with apathy. The association between apathy and rCBF in the dorsal striatum was at trend level ( $r_{26} = 0.34$ ,  $p = 0.08$ ), and the association with the ventral striatum was no longer significant ( $r_{26} = 0.25$ ,  $p = 0.19$ ).

In an exploratory analysis, we evaluated the associations with apathy and diminished expression in the left and right striatum, and found the same pattern as in the bilateral analysis (Table 3).

We also performed an exploratory voxel-wise analysis of rCBF in the prefrontal cortex and anterior cingulate cortex. The statistical threshold was set at a peak-level family-wise error rate correction of  $p = 0.05$ . No voxels were significantly associated with apathy in the patient group.

## Discussion

We observed no significant differences in striatal rCBF between patients with schizophrenia and healthy controls. Importantly, apathy — but not diminished expression — was associated with dorsal striatal rCBF and (to a lesser extent) ventral striatal rCBF.

For this reason, our first hypothesis concerning group differences could not be confirmed. This was at odds with some studies, which reported increased striatal rCBF in patients with schizophrenia,<sup>11,12,14,16</sup> but other studies did not observe these effects.<sup>17,18</sup> Potential explanations for these differences between studies include variations in image acquisition and data analysis. Most importantly, the patient populations differed in numerous ways. In our study, we specified inclusion and exclusion criteria to assess primarily for negative symptoms, so our patients had low levels of positive symptoms. In contrast, patients in the study by Kindler and colleagues<sup>11</sup> had treatment-resistant auditory hallucinations. Another important factor might be the type of antipsychotic medication used for treatment.<sup>14,52,53</sup> In our study, all patients were treated with atypical antipsychotic medication, which in fMRI studies has been shown to attenuate group differences in striatal activation.<sup>4,8,25</sup>

Regarding our main hypothesis, we found a significant association between the severity of apathy and rCBF in both the

**Table 2: Mean rCBF values by region of interest and group**

Region of interest	Patients, mean $\pm$ SD	Healthy controls, mean $\pm$ SD	Statistical test	$p$ value
Ventral striatum	33.8 $\pm$ 7.9 mL/100 g/min	31.5 $\pm$ 9.3 mL/100 g/min	$t_{47} = -0.91$	0.37
Dorsal striatum	28.4 $\pm$ 9.1 mL/100 g/min	26.1 $\pm$ 7.8 mL/100 g/min	$t_{47} = -0.95$	0.35

rCBF = regional cerebral blood flow; SD = standard deviation.

**Table 3: Spearman correlations between apathy and diminished expression and the left and right ventral and dorsal striatum in patients with schizophrenia**

Mean rCBF	Apathy		Diminished expression	
	$r_{27}$	$p$ value	$r_{27}$	$p$ value
Left and right ventral striatum	0.38	0.040	0.02	0.91
Left and right dorsal striatum	0.48	0.008	0.17	0.39
Left ventral striatum	0.32	0.09	0.009	0.96
Right ventral striatum	0.40	0.030	0.003	0.99
Left dorsal striatum	0.44	0.017	0.19	0.32
Right dorsal striatum	0.51	0.005	0.10	0.61

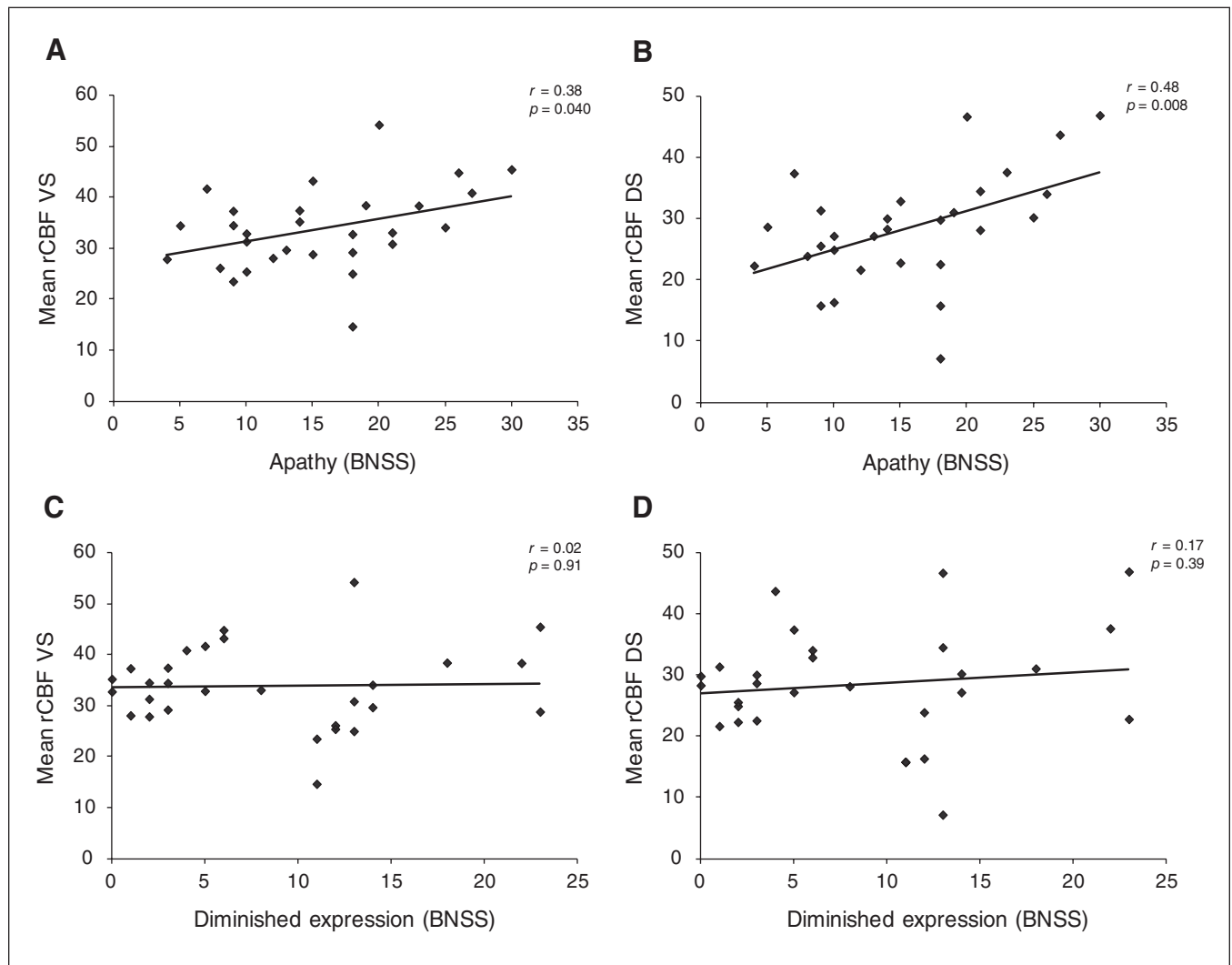
rCBF = regional cerebral blood flow.

ventral and dorsal striatum, a relationship that we did not find for diminished expression. This differential effect for the 2 negative symptom dimensions might account at least in part for the lack of consistent previous findings for the rCBF correlates of negative symptoms. In our study, an aggregation of overall negative symptoms would have led to a non-significant finding. The only other ASL study that specifically assessed apathy evaluated rCBF during planning-task performance, during which the authors observed reduced parietal and thalamic perfusion.<sup>32</sup> However, they did not report striatal perfusion, and comparison with our resting-state approach is difficult. It seems to be important for future ASL studies to assess both dimensions of negative symptoms separately, because different neural mechanisms may underlie these symptoms.<sup>21,33,54</sup>

While the distinction between apathy and diminished expression (the 2 negative symptom dimensions) has re-

ceived very limited interest in previous ASL studies, the blood-oxygen-level-dependent (BOLD) fMRI literature has provided evidence for dissociation of their neural correlates. For instance, Kirschner and colleagues<sup>25</sup> reported reduced activity in the ventral striatum during reward anticipation that correlated with apathy, but not with diminished expression. For the dorsal striatum, an association between reduced activity and avolition — but not anhedonia — has been shown. Importantly, reduced activity in these fMRI studies reflects attenuated signal differences between rewarding and nonrewarding stimuli. Therefore, an association of apathy with both a reduced task-related fMRI signal and increased resting-state rCBF in the striatum is not contradictory.

At this point, a mechanistic explanation for the association of apathy with striatal rCBF remains speculative. Several studies have found increased rCBF in the striatum to be



**Fig. 2:** Spearman correlation, including significance test, of (A) mean rCBF of the left and right ventral striatum with apathy; (B) mean rCBF of the left and right dorsal striatum with apathy; (C) mean rCBF of the left and right ventral striatum with diminished expression; (D) mean rCBF of the left and right dorsal striatum with diminished expression. BNSS = Brief Negative Symptom Scale; DS = dorsal striatum; rCBF = regional cerebral blood flow; VS = ventral striatum.

**Table 4: Spearman correlations between striatal rCBF, confounding variables and PANSS negative factor scores in patients with schizophrenia**

Correlation factor	Mean rCBF ventral striatum		Mean rCBF dorsal striatum	
	$r_{27}$	$p$ value	$r_{27}$	$p$ value
PANSS positive factor	-0.15	0.44	-0.24	0.21
PANSS negative factor	0.17	0.39	0.30	0.12
CDSS total score	0.23	0.24	0.35	0.06
Chlorpromazine equivalents	-0.05	0.80	-0.17	0.39
Composite cognitive ability score	0.27	0.17	0.11	0.58
Age	-0.39	0.04	-0.50	0.006

CDSS = Calgary Depression Scale for Schizophrenia; PANSS = Positive and Negative Syndrome Scale; rCBF = regional cerebral blood flow.

related to higher dopaminergic activity.<sup>55,56</sup> In addition, a PET study reported an association between increased dorsal striatal dopamine release and negative symptoms,<sup>57</sup> which might seem at odds with the observation that decreased dopamine availability can lead to apathy in neurologic patients and in animal models.<sup>57-59</sup> However, the hypothesis of aberrant salience attribution in schizophrenia proposes that increased dopaminergic activity in the striatum leads to difficulties in distinguishing between relevant and irrelevant stimuli.<sup>54,60</sup> This model has also been employed to account for the attenuated striatal reward signal in fMRI studies that has been associated with negative symptoms.<sup>61</sup> Thus, this inability to differentiate relevant and (in particular) rewarding stimuli could lead to a decrease in goal-directed behaviour and promote apathy.<sup>62</sup>

We found no significant correlation between positive symptoms or cognition and striatal rCBF. For positive symptoms, it needs to be kept in mind that the aim of the study was to investigate the neural correlates of negative symptoms, and patients with significant positive symptoms were excluded, considerably reducing variance. Cognitive deficits were not an exclusion criterion, but patients had to be able to take part in this relatively demanding study, and the overall cognitive performance of the patient group was less than 1 standard deviation below the control group.

Surprisingly, we did not find a significant group difference in rCBF of the striatum, despite the relationship between apathy and striatal rCBF. Striatal rCBF was slightly higher in patients than in controls, although this difference was not significant. This type of pattern can best be explained by a difference between patients and controls that is present only for patients with a high level of apathy. In addition, treatment with antipsychotics might have attenuated group differences in striatal rCBF to some extent.<sup>63</sup>

We observed that greater age was associated with reduced striatal rCBF and lower apathy, although effects of age have not been reported in previous studies of patients with schizophrenia. However, our finding was consistent with previous reports of reduced rCBF with increasing age in healthy individuals.<sup>64,65</sup> Interestingly, Bijanki and colleagues<sup>66</sup> found a negative relationship between age and negative symptoms, as well as white matter integrity measured by diffusion tensor imaging, emphasizing the need to include age as a confounding variable. Our finding that younger patients showed stronger apathy than older participants might seem surpris-

ing, but it was consistent with the study by Bijanki and colleagues.<sup>66</sup> Overall, the inclusion of age in partial correlations of apathy and striatal rCBF attenuated the association, but the effect in the dorsal striatum remained at trend level.

### Limitations

This study provides evidence for a positive association between increased striatal rCBF and the negative symptom dimension of apathy. However, several limitations need to be taken into account in the interpretation of these findings. First, our sample size was moderate; these findings require replication in a larger sample, which would also allow for further evaluation of the effect of age on the observed associations. Second, our sample was recruited with the aim of investigating the neural correlates of negative symptoms, and is thus not representative of the entire population of patients with schizophrenia. Different associations between symptoms and striatal rCBF could be found in patients with higher levels of positive or depressive symptoms. Third, all patients in our study took second-generation antipsychotic medication. Previous research has suggested an influence of antipsychotic medication on striatal rCBF.<sup>52,63,67,68</sup> While we did not observe an association between striatal rCBF and antipsychotic dose, we cannot exclude a potential effect of antipsychotic medication. Thus, future studies should include nonmedicated patients and patients taking first-generation antipsychotics to generalize the relationship between apathy and striatal activity to these populations.

### Conclusion

The association between increased striatal rCBF and the negative symptom dimension of apathy, but not diminished expression, provides further evidence for the assumption of different underlying neural bases. These dimensions should be considered separately in future research on negative symptoms. Furthermore, ASL seems to provide a direct and quantitative technique for investigating negative symptoms, circumventing the limitations of task-based measures often employed for BOLD-fMRI and the invasiveness of PET and SPECT. This may qualify ASL as an alternative technique for developing biomarkers that reflect the pathomechanisms of negative symptoms.

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