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ORIGINAL ARTICLE

Striatal function in relation to negative symptoms in schizophrenia

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Background. Previous studies have suggested that motivational aspects of executive functioning, which may be disrupted in schizophrenia patients with negative symptoms, are mediated in part by the striatum. Negative symptoms have been linked to impaired recruitment of both the striatum and the dorsolateral prefrontal cortex (DLPFC). Here we tested the hypothesis that negative symptoms are associated primarily with striatal dysfunction, using functional magnetic resonance imaging (fMRI).

Method. Working-memory load-dependent activation and gray matter volumes of the striatum and DLPFC were measured using a region-of-interest (ROI) approach, in 147 schizophrenia patients and 160 healthy controls. In addition to testing for a linear relationships between striatal function and negative symptoms, we chose a second, categorical analytic strategy in which we compared three demographically and behaviorally matched subgroups: patients with a high burden of negative symptoms, patients with minimal negative symptoms, and healthy subjects.

Results. There were no differences in striatal response magnitudes between schizophrenia patients and healthy controls, but right DLPFC activity was higher in patients than in controls. Negative symptoms were inversely associated with striatal, but not DLPFC, activity. In addition, patients with a high burden of negative symptoms exhibited significantly lower bilateral striatal, but not DLPFC, activation than schizophrenia patients with minimal negative symptoms. Working memory performance, antipsychotic exposure and changes in gray matter volumes did not account for these differences.

Conclusions. These data provide further evidence for a robust association between negative symptoms and diminished striatal activity. Future work will determine whether low striatal activity in schizophrenia patients could serve as a reliable biomarker for negative symptoms.

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Key words: Dorsolateral prefrontal cortex, functional MRI, negative symptoms, schizophrenia, striatum.

Introduction

The striatum, which includes the caudate nucleus and putamen, has been hypothesized to play a central role in the pathophysiology of schizophrenia for many decades (Carlsson, 1995). Several studies have suggested that changes in the striatum may occur early in the illness. For example, adolescents who later go on to develop schizophrenia (Mittal & Walker, 2007), and also neuroleptic-naïve schizophrenia patients (Fenton *et al*. 1994; Honer *et al*. 2005), exhibit subtle motor abnormalities that may be indicative of dysfunction of the striatum or other basal ganglia structures. There is also strong pharmacological (Seeman, 1987) and *in vivo* (Laruelle *et al*. 1996; Abi-Dargham *et al*. 2000; Kegeles *et al*. 2010) evidence for overactivity of dopamine neurotransmission within the striatum in schizophrenia.

However, the results of functional neuroimaging studies of the striatum in schizophrenia patients have been mixed, with some showing increases (Manoach *et al*. 2000; Jensen *et al*. 2008; Walter *et al*. 2009) and others showing decreases (Crespo-Facorro *et al*. 2001; Morey *et al*. 2005; Taylor *et al*. 2005; Juckel *et al*. 2006*b*; Koch *et al*. 2008; Dowd & Barch, 2010) in task-elicited striatal responses in schizophrenia, compared to

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responses of healthy subjects. Similarly, the results of fluorodeoxyglucose positron emission tomography (FDG-PET) studies have been conflicting, with some studies demonstrating elevated (Wolkin *et al*. 1985; Biver *et al*. 1995) and others finding reduced (Buchsbaum *et al*. 1982; Siegel *et al*. 1993) striatal metabolic rates in schizophrenia.

One possible explanation for these variable findings is that the pattern of striatal dysfunction in schizophrenia varies with symptomatic state (Laruelle & Abi-Dargham, 1999; Dowd & Barch, 2010; Harvey *et al*. 2010) and/or subtype of the illness. Empirical studies using factor analytic and taxometric statistical methods have provided evidence for the existence of at least two categories of schizophrenia patients: those with and those without high levels of persistent negative symptoms (Blanchard *et al*. 2005; Blanchard & Cohen, 2006; Buchanan, 2007). Negative symptoms include flat or blunted affect, poverty of speech, inability to experience pleasure (anhedonia), lack of desire to form relationships and lack of motivation (avolition) (Carpenter *et al*. 1988). Several proposed subtyping schemes of schizophrenia, such as Deficit *versus* Non-deficit (Carpenter *et al*. 1988) and paranoid *versus* non-paranoid subtypes (Magaro, 1980), generally correspond to this 'bipartite' model of the illness. However, the data may also be consistent with a continuous distribution of negative symptoms (Smith *et al*. 1998; Blanchard *et al*. 2005).

Neuroimaging studies conducted in healthy subjects have demonstrated the central role of the striatum in motivational processes thought to be disrupted in negative symptoms (Harvey *et al*. 2007; Wacker *et al*. 2009). In addition, in patients with schizophrenia, inverse correlations between striatal response magnitude and severity of negative symptoms (Juckel *et al*. 2006*a*, *b*) or of individual negative symptoms, such as anhedonia (Dowd & Barch, 2010; Harvey *et al*. 2010) and apathy (Simon *et al*. 2010), have been reported. Previous studies testing associations between striatal dysfunction and negative symptom severity in schizophrenia patients have used reward paradigms (Juckel *et al*. 2006*a*, *b*; Simon *et al*. 2010) or emotion recognition tasks (Dowd & Barch, 2010; Harvey *et al*. 2010).

However, studies conducted in non-human primates and in humans have found that working memory-related processes also rely on the striatum (Goldman & Rosvold, 1972; Dunnett & Iversen, 1981; Lewis *et al*. 2004; Chang *et al*. 2007; Landau *et al*. 2009) and the dorsolateral prefrontal cortex (DLPFC) (Wager & Smith, 2003; Castner *et al*. 2004). Because of the central role of executive control processes such as working memory in self-directed, volitional behavior, it has been hypothesized that impairments in executive function in schizophrenia give rise to negative symptoms (Carter *et al*. 1996). However, surprisingly weak associations between DLPFC activation during executive processes, as measured by functional magnetic resonance imaging (fMRI), and negative symptoms have been reported (for a meta-analysis, see Goghari *et al*. 2010). Therefore, in the present study, we sought to test the hypothesis that working memory-related striatal dysfunction represents a neural correlate of negative symptoms in schizophrenia.

Although the study of reward processing in negative symptoms has a high degree of face validity because reward and/or emotional function are likely to be impaired in high negative symptom patients (Barch & Dowd, 2010; Foussias & Remington, 2010), the use of working memory paradigms, such as the Sternberg Item Recognition Paradigm (SIRP) used in the current study, to measure striatal responses in schizophrenia patients has some advantages. First, neural responses during working memory tasks can be measured quantitatively because activation magnitude is directly proportional to the number of items maintained in working memory (Manoach *et al*. 2000). The contrast between a moderate and very low working memory load (e.g. five items *versus* one item) provides a reliable measure of working memory efficiency that is independent of perceptual and motor functions. Second, responses during standardized working memory tasks are less likely to be influenced by individual subjective experience/preferences and transient emotional states, which may be a confounding factor in paradigms using emotionally laden stimuli. Third, the SIRP reliably recruits both the striatum and the DLPFC, permitting a direct comparison of the function of the two structures and their relative associations with negative symptom burden.

Thus, in the present investigation, functional and structural MRI data collected during a large multi-site neuroimaging study of schizophrenia (Roffman *et al*. 2008; Ehrlich *et al*. 2010; White *et al*. 2010) were used to test the relationship between negative symptoms and frontostriatal function during a working memory task (Sternberg, 1969; Manoach *et al*. 2000).

We used two statistical strategies. Assuming a continuous distribution, we studied the relationship between the severity of negative symptoms and striatal function in the full cohort of schizophrenia patients. Because of the evidence for distinct subgroups of schizophrenia patients with high and low levels of negative symptoms (Blanchard *et al*. 2005; Blanchard & Cohen, 2006; Buchanan, 2007), we also compared three groups of subjects: (1) schizophrenia patients with a high burden of negative symptoms, (2) schizophrenia patients with minimal negative symptoms, and (3) demographically matched healthy subjects.

In this analysis, the two patient groups were matched with respect to behavioral performance, IQ, positive symptoms and duration of illness.

Working memory-related activation was measured in the striatum and DLPFC using an anatomical region-of-interest (ROI) approach (Kuperberg *et al*. 2007; Yendiki *et al*. 2010). Volumes of these structures were also measured and compared across groups to determine whether any associations between striatal or DLPFC volumes and negative symptoms or antipsychotic exposure were present. We predicted that: (1) the magnitude of responses of the striatum, but not the DLPFC, would show a relationship with negative symptom severity in both the dimensional and categorical analyses; and (2) these findings would not be secondary to the effects of antipsychotic exposure or changes in striatal volumes.

Method

Participants

In the Mind Clinical Imaging Consortium (MCIC) study of schizophrenia (Roffman *et al*. 2008; Ehrlich *et al*. 2010; White *et al*. 2010), structural and functional MRI scans were collected in a total of 328 subjects from four participating sites: the Universities of Iowa (UI), Minnesota (UMN) and New Mexico (UNM) and Massachusetts General Hospital in Boston (MGH). After complete description of the study to the participants, written informed consent was obtained. The human subjects research committees at each of the four sites approved the study protocol. The patient group (SCZ) included subjects with a DSM-IV diagnosis of schizophrenia, established using structured clinical interviews and review of case files by trained clinicians. Healthy controls (HC) were included if they had no history of a medical or Axis I psychiatric diagnosis. All participants were at least 18 years old and no older than 60, and fluent in English. Participants were excluded if they had a history of neurologic disease, or psychiatric disease other than schizophrenia, history of a head injury, history of substance abuse or dependence within the past month, severe or disabling medical conditions, contraindication to MR scanning or IQ < 70, based on the reading subtest from the Wide Range Achievement Test 3 (WRAT-3-RT).

The final sample with complete and high-quality [for quality assurance procedures see online Supplementary Material (SM) 1.2, SM 1.3 and the section on Structural and functional image data processing] structural MRI, fMRI and behavioral data comprised 160 HC and 147 SCZ. Using the upper (>33 points) and lower quartiles (<15 points) of the distribution of the Scale for the Assessment of Negative Symptoms (SANS; Andreasen, 1983) composite score of this sample as thresholds, we selected a subsample of patients with very high levels of negative symptoms ($n = 33$; the 'High SANS' group) and another group with very low levels of negative symptoms ($n = 34$; the 'Low SANS' group). We censored our data to match patients from both groups with respect to: scanner field strength, behavioral accuracy during the working memory paradigm, pre-morbid IQ, severity of positive symptoms and duration of illness (Table 2). Within the cohort of healthy comparison subjects, a subgroup of participants ($n = 34$) was identified in an unbiased manner using a propensity score-matching algorithm (Joffe & Rosenbaum, 1999), to construct a healthy comparison group of comparable size to the two patient groups that was matched to the 67 patients with respect to mean behavioral accuracy and pre-morbid intelligence (see Table 1).

Clinical measures

All study participants underwent an extensive clinical diagnostic assessment (see SM 1.1, Table 1 and Ehrlich *et al*. 2010). Severity of positive and negative symptoms was rated using the Scale for the Assessment of Positive Symptoms (SAPS; Andreasen, 1984) and the SANS (Andreasen, 1983). Antipsychotic history was collected as part of the psychiatric assessment using the PSYCH instrument (Andreasen, 1987), and cumulative and current antipsychotic exposure was calculated using the chlorpromazine (CPZ) conversion factors of Andreasen *et al*. (2010) (see SM 1.1).

SIRP

The SIRP was administered during six 46-s blocks per run for two 360-s runs. In each block a memory set, composed of one (1t), three (3t) or five (5t) digits, was presented (two blocks/load condition). The Encode phase was followed by a presentation of 14 digits, one at a time (the Probe phase), and participants responded to each probe to indicate whether or not the probe digit was in the memory set. The subjects were instructed to respond as quickly and accurately as possible and were given a bonus of 5 cents for each correct response. This bonus was provided after completion of the scan. (For additional details about the paradigm, see SM 1.2 and Manoach *et al*. 2001.) The stimuli and responses were presented and collected using E-prime software (EPrime v. 1.1, Psychology Software Tools, Inc., USA). All participants had a mean accuracy of at least 80%.

Structural and functional image acquisition

Structural MRI data were acquired with either a 1.5-T Siemens Sonata (UNM, MGH, UI) or a 3-T Siemens

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Table 1. *Demographics, behavioral and clinical variables of all participants by acquisition site with different scanner field strengths*

	1.5 T		3 T		All sites	
	HC	SCZ	HC	SCZ	HC	SCZ
Sample size	43	42	117	105	160	147
Gender, males, *n* (%)	34 (79.07)[k]	32 (76.19)	65 (55.56)[k]	79 (75.24)	99 (61.87)[o]	111 (75.51)[o]
Age (years)	28.81 (11.61)	31.60 (11.97)	32.47 (10.97)	33.76 (10.29)	31.49 (11.23)	33.14 (10.80)
Pre-morbid IQ[a]	49.86 (5.13)	47.15 (5.85)	50.87 (3.88)	47.03 (6.58)	50.60 (4.26)[p]	47.06 (6.36)[p]
Parental SES[b]	2.37 (0.82)[m]	2.98 (1.27)	2.79 (0.67)[m]	2.85 (0.94)	2.68 (0.73)[q]	2.88 (1.04)[q]
Handedness[c]	0.77 (2.00)	0.80 (2.19)	0.71 (2.36)	1.01 (2.78)	0.73 (2.27)	0.95 (2.62)
Accuracy (%)	98.22 (1.36)	95.69 (3.97)	98.31 (1.68)	95.81 (4.18)	98.29 (1.60)[r]	95.78 (4.11)[r]
Reaction time (ms)	627.91 (71.24)	707.02 (90.60)	634.71 (86.65)	700.28 (119.55)	631.57 (79.55)[s]	702.88 (108.91)[s]
SANS composite score	N.A.	26.71 (12.81)	N.A.	24.48 (14.51)	N.A.	25.12 (14.04)
SAPS composite score	N.A.	27.11 (16.68)[n]	N.A.	20.51 (15.68)[n]	N.A.	22.42 (16.20)
Duration of illness (years)	N.A.	8.34 (9.90)	N.A.	11.01 (9.77)	N.A.	10.25 (9.85)
Abnormal Involuntary Movement Scale	N.A.	0.29 (0.67)	N.A.	0.42 (0.77)	N.A.	0.38 (0.75)
Barnes Akathisia Rating Scale	N.A.	0.50 (0.74)	N.A.	0.58 (0.83)	N.A.	0.55 (0.81)
Lifetime antipsychotic dose (CPZ dose years)[d]	N.A.	21.32 (30.72)	N.A.	55.01 (122.48)	N.A.	45.86 (106.66)
Current antipsychotic dose (CPZ units)	N.A.	479.51 (438.18)	N.A.	548.60 (620.58)	N.A.	530.58 (577.84)

SCZ, Patients with schizophrenia; HC, healthy controls; SES, socio-economic status; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; CPZ, chlorpromazine; N.A., not applicable.

Means are given with standard deviations in parentheses.

[a] Pre-morbid cognitive achievement was estimated by the Wide Range Achievement Test (WRAT-3-RT; Wilkinson, 1993).

[b] Parental SES was determined using the Hollingshead index (Hollingshead, 1965).

[c] Handedness was determined using the Annett Scale of Hand Preference (Annett, 1970).

[d] 1 dose year = 100 CPZ equivalents per day for 1 year.

At the 1.5-T site the (k) percentage of male HC was higher than at the 3-T sites ($\chi^2 = 7.370$, df = 1, $p = 0.007$) and (m) the mean parental SES of HC at the 1.5-T site was lower than at the 3-T sites ($T = -3.270$, df = 158, $p = 0.001$). SAPS scores (n) at the 1.5-T site were higher than at the 3-T sites ($T = 2.261$, df = 144, $p = 0.025$).

Patients had (p) a lower WRAT score ($T = 5.725$, df = 299, $p < 0.001$), (q) a higher parental SES score ($T = -2.021$, df = 302, $p = 0.044$), (r) a lower Sternberg Item Recognition Paradigm (SIRP) accuracy ($T = 7.128$, df = 305, $p < 0.001$) and (o) a lower percentage of female participants ($\chi^2 = 6.590$, df = 1, $p = 0.010$).

Trio (UMN). Functional MRI data were acquired with either a 1.5-T Siemens Sonata (UNM) or a 3-T Siemens Trio (UMN, MGH, UI).

The T1-weighted structural brain scans at each of the four sites were acquired with a coronal gradient echo sequence: repetition time (TR) = 2530 ms for 3T, 12 ms for 1.5T; echo time (TE) = 3.79 ms for 3T, 4.76 ms for 1.5T; inversion time (TI) = 1100 for 3T; bandwidth = 181 for 3T, 110 for 1.5T; 0.625 × 0.625 voxel size; slice thickness 1.5 mm; 256 × 256 × 128 cm matrix; field of view (FOV) = 16 cm; number of excitations (NEX) = 1 for 3T, 3 for 1.5T.

For all sites, functional images were acquired by using single-shot echo–planar imaging with identical parameters [orientation: AC–PC line; number of slices = 27; slice thickness = 4 mm, 1-mm gap; TR = 2000 ms; TE = 30 ms (3T) or 40 ms (1.5 T), FOV = 22 cm; 64 × 64 matrix; flip angle = 90°; voxel dimensions = 3.44 × 3.44 × 4 mm]. Cross-site calibration and reliability was established prior to the study (Friedman & Glover, 2006*a*, *b*; Han *et al*. 2006; Friedman *et al*. 2008; Jovicich *et al*. 2009; Yendiki *et al*. 2010).

Structural and functional image data processing

Structural MRI data were analyzed in an automated manner with atlas-based FreeSurfer segmentation software, version 4.0.1 (http://surfer.nmr.mgh.harvard.edu) to generate cortical and subcortical

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volumetric measures of ROIs according to each participant's individual anatomy (Fischl *et al*. 2002). Striatal ROIs were generated by merging the caudate nucleus and putamen segmentations in each hemisphere (i.e. the dorsal striatum). DLPFC ROIs were derived from FreeSurfer cortical parcelations as described previously (Ehrlich *et al*. 2010; Yendiki *et al*. 2010).

We evaluated the quality of the fMRI data by manual inspection and using Artifact Detection Tools (ART; Whitfield-Gabrieli, 2009). Functional images were processed using the Function Biomedical Informatics Research Network (FBIRN) Image Processing Stream (FIPS), a pipeline using the Functional MRI of the Brain (FMRIB) Software Library of FSL (Smith *et al*. 2004). Functions used from FSL included motion correction using MCFLIRT (Jenkinson *et al*. 2002), removal of non-brain voxels using BET (Smith, 2002), spatial smoothing using a three-dimensional (3D) Gaussian kernel with a full-width at half-maximum (FWHM) of 5 mm, normalization of all volumes to a common average scan intensity and high-pass temporal filtering.

A Functional Imaging Linear Model (FILM; Woolrich *et al*. 2001) was fit to model the Probe phases of each subject's preprocessed functional time series. We used the following linear Contrasts Of Parameter Estimates (COPEs): Probe-5t *versus* Probe-1t and all loads (average of Probe-1t, Probe-3t and Probe-5t) *versus* fixation. Here we refer to responses to the Probe-5t *versus* Probe-1t condition as 'load-dependent' activation.

We obtained indices of activation for the striatal and DLPFC ROIs using the COPEs obtained from the second-level fixed-effects analysis for each participant. We applied an additional functional mask, based on the COPE of all loads (1t, 3t and 5t) *versus* fixation exceeding a threshold of $Z=2.3$, and extracted the maximum percentage signal change (Max%Δ), defined as the maximum COPE of Probe-5t *versus* Probe-1t. The use of a functional mask (within anatomical ROIs) from all working memory loads protects against biases in signal change calculations derived from individual conditions (Mitsis *et al*. 2008). Additional details about the analysis methods are included in SM 1.3.

Statistical analyses

Percentage signal change and gray matter volumes (adjusted for differences in intracranial volume following O'Brien *et al*. 2006) were compared by Student's *t* tests, multiple regression analyses or one-way ANOVA followed by Scheffé *post-hoc* tests when appropriate. Means are shown with standard deviations (S.D.) unless indicated otherwise, and all statistical tests were two-tailed. All analyses were carried out with SPSS version 17.0 (SPSS Inc., USA).

Results

Sample characteristics

Demographic and clinical characteristics of the 147 schizophrenia patients and 160 healthy controls are presented in Table 1. For 11 of the 14 control variables studied, there were no differences among acquisition sites with different field strengths. Site differences were found in the distribution of gender and parental socio-economic status (SES) for the healthy control group, and in mean SAPS scores for the schizophrenia group (see Table 1).

The schizophrenia group had the same mean age and same handedness as the healthy control group but had a higher parental SES score (corresponding to a lower status), lower WRAT score, somewhat lower SIRP accuracy and a lower percentage of female participants in comparison to the controls (see Table 1).

The three matched subgroups (High SANS, Low SANS, and healthy controls) did not differ in any of the demographic or clinical variables (except for SANS score; Table 2).

Working memory-related blood oxygen level-dependent (BOLD) responses

Striatum

There were no differences in left and right load-dependent striatal activity between schizophrenia patients and healthy controls (left: 0.142 ± 0.132 in SCZ and 0.125 ± 0.121 in HC, $t=1.11$, df$=305$, $p=0.268$; right: 0.131 ± 0.129 in SCZ and 0.115 ± 0.129 in HC, $t=1.16$, df$=305$, $p=0.249$; Fig. 1*a*).

In the schizophrenia group, negative symptoms were significantly correlated with left and right striatal activity (left: $r=-0.222$, $p=0.007$; right: $r=-0.267$, $p=0.001$; Fig. 1*a*). There were no correlations between negative symptoms and SIRP performance (accuracy $r=-0.082$, $p=0.323$).

When we compared the matched subgroups, the High SANS group exhibited significantly less load-dependent activation of the left and right striatum than the Low SANS group (left: $F=5.08$, df$=2/98$, $p=0.008$; right: $F=7.19$, df$=2/98$, $p=0.001$; Fig. 2*a*). In addition, the Low SANS group showed greater right striatal activation than the healthy control group (Fig. 2*a*).

DLPFC

Patients showed a higher left, but not right, load-dependent signal change in the DLPFC when

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Table 2. *Demographics, behavioral, clinical variables and gray matter volumes of the matched subgroups*

	Low SANS SCZ	High SANS SCZ	HC
Sample size (*n*)	34	33	34
Participants per scanner field strength (3T/1.5T)	24/10	21/12	24/10
Gender (*n* of males)	25	25	19
Age (years)	34.2 (10.4)	30.0 (10.7)	32.5 (12.7)
Pre-morbid IQ[a]	47.6 (5.6)	46.7 (7.2)	48.9 (4.1)
Parental SES[b]	2.7 (1.1)	2.7 (1.0)	2.7 (0.6)
Handedness[c]	1.2 (2.7)	0.2 (0.6)	0.7 (2.1)
Accuracy (%)	95.6 (4.0)	95.4 (4.0)	96.8 (1.7)
Reaction time (ms)	689.5 (81.6)[e]	678.3 (93.5)[e]	631.5 (76.4)[e]
SANS	9.2 (4.1)[f]	43.9 (9.6)[f]	N.A.
SAPS	17.8 (15.8)	23.6 (13.7)	N.A.
Duration of illness (years)	10.6 (9.3)	7.1 (8.4)	N.A.
Abnormal Involuntary Movement Scale	0.44 (0.70)	0.27 (0.67)	N.A.
Barnes Akathisia Rating Scale	0.56 (0.70)	0.52 (0.83)	N.A.
Lifetime antipsychotic dose (CPZ dose years)[d]	72.4 (189.9)	42.3 (96.2)	N.A.
Current antipsychotic dose (CPZ units)	629.0 (617.2)	514.5 (524.1)	N.A.
lh striatal volume (mm^3)	9832.0 (729.3)	9743.5 (1325.3)	9397.1 (889.4)
rh striatal volume (mm^3)	9537.9 (833.4)	9581.0 (1102.4)	9202.4 (923.2)
lh DLPFC volume (mm^3)	20886.8 (2868.0)	20776.3 (2668.5)	21278.1 (2966.8)
rh DLPFC volume (mm^3)	20698.7 (2750.4)	20754.8 (2734.3)	21006.4 (3091.4)

SCZ, Patients with schizophrenia; HC, healthy controls; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; SES, socio-economic status; CPZ, chlorpromazine; lh, left; rh, right; DLPFC, dorsolateral prefrontal cortex; N.A., not applicable.

Means are given with standard deviations in parentheses.

[a] Pre-morbid cognitive achievement was estimated by the Wide Range Achievement Test (WRAT-3-RT; Wilkinson, 1993).

[b] Parental SES was determined using the Hollingshead index (Hollingshead, 1965).

[c] Handedness was determined using the Annett Scale of Hand Preference (Annett, 1970).

[d] 1 dose year = 100 CPZ equivalents per day for 1 year.

The distribution across acquisition sites was not significantly different among the groups.

The groups differed on the following variables:

[e] Low and High SANS patients had significantly longer reaction times compared to HC on the basis of Fisher's least significant difference *post-hoc* tests following one-way ANOVA ($p < 0.05$).

[f] Low SANS patients had significantly lower SANS composite scores compared to High SANS patients on the basis of a Student *t* test ($p < 0.001$).

compared to healthy controls (left: 0.349 ± 0.243 in SCZ and 0.291 ± 0.217 in HC, $t = 2.13$, df = 305, $p = 0.034$; right: 0.316 ± 0.259 in SCZ and 0.276 ± 0.217 in HC; $t = 1.37$, df = 305, $p = 0.173$; Fig. 1*b*).

Negative symptoms did not correlate with left or right DLPFC activity (left: $r = -0.087$, $p = 0.296$; right: $r = -0.132$, $p = 0.111$; Fig. 1*b*).

In the matched subgroups analysis, the load-dependent signal change in the left and right DLPFC did not differ between the Low SANS group and the High SANS group (Fig. 2*b*). The Low SANS group exhibited greater load-dependent activation of the left DLPFC than the healthy controls (left: $F = 4.49$, df = 2/98, $p = 0.014$; right: $F = 2.46$, df = 2/98, $p = 0.091$; Fig. 2*b*).

Gray matter volumes

Striatum

Schizophrenia patients had significantly larger left and right striatal volumes in comparison to the controls (left: 9771 ± 1018 *v.* 9454 ± 913, $t = -2.87$, df = 305, $p = 0.004$; right: 9519 ± 939 *v.* 9237 ± 921, $t = -2.66$, df = 305, $p = 0.008$). Striatal volumes were not related to negative symptoms (left: $r = -0.035$, $p = 0.676$; right: $r = 0.036$, $p = 0.668$) and there were no differences between the High and the Low SANS groups, nor were there differences between either patient group and the controls (Table 2; left: $F = 1.76$, df = 2/98, $p = 0.178$; right: $F = 1.58$, df = 2/98, $p = 0.211$).

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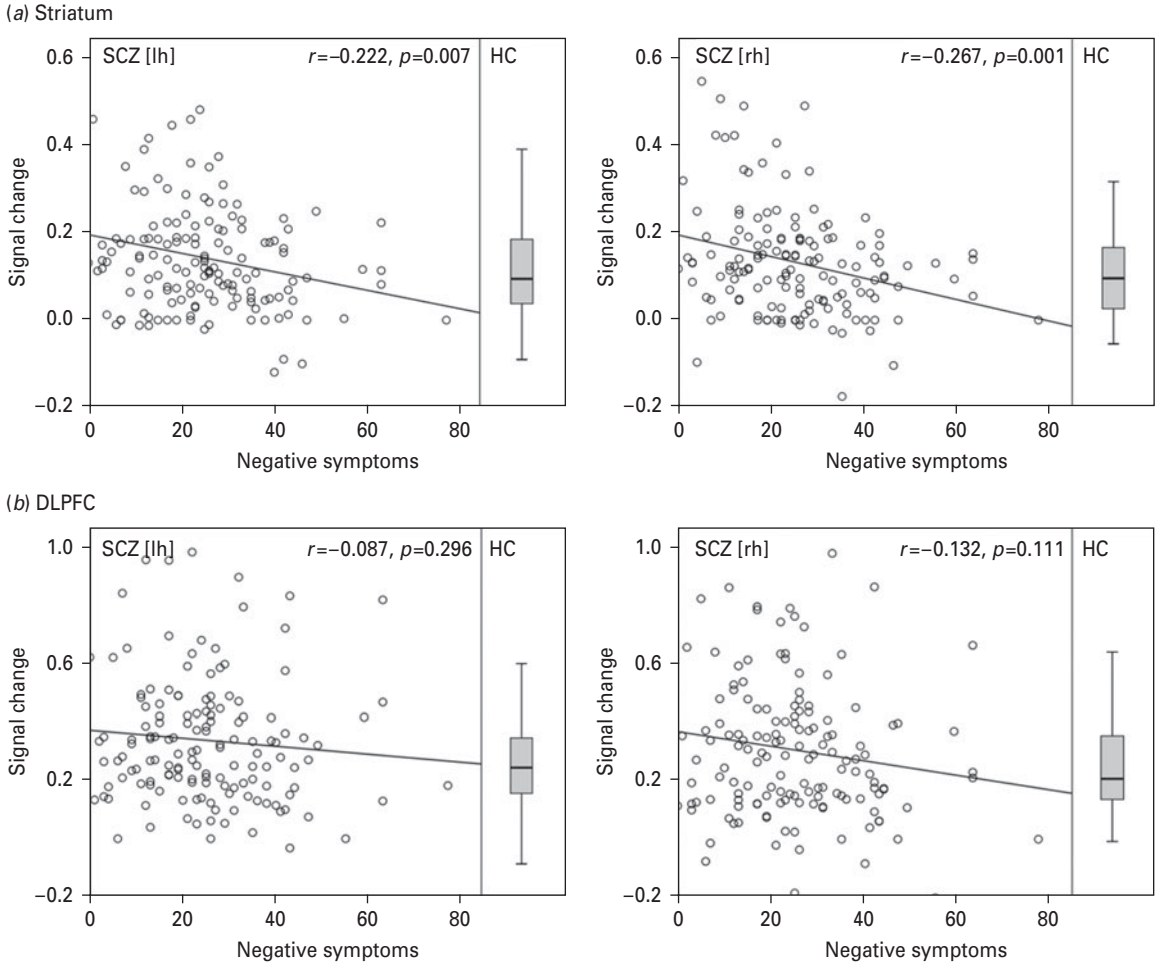

Fig. 1. Working memory-related load-dependent percentage signal change in schizophrenia patients (SCZ, scatter plot with negative symptoms) and healthy controls (HC, box plot): (*a*) in the left and right striatum; and (*b*) in the left and right dorsolateral prefrontal cortex (DLPFC). lh, Left hemisphere; rh, right hemisphere.

DLPFC

Schizophrenia patients had significantly smaller left and right DLPFC volumes in comparison to the controls (left: 20 863 ± 2475 *v.* 22 054 ± 2572, $t = 4.12$, df = 305, $p < 0.001$; right: 20 660 ± 2719 *v.* 21 775 ± 2590, $t = 3.67$, df = 305, $p < 0.001$). DLPFC volumes were not correlated with negative symptoms (left: $r = 0.017$, $p = 0.837$; right: $r = 0.057$, $p = 0.498$) and there were no differences between the High and the Low SANS groups in DLPFC volumes, nor were there differences between either patient group and the controls (Table 2; left striatum $F = 0.29$, df = 2/98, $p = 0.752$; right: $F = 0.11$, df = 2/98, $p = 0.897$).

Secondary analyses

Potential confounding effects of acquisition site

All of the statistically significant effects reported above remained significant after covarying for the potential effects of acquisition site (SM Tables 1 and 2). For the models comparing patient subgroups and matched controls, we did not covary for the effects of different field strengths because the distribution of participants across sites was similar in each subgroup.

Potential relationships among the variables

There were no correlations between striatal activity or DLPFC activity and SIRP performance in any of the groups. In addition, striatal and DLPFC volumes, and also current or cumulative antipsychotic exposure, did not correlate with working memory-induced signal change in the striatum or the DLPFC, or with SIRP performance, in any of the groups (Table 3).

Striatal and DLPFC volumes showed a highly significant bilateral negative association with age. Therefore, all analyses that examined striatal and DLPFC volumes were performed with the addition of age as a covariate; in these analyses, striatal volumes

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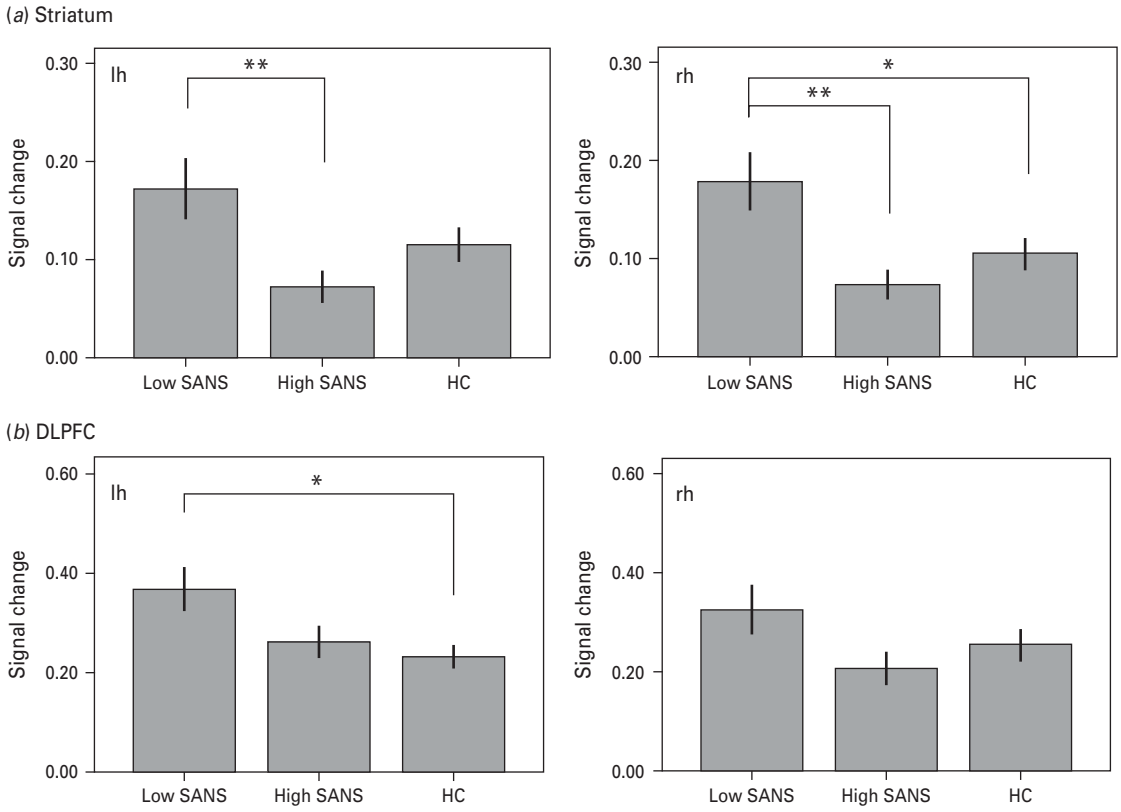

Fig. 2. Working memory-related load-dependent percentage signal change within the Low Scale for the Assessment of Negative Symptoms (SANS), High SANS and healthy control (HC) groups in: (*a*) the left and right striatum; and (*b*) the left and right dorsolateral prefrontal cortex (DLPFC). Asterisks indicate significant differences on Scheffé *post-hoc* tests following one-way ANOVA (* $p<0.05$, ** $p<0.01$, *** $p<0.001$). lh, Left hemisphere; rh, right hemisphere.

were not correlated with current or cumulative antipsychotic exposure. However, DLPFC volumes showed a negative partial correlation with current antipsychotic exposure (Table 3).

Discussion

Summary of findings

In this study, we found an inverse relationship between negative symptom severity and striatal activation during a working memory paradigm, in both a dimensional and a categorical analysis of the data, accompanied by an absence of an overall difference between the schizophrenia patients and controls in mean striatal activation. By contrast, we found no association between working memory-related DLPFC activation and negative symptoms, even though left DLPFC activity was higher overall in the schizophrenia group than in the controls. In addition, mean striatal volume was higher, and mean DLPFC volume was lower, in the schizophrenia patients in comparison to the controls. However, these changes in gray matter volume did not account for the changes in working memory-related striatal and DPLFC activation found in the schizophrenia patients.

Link between poor striatal function and negative symptoms

Several previous studies have found evidence for diminished striatal responsiveness to rewarding or to generally emotionally salient information in schizophrenia, in comparison to healthy controls (Crespo-Facorro *et al*. 2001; Taylor *et al*. 2005; Juckel *et al*. 2006*a*, *b*; Dowd & Barch, 2010). In addition, an inverse relationship between negative symptoms and neural activity in the ventral striatum during the anticipation of monetary gain has been found in antipsychotic-naïve (Juckel *et al*. 2006*b*) and antipsychotic-treated (Juckel *et al*. 2006*a*; Schlagenhauf *et al*. 2008) patients with schizophrenia. Our data, a large multi-site cohort, confirm and extend these previous reports by demonstrating this association using a working memory paradigm. The relative 'paradigm independence' of this association suggests that negative symptoms may be linked to a global impairment in striatal function.

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Table 3. *Correlations between outcome variables and control variables*

		Striatal activity		DLPFC activity		Striatal volume		DLPFC volume	
		lh	rh	lh	rh	lh	rh	lh	rh
SIRP accuracy	SCZ	0.040	0.121	0.060	−0.009	0.026[a]	0.011[a]	0.086[a]	0.062[a]
	HC	−0.115	−0.011	−0.034	−0.111	0.104[a]	0.155[a]	0.127[a]	0.093[a]
Signal change in same region and hemisphere	SCZ	N.A.	N.A.	N.A.	N.A.	0.114	0.051	−0.021	−0.031
	HC	N.A.	N.A.	N.A.	N.A.	−0.059	0.130	0.023	−0.035
Current antipsychotic dose (CPZ units)	SCZ	0.151	−0.023	−0.057	−0.143	−0.009[a]	0.011[a]	−0.336[a]***	−0.267[a]***
Lifetime antipsychotic dose (CPZ dose years)	SCZ	0.008	0.929	−0.072	−0.066	0.033[a]	0.001[a]	−0.147[a]	−0.169[a]

DLPFC, dorsolateral prefrontal cortex; lh, left hemisphere; rh, right hemisphere; SIRP, Sternberg Item Recognition Paradigm; CPZ, chlorpromazine; SCZ, patients with schizophrenia; HC, healthy controls; N.A., not applicable.

[a] Partial correlations covarying for the effects of age.

Asterisks indicate significant correlations: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.01$.

Studies that used paradigms with rewarding or emotional stimuli evoke primarily ventral striatal activation, whereas here we report changes in the dorsal striatum (caudate nucleus and putamen), the portion of the striatum that receives input from the DLPFC (Alexander *et al*. 1986; Middleton & Strick, 2000) which is involved in working memory (Goldman & Rosvold, 1972; Dunnett & Iversen, 1981; Lewis *et al*. 2004; Chang *et al*. 2007; Landau *et al*. 2009). Thus, the striatal deficit associated with negative symptoms may involve all or the majority of the striatum; regional variation in findings across studies may be related to the specific paradigms used.

An alternative interpretation of the similarity between our findings and results of studies using reward paradigms is that the impairment in striatal function detected here in patients with prominent negative symptoms is due to a deficit in reward anticipation during working memory. Consistent with this interpretation are findings of single cell recording studies in non-human primates, which have identified reward-responsive neurons throughout both the dorsal and ventral portions of the striatum (Schultz, 2002). Reward anticipation has been associated with motivational processes that promote goal-directed behaviors, including higher-order executive function (Schultz, 2002). Current research suggests that schizophrenia patients do not have a deficit in hedonic experience (consummatory aspects of reward processing) but instead experience a lack of motivation and reduced ability to anticipate reward (Horan *et al*. 2006; Burbridge & Barch, 2007; Gard *et al*. 2007; Herbener *et al*. 2008; Barch & Dowd, 2010). Loss of motivation, leading to a reduction in goal-directed behaviors, may correlate with diminished striatal responses during both the anticipatory phase of reward and executive tasks.

It is important to note that the version of the SIRP used in this study included a monetary reward following the scan; although participants did not receive any direct feedback during performance of the task, they were told prior to the scanning session that they would earn 5 cents for each correct response, which was paid to them after the completion of the study. Thus, unlike classic reward paradigms, our paradigm did not parametrically vary reward in a quantifiable, condition-specific manner; this one-time monetary reward for correct responses was included only for the purpose of generally enhancing motivation and performance on the task. Given this, it is interesting that the association between impaired striatal functioning and negative symptom burden was evident despite this motivation-enhancing manipulation. There were no accuracy differences between the high and low negative symptom patient groups that would suggest that this incentive was more effective in patients with low levels of negative symptoms compared to those with elevated negative symptom levels.

Overall, it is not clear if the poor striatal recruitment in patients with negative symptoms seen here and in prior studies is linked to a deficit in reward processing specifically or to a more basic abnormality in circuitry function within the striatum that would impact cognitive and affective processes. Follow-up studies that make use of event-related designs and parallel executive and reward components can potentially resolve this question.

Previous studies and the current results highlight the relationship between negative symptoms and individual differences among patients with schizophrenia

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in striatal activity; the effect of variation across individuals was often greater than the effect of diagnosis, which was weak (Dowd & Barch, 2010) or absent (Harvey *et al*. 2010; Simon *et al*. 2010) as in the current study. Thus, negative symptoms predict a small portion of the within-group heterogeneity of striatal activity and may help to explain contradictory results from previous studies, i.e. reports of striatal hypo- or hyperactivity in schizophrenia patients compared to healthy controls.

Striatal function and schizophrenia subtypes

Patients with high levels of negative symptoms showed diminished striatal activation compared to patients with low levels of negative symptoms. Of note, we also found that the magnitude of striatal activation in patients with high levels of negative symptoms was lower than that in patients with intermediate levels of negative symptoms, that is SANS scores falling into the two middle quartiles ($n=79$), as well (see SM 2). These results are consistent with the evidence for a schizophrenia subtype characterized by a high burden of negative symptoms (Carpenter *et al*. 1988; Buchanan, 2007). Thus, we speculate that a subtype of schizophrenia characterized by reduced striatal function could be manifested clinically as prominent negative symptoms.

A large body of literature supports the existence of a subtype of schizophrenia (i.e. Deficit Syndrome) characterized by a very high and persistent negative symptom burden (Carpenter *et al*. 1988; Blanchard *et al*. 2005; Kirkpatrick & Galderisi, 2008). The possibility that patients with high levels of negative symptoms represent a separate, biologically unique entity within the schizophrenia syndrome is supported by studies showing that patients with primary negative symptoms have poorer pre-morbid adjustment during childhood and early adolescence, and exhibit more cognitive impairment (Crow, 1985; Galderisi *et al*. 2002) than schizophrenia patients without this clinical phenotype. Family studies suggest that the Deficit/Non-deficit distinction is genetically mediated (Dollfus *et al*. 1996; Ross *et al*. 2000).

Our results are based on a continuous measure of current negative symptom severity (SANS; Andreasen, 1982). The differences in striatal activity found between matched patient subgroups corroborate our finding of an inverse linear relationship between negative symptoms and striatal activity, while minimizing the effects of possibly confounding variables. However, our findings cannot answer the question of whether negative symptoms should be conceptualized as dimensional only or as clustered to distinguish two discrete subtypes of schizophrenia. Future fMRI studies using the Schedule for the Deficit Syndrome (Kirkpatrick *et al*. 1989) or taxonometric statistical methods may be able to further test the 'categorical hypothesis', i.e. the existence of a subgroup of schizophrenia patients with severe enduring negative symptoms and impaired striatal function.

Frontobasal ganglia circuitry and negative symptoms

In the present study, there were no significant associations between negative symptoms and working memory-related DLPFC activation. However, inspection of Fig. 1 reveals that the overall pattern of activation in the DPLFC, particularly in the right hemisphere, was similar to that seen in the striatum. This is not surprising given that working memory function is mediated by a frontobasal ganglia-thalamocortical circuit, which begins with a projection from the DLPFC to the dorsal striatum and is completed by a projection from the ventral anterior and medial dorsal nuclei of the thalamus to the DLPFC (Alexander *et al*. 1986; Middleton & Strick, 2000). Thus it is possible that the relationship between BOLD responses and negative symptoms reached significance in the striatum but not in the DLPFC because the underlying functional abnormality associated with negative symptoms is located in the striatum. This impairment in the dorsal striatum may then lead to some reduction in activity in subsequent portions of the circuit, including the DLPFC (Middleton & Strick, 2000; Ashby *et al*. 2005). Consistent with this model are the findings of three PET studies of significant reductions in frontal cortical function in Deficit Syndrome patients (Tamminga *et al*. 1992; Heckers *et al*. 1999; Lahti *et al*. 2001). However, a recent meta-analysis (Goghari *et al*. 2010) that included eight fMRI studies, totaling 136 patients, found no significant association between DLPFC activity and negative symptoms (overall effect size: −0.002). Meta-analyses are limited by the assumptions inherent in equating equipment, task-paradigms and analytic approaches from different studies. However, the current study, which included more schizophrenia patients than the aforementioned meta-analysis, confirms that the relationship between DLPFC dysfunction and negative symptoms is weak at best.

It is interesting to consider the implications of our findings in light of recent reports of elevated dopamine neurotransmission localized to the dorsal striatum in medication-free schizophrenia (Howes & Kapur, 2009; Kegeles *et al*. 2010) and prodromal (Howes & Kapur, 2009) patients, and previous reports of elevated striatal dopamine activity in acutely psychotic compared to stable, non-psychotic patients with schizophrenia (Abi-Dargham *et al*. 2000). These

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findings, taken together with the present results, raise the possibility that negative and positive symptoms arise from dysfunction of distinct circuits within the dorsal striatum (e.g. the 'direct' and 'indirect' pathways; Bolam *et al*. 2000; Onn *et al*. 2000), or from a common dorsal striatal abnormality occurring at different phases of the illness (Grace, 2000) or alongside other symptom-specific circuitry abnormalities (Goghari *et al*. 2010).

Hyperactivation of the DLPFC in schizophrenia patients compared to controls

The left DLPFC showed elevated activation in the schizophrenia patients in comparison to controls, and the right striatum showed increased activation in the schizophrenia patients with minimal negative symptoms in comparison to matched controls. This replicates previous findings of non-symptom focused studies (Manoach *et al*. 1999, 2000; Kim *et al*. 2009; Potkin *et al*. 2009), although other studies have reported hypoactivation of the DLPFC in schizophrenia (Minzenberg *et al*. 2009). DLPFC hypoactivation in patients with schizophrenia compared to healthy controls is primarily seen in fMRI studies using the N-back task (Minzenberg *et al*. 2009). This task is more difficult than the version of the SIRP used in our study and frequently leads to marked differences in accuracy between patients and healthy controls. Neural activity is thought to decrease when working memory load exceeds an individual's capacity (Callicott *et al*. 1999; Manoach, 2003; Jansma *et al*. 2004). In fact, a study using a version of the SIRP with higher memory loads found prefrontal hypoactivation in schizophrenia patients when compared to healthy controls (Johnson *et al*. 2006). By contrast, abnormally elevated neural activity, in the context of low task difficulty and relatively high accuracy as in our study, may reflect overall neural inefficiency (Callicott *et al*. 1999; Manoach *et al*. 1999; Callicott *et al*. 2003; Manoach, 2003).

Limitations

In the present study, the approach of using quantitative functional and morphometric data, collected at multiple acquisition sites, is associated with both advantages and disadvantages. The rapid collection of data from a large cohort of subjects provided increased statistical power that enabled us to isolate neural effects specifically associated with negative symptoms; because of the large sample size, both a dimensional approach and a comparison of two groups of schizophrenia patients who were relatively 'pure' in terms of negative symptom burden (very high *versus* minimal) and matched on other clinical characteristics could be used. A disadvantage of this design is that our results could have been influenced by differences in MR scanner field strength. However, covarying for the effects of acquisition site did not alter our findings. In addition, a calibration study preceding the current study (carried out at the same acquisition sites and using the same paradigm) revealed that the proportion of the variance in activation measures that can be attributed to across-site variability was an order of magnitude smaller than the proportion that could be attributed to across-subject variability (Yendiki *et al*. 2010).

Another potential limitation is related to the unknown influence of antipsychotic medications. We attempted to determine the relationships between striatal and DLPFC activity and antipsychotic exposure by calculating antipsychotic dose equivalents for each patient. However, given that this method does not account for (*a*) interactive effects of polypharmacy, (*b*) findings suggesting that antipsychotics influence different brain structures in distinct ways (Navari & Dazzan, 2009; Smieskova *et al*. 2009) and (*c*) that the metabolism of antipsychotic medication varies extensively across individuals (Arranz & de Leon, 2007), striatal and prefrontal cortical volumes could represent an additional and perhaps more accurate index of the direct biological effects of D2 dopamine receptor blockade on neurons, than estimated CPZ units. In our cohort, striatal volumes were significantly greater and DLPFC volumes were significantly lower in the schizophrenia patients than in the controls. These findings replicate the results of several previous studies that have shown that antipsychotic medications, particularly those with high affinity at the D2 dopamine receptor, induce striatal hypertrophy (Chakos *et al*. 1994; Keshavan *et al*. 1994; Gur *et al*. 1998; Navari & Dazzan, 2009) and reductions in prefrontal volume (Lieberman *et al*. 2005; Smieskova *et al*. 2009). However, we found no relationships between striatal and prefrontal volumes and the outcome measures of interest, suggesting that antipsychotic-induced striatal enlargement (and by inference, antipsychotic treatment in general) does not strongly influence the relationship between working memory related striatal activation and negative symptoms. However, additional, pre-clinical studies are needed to better understand the relationships between antipsychotic-related changes in brain structure and brain function as measured by fMRI, and the results of our study warrant replication in antipsychotic-free patients.

Conclusions

In summary, in a large, multi-site dataset, we found that working memory-related activation of the

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striatum, but not the DLPFC, shows an inverse association with negative symptom severity in schizophrenia patients. This finding may have important implications for the search for effective treatments for negative symptoms. For example, striatal function could serve as a quantitative, surrogate end-point (Cho *et al*. 2005) in trials of novel therapeutic agents aimed at ameliorating cognitive dysfunction and negative symptom burden in schizophrenia patients.

Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/psm).

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Declaration of Interest

In the past two years, Dr Schulz has had financial relationships with AstraZeneca (Investigator initiated grant) and Eli Lilly (Consultant; Investigator initiated grant). Dr Goff has served on the advisory board of Indevus, Takeda and Schering-Plough, has served as a consultant for Lundbeck, Eli Lilly, Medication Neurology and Schering-Plough and on a DSMB for Otsuka.

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