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The relationship between grey matter volume and striatal dopamine function in psychosis: a multi-modal ¹⁸F-DOPA PET and voxel-based morphometry study

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Abstract

A leading hypothesis for schizophrenia and related psychotic disorders proposes that cortical brain disruption leads to subcortical dopaminergic dysfunction, which underlies psychosis in the

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Conflict of interest

Professor Howes has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organised by Astra-Zeneca, Autifony, BMS, Eli Lilly, Heptares, Janssen, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche. Neither Professor Howes nor his family have been employed by or have holdings/a financial stake in any biomedical company. The other authors have nothing to declare.

majority of patients who respond to treatment. Although supported by preclinical findings that prefrontal cortical lesions lead to striatal dopamine dysregulation, the relationship between prefrontal structural volume and striatal dopamine function has not been tested in people with psychosis. We therefore investigated the in vivo relationship between striatal dopamine synthesis capacity and prefrontal grey matter volume in treatment responsive patients with psychosis, and compared them to treatment non-responsive patients, where dopaminergic mechanisms are not thought to be central. 40 patients with psychosis across two independent cohorts underwent ^{18}F -DOPA PET scans to measure dopamine synthesis capacity (indexed as the influx rate constant K_i^{cer}) and structural 3T MRI. The PET, but not MR, data have been reported previously. Structural images were processed using DARTEL-VBM. GLM analyses were performed in SPM12 to test the relationship between prefrontal grey matter volume and striatal K_i^{cer} . Treatment responders showed a negative correlation between prefrontal grey matter and striatal dopamine synthesis capacity, but this was not evident in treatment non-responders. Specifically, we found an interaction between treatment response, whole striatal dopamine synthesis capacity and grey matter volume in left (pFWE corr.= 0.017) and right (pFWE corr.= 0.042) prefrontal cortex. We replicated the finding in right prefrontal cortex in the independent sample (pFWE corr.= 0.031). The summary effect size was 0.82. Our findings are consistent with the long-standing hypothesis of dysregulation of the striatal dopaminergic system being related to prefrontal cortex pathology in schizophrenia, but critically also extend the hypothesis to indicate it can be applied to treatment-responsive schizophrenia only. This suggests that different mechanisms underlie the pathophysiology of treatment-responsive and treatment-resistant schizophrenia.

Keywords

schizophrenia; treatment response; neurobiology; antipsychotics; imaging; resistant; biomarker; neurochemistry

Introduction

Schizophrenia is a severe mental illness, affecting approximately 1% of the population¹ and ranks as a leading cause of disability and functional impairment.² Disability is compounded by the fact that approximately one third of patients with schizophrenia show limited or no response to first-line antipsychotic drugs.^{3–6} It has recently been suggested that there may be two different subtypes of schizophrenia (hyperdopaminergic and normodopaminergic) with differing neurobiological mechanisms.^{7, 8} Investigating the pathophysiology of schizophrenia is essential for screening, early intervention, secondary prevention and treatment of this illness.

One focus of research exploring the neurobiology of schizophrenia has been the interaction between prefrontal cortex (PFC) and striatal function. Two of the most robust neuroimaging alterations in schizophrenia are increased striatal dopamine synthesis and release capacity⁹, and reduced grey matter volume in the prefrontal cortex.^{10–15} Preclinical studies have provided evidence for a key role of PFC in regulating dopaminergic neuronal firing and striatal dopamine release: PFC lesions in rats have been linked to increased striatal dopamine levels^{16, 17} and to increased release of subcortical dopamine evoked by drug challenges or

stress^{18–20}. These findings have led to the hypothesis that increased striatal dopaminergic transmission in schizophrenia may be a consequence of a primary prefrontal alteration.^{16, 21–24}

Recent human studies showed an inverse correlation between frontal cortical thickness and d-amphetamine-induced striatal dopamine response in healthy subjects.^{25, 26} Moreover, correlations between striatal dopaminergic function and prefrontal functional activation during cognitive tasks have been reported both in individuals at clinical high risk for psychosis²⁷ and in patients with schizophrenia.²⁸ Furthermore, a correlation was demonstrated between reduced *N*-acetyl-aspartate, a measure of neuronal integrity, in the PFC and increased amphetamine-induced dopamine release in patients with schizophrenia.²⁹ The most clear-cut elevation in dopamine synthesis and release capacity has been found in the part of the striatum that receives projections from prefrontal cortical regions, termed the associative striatum^{30–34} and confirmed by meta-analysis³⁵, further suggesting a link between prefrontal cortex and striatum in schizophrenia. However, it is not known if reduced PFC volume is associated with elevated striatal dopaminergic function *in vivo* in patients with schizophrenia, as suggested by the preclinical studies reviewed above.

We therefore investigated the *in vivo* relationship between presynaptic striatal dopamine function and prefrontal grey matter volume in patients with first episode psychosis. ¹⁸F-DOPA PET was used to assess dopamine synthesis capacity in the striatum, and voxel-based morphometry was employed to evaluate grey matter volume. Consistent with the preclinical findings, we hypothesised that there would be an inverse correlation between grey matter volume in the PFC and striatal dopamine synthesis capacity in treatment responsive patients, who are hypothesised to have a dopaminergic disorder.⁸ In contrast, we predicted that treatment non-responders would not show a relationship between striatal dopamine function and prefrontal volume on the basis of the hypothesis that they do not show a dopaminergic disorder and prior findings that non-responders do not show elevated dopamine synthesis capacity.^{7, 36, 37} We further tested our findings in an independent replication sample of treatment responders and non-responders.

Methods and Materials

Participants

Discovery sample—The study was approved by the East of England-Cambridge East NHS Research Ethics Committee.

We studied 16 patients who had presented to specialised mental health services for first episode psychosis in London. Inclusion criteria were: diagnosis of a psychotic disorder according to ICD 10 criteria³⁸; and within 5 years of the first onset of illness³⁹. All participants provided informed written consent to participate.

Exclusion criteria were: history of significant head trauma, history of neurological disorder, pregnancy or breast-feeding, history of alcohol or any other substance abuse or dependence, any significant medical disorder, use of antipsychotic drugs for longer than two weeks at baseline.⁴⁰

All patients were assessed at baseline, when they received a clinical assessment and PET and MRI scan. The clinical assessment was repeated after they had received at least 4 weeks of antipsychotic treatment at a therapeutic dose to determine clinical response. This period of minimum 4 weeks did not include the time to titrate the antipsychotic to the therapeutic dose. This is in keeping with inclusion criteria for a recent large randomised controlled trial of antipsychotic response in first episode schizophrenia.⁴¹ All patients then received clinical follow-up for at least six months to determine if non-responders showed a subsequent response with a longer duration of treatment. The choice of antipsychotic was made by the patient in discussion with their treating clinician in line with standard clinical practice. All doses were within the therapeutic range defined in the Maudsley Prescribing Guidelines,⁴² and measures of concordance used (antipsychotic blood monitoring, self-report and pharmacy records).⁴³ Chlorpromazine-equivalent dose-years⁴⁴ was calculated to measure antipsychotic exposure (see Supplementary Table 1). Use of other psychotropic medication (such as antidepressants and benzodiazepines) was permitted.

The definitions of response and non-response used the Positive and Negative Syndrome Scale (PANSS), which was rated at both time-points (ratings were conducted blind to the PET imaging data). We defined treatment response as a total PANSS reduction of $\geq 50\%$.⁴⁵ Percentage change was adjusted for minimum scores (% change in total PANSS = $\frac{[(\text{baseline score} - 30) - (\text{follow up score} - 30)] * 100}{(\text{baseline score} - 30)}$)⁴⁵ All the subjects received follow-up for six months to determine subsequent response in patients. Moreover, treatment response was confirmed using two additional criteria. The first approach was based on the administration of the Clinical Global Impression Improvement scale (CGI-I).⁴⁶ A rating of 1 or 2 on the CGI-I (corresponding respectively to “very much improved” and “much improved”) equates to a clinically significant improvement.^{47, 48} Based on this, we defined a treatment response as a CGI-I score of 1 or 2, and non-response as a rating of ≥ 3 . The other one was based on the remission criteria evaluated at 6 months.⁴⁹

Replication sample—The study was approved by the institutional review board of Seoul National University Hospital, Seoul, Korea, and was carried out in accordance with the Helsinki Declaration of 1975, as revised in 2008. An independent replication sample of patients with schizophrenia was recruited from the Seoul National University Hospital: 12 responders (patients whose illness had responded to first-line antipsychotic drugs) and 12 non-responders (patients on clozapine who had a history of non-response to at least two different first-line antipsychotics but who had shown a response to clozapine, defined as a total score of ≤ 80 in the PANSS and no items with a score > 3 on the positive subscale of the PANSS, as reported for this sample before).³⁷ Written informed consent was obtained from all subjects. Inclusion criteria: diagnosis of schizophrenia according to DSM-IV criteria⁵⁰ and having been on a stable dose of a first-line antipsychotic drug including risperidone, olanzapine and paliperidone (responders group) or clozapine (non-responders group) for at least 12 weeks. Exclusion criteria were: presence of other DSM-IV axis I disorders (including affective episodes), history of alcohol or any other substance dependence or abuse, history of significant head trauma, history of neurological disorder, pregnancy or breast-feeding, any significant medical disorder. Clinical measures were assessed using the PANSS and Clinical Global Impression Severity scale (CGI-S).⁴⁶ To be classified as

treatment responders, patients were required to have a CGI-S score of ≤ 3 , a total score of 80 in the PANSS and no items with a score > 3 on the positive subscale of the PANSS, to have not experienced a symptomatic relapse in the 6 months prior to the study, and not to have history of being given clozapine or being resistant to first-line antipsychotic drug treatments.³⁷

MRI scanning

Image acquisition— *Discovery sample:* Images were acquired on a 3.0 Tesla Signa (GE) system at the Centre for Neuroimaging Sciences, IoPPN, London. 196 high-resolution T1-weighted images were acquired using a three-dimensional enhanced fast gradient echo sequence using the following scan parameters: repetition time – 6.98 msec, echo time – 2.85 msec, flip angle - 11° , matrix – 256 x 256, FoV – 260, slice thickness - 1.2 mm.

Replication sample: Images were acquired on a 3.0 Tesla Siemens Trio MRI scanner. 208 high-resolution T1-weighted images were acquired using a three-dimensional enhanced fast gradient echo sequence using the following scan parameters: repetition time – 1.67 msec, echo time – 1.89 msec, flip angle - 9° , matrix – 256 x 256, FoV – 250, slice thickness – 1.0 mm.

Analysis of MRI data—Voxel Brain Morphometry Analysis (VBM) of the MRI data was performed using the standard Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL)⁵¹ processing pipeline in Statistical Parametric Mapping (SPM12; Wellcome Trust Centre for Neuroimaging, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>) via Matlab 8.2 (Mathworks, Natick, MA, USA). The same pipeline was used on both discovery and replication sample. Prior to data processing, all the scans were checked for artefacts and poor image quality. Subsequently, each image was reoriented in order to set the anterior commissure at the origin of the Montreal Neurological Institute (MNI) coordinate system. Following this, the T1-weighted scans were partitioned into different tissue classes - grey matter (GM), white matter (WM) and non-brain voxels (cerebrospinal fluid, skull) based on separate tissue probability maps for each tissue class using the segmentation approach implemented in SPM12. The DARTEL algorithm was used to generate a study-specific template and the resulting flow fields generated by DARTEL were used to obtain GM images of each subject; these images were spatially normalised in the MNI space, modulated, resliced (1.5 mm isotropic voxels) and smoothed with a 10-mm full width at half maximum (FWHM). Total intra-cranial volumes (TIV) were computed using the new “Tissue Volumes” utility implemented in SPM12.⁵²

PET scanning

Image acquisition— *Discovery sample:* Dynamic scans were acquired using a Siemens Biograph™ 6 HiRez PET/CT scanner (Siemens Medical Systems, Germany) in three-dimensional mode (transaxial resolution of ~ 5 mm full width at half maximum.⁵³ All subjects received 400 mg entacapone, a peripheral catechol-o-methyl-transferase inhibitor, and 150 mg carbidopa, a peripheral aromatic acid decarboxylase inhibitor, to increase specific signal, as these compounds decrease the formation of radiolabelled metabolites that may cross the blood–brain barrier.^{54, 55} Participants were positioned with the orbitomeatal

line parallel to the transaxial plane of the tomograph. Head position was marked and monitored and movement was minimised using a head strap. After a CT scan for attenuation correction and scatter correction, approximately 150 MBq of ^{18}F -DOPA was administered by intravenous injection following a 30-s background frame. PET data were acquired in 32 frames of increasing duration over the 95 min scan (frame intervals: 8x15 seconds, 3x60 seconds, 5x120 seconds, 16x300 seconds). The PET imaging data acquired in a list mode were reconstructed using DIFT (discrete inverse Fourier transform) and a 5mm isotropic Gaussian smoothing. The resulting image consisted in 82 axial slices, an image size of 128 x 128 and a voxel size of 2.0509 x 2.0509 x 2 mm.

Replication sample: Participants underwent a short CT for attenuation correction and PET imaging on a Siemens Biograph 40 Truepoint PET/CT scanner (Siemens, Knoxville, Tennessee, USA) for 95 minutes after an intravenous bolus injection of approximately 370 MBq of ^{18}F -DOPA (transaxial resolution of ~4.2 mm full width at half maximum).³⁷ All the subjects were instructed to take their antipsychotic medication at 9 PM a day before the scan, which was performed approximately 17 hours later. They received 150 mg carbidopa and 400 mg entacapone orally 1 hour prior to scanning to reduce the formation of radiolabeled metabolites. Images were collected in a three-dimensional mode with 148 axial slices, an image size of 256 x 256 and a voxel size of 1.3364 x 1.3364 x 3 mm. The dynamic volumetric images were reconstructed using filter-back projection into 27 frames sequenced using the following framing: 2x30 seconds, 4x60 seconds, 3x120 seconds, 3x180 seconds, and 15x300 seconds.

Analysis of PET data—In both discovery and replication sample, head movement correction was conducted using a level 2, order 64 Battle-Lemarie wavelet filter to denoise non-attenuation-corrected dynamic images. Frames were realigned to a single reference frame (characterised with the highest measured PET activity), acquired 20 minutes post-injection, employing a mutual information algorithm.^{56, 57} The transformation parameters were then applied to the corresponding attenuated-corrected dynamic images, creating a movement-corrected dynamic image, which was used in the analysis. Realigned frames were then summated to create an individual motion-corrected reference map for the brain tissue segmentation. SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>) was used to normalize a tracer-specific (^{18}F -DOPA) template^{33, 58} together with the striatal probabilistic brain atlas⁵⁹ to each individual PET summation image. Importantly, the PET pre-processing was not based on the MRI images; thus, the correlations between PET and MRI data were independent of co-registration. An eroded cerebellar region was used as reference for tissue quantification in agreement with previous analyses.⁶⁰ Tracing and tractography studies have shown that the cortical projections to the striatum show a topographical distribution across the striatum.^{61–63} Projections from limbic regions such as the hippocampus project to anterior and ventral regions of the striatum, projections from regions involved in associative cognitive functions such as the dorsolateral prefrontal cortex (DLPFC) project to the head of caudate and anterior putamen, and projections from sensorimotor cortex project to more dorsal and posterior regions of the striatum, predominantly putamen. The striatum can thus be subdivided into limbic, associative and sensorimotor sub-divisions respectively based on this topography. We sub-divided the striatum into these sub-regions as previously described.^{33, 59}

The striatal influx constant (K_i^{cer} , written as K_i in some previous publications)³³ was calculated relative to uptake in the reference region using a graphical approach adapted for a reference tissue input function.⁶⁴ A previous test/re-test study has shown this approach has good reliability with an intra-class correlation coefficient of >0.84 for the whole striatum.⁵⁸ Further details of the image analysis approach are given in Jauhar et al⁶⁵ and Bloomfield et al.⁶⁰ The PET, but not MR, data have been reported for the discovery sample in Jauhar et al^{7, 66} and for the replication sample in Kim et al.³⁷

Integration of MRI and PET data - statistical analyses

A general linear model in SPM12 was used to test the negative interaction between treatment response, whole striatum dopamine synthesis capacity (entered in the statistical model as K_i^{cer} value) and grey matter volume. The analysis was masked using the WFU Pick-Atlas⁶⁷ with an ROI in the DLPFC identified as lateral BA9 and BA 46^{68, 69} because of our a priori hypothesis based on the fact this brain region has been consistently implicated in the pathophysiology of schizophrenia^{70, 71} and sends a large number of cortico-striatal projections^{63, 72}. Results were initially visualised at the statistical threshold of $p < 0.001$ uncorrected with a minimal cluster size (k) of 50 contiguous voxels and then corrected for multiple comparisons at the voxel level (FWE correction). The software MRICroGL (<http://www.mccauslandcenter.sc.edu/mricrogl/>) was used for the visualisation of the results. For descriptive purposes, grey matter volume values were extracted from the significant clusters using the MarsBar 0.44 SPM toolbox (<http://marsbar.sourceforge.net/>) and plotted against K_i^{cer} values using GraphPad Prism 7.02 (<http://www.graphpad.com/>). The analysis in the replication sample was performed using the same procedure.

The grey matter volume values extracted from the significant clusters in DLPFC were compared between responders and non-responders. Moreover, whole brain VBM analyses were performed in each sample to test for any GM volumetric differences between responders and non-responders.

Separate exploratory analyses in the discovery and replication samples were conducted using associative striatum, limbic striatum and sensorimotor striatum K_i^{cer} as predictors. Moreover, to test the specificity of the findings, we performed exploratory ROI analyses, examining the correlation between dopamine synthesis capacity in the limbic and sensorimotor striatal subdivisions and GM volume of the corresponding frontal regions.³⁵ Specifically, we used a ROI in the limbic areas of the frontal cortex, which included medial prefrontal cortex and orbitofrontal cortex, for the limbic striatum K_i^{cer} analysis; and a ROI in primary and supplementary motor cortex for the sensorimotor striatum K_i^{cer} analysis.^{73, 74} The correlation between associative striatum K_i^{cer} and DLPFC (the corresponding cortical region)⁶³ was not repeated, as it was already included in the above analyses.

A further confirmation of the specificity of the finding was obtained by performing ROIs analyses with K_i^{cer} as predictors and ROIs in all the brain areas other than PFC (ROIs selected by using the WFU Pick-Atlas).⁶⁷

All the statistical models above included age, gender and total intra-cranial volume (TIV) as “nuisance” variables, in order to control for any independent effects on our findings and to ensure that the analysis identified regionally specific “non-global” effects.^{75, 76}

For illustrative purposes, we computed effect sizes from the maximum T statistic obtained from the significant clusters⁷⁷ and meta-analysed them using Comprehensive Meta-Analysis Version 3.⁷⁸

Results

Demographic (\pm SD) and K_i^{cer} values of the samples included in the experiments are reported in Table 1 and Supplementary Table 1.

Discovery sample

All the subjects defined as responders according to the PANSS criterion had a CGI-I score of 1 or 2 (mean= 1.3). All the non-responders (as for the PANSS criterion) had a CGI-I score of 3 (mean= 4.1). At six-month follow up there were no changes in terms of treatment response status. We found an interaction between treatment response, whole striatal dopamine synthesis capacity and grey matter volume in left (BA 9: $x= -40$, $y= 36$, $z= 38$; $k= 158$, $Z= 4.22$, $pFWE$ corrected= 0.017) and right (BA 9: $x= 32$, $y= 54$, $z= 33$; $k= 163$, $Z= 3.94$, $pFWE$ corrected= 0.042) prefrontal cortex [Table 2]. Figure 1 illustrates that treatment responders show a negative correlation between prefrontal grey matter and striatal dopamine synthesis capacity but this is not present in treatment non-responders.

Responders and non-responders did not differ in terms of grey matter volume values extracted from the significant clusters. Moreover, the VBM whole brain analysis did not show any significant differences in terms of grey matter volume between the two groups (no clusters surviving FWE correction).

Replication sample

None of the responders had a score of 4 or more on any item of the PANSS positive subscale. All the patients had been clinically stable for longer than 6 months (responders: 37.9 ± 20.4 months; non-responders: 40.2 ± 19.9 months). There was an interaction between treatment response to first-line antipsychotics, whole striatal dopamine synthesis capacity and grey matter volume in right prefrontal cortex (BA 9: $x= 20$, $y= 46$, $z= 38$; $k= 57$, $Z= 3.93$, $pFWE$ corrected= 0.031) [Table 3]. Patients who responded to first-line antipsychotics showed a negative correlation between prefrontal grey matter and striatal dopamine synthesis capacity. In non-responders no relationship was present [Figure 2].

Also in this sample there were no differences in terms of grey matter volume in the DLPFC or at a whole brain level.

The summary (discovery + replication samples) effect size for the interaction between treatment response, whole striatal dopamine synthesis capacity and prefrontal grey matter volume was 0.82 (calculated using Hedges' g approach).

Exploratory analyses: correlations with K_i^{cer} in the different striatal subdivisions in the discovery sample

We found an interaction between treatment response, K_i^{cer} value in the associative striatum and grey matter volume in left (BA 9: $x = -42$, $y = 34$, $z = 38$; $k = 166$, $Z = 4.30$, p_{FWE} corrected = 0.013) and right (BA 9: $x = 32$, $y = 54$, $z = 34$; $k = 138$, $Z = 3.92$, p_{FWE} corrected = 0.046) prefrontal cortex [Supplementary Table 2] [Supplementary Figure 1]. The exploratory analysis with the sensorimotor subdivision K_i^{cer} as predictor revealed that only the cluster in right prefrontal cortex survived FWE correction (BA 9: $x = 34$, $y = 50$, $z = 34$; $k = 190$, $Z = 3.93$, p_{FWE} corrected = 0.043) [Supplementary Table 2] [Supplementary Figure 2]. The results from the exploratory analysis with the limbic subdivision K_i^{cer} as predictor did not survive FWE correction.

Exploratory analysis with limbic striatal K_i^{cer} as predictor and ROI in the limbic area of frontal cortex did not show significant clusters.

Exploratory analysis with sensorimotor K_i^{cer} as predictor and ROI in the primary and supplementary cortex did not show any significant clusters. All the ROI exploratory analyses with dopamine synthesis capacity as predictor and ROIs in all the brain areas other than PFC did not show voxels surviving FWE correction.

Exploratory analyses: correlations with K_i^{cer} in the different striatal subdivisions in the replication sample

We found an interaction between treatment response, K_i^{cer} value in the sensorimotor striatum and grey matter volume in right prefrontal cortex (BA 9: $x = 18$, $y = 48$, $z = 38$; $k = 46$, $Z = 3.89$, p_{FWE} corrected = 0.034) [Supplementary Table 2] [Supplementary Figure 3]. The results from the exploratory analyses with the limbic and associative subdivisions K_i^{cer} as predictors did not survive FWE correction.

Discussion

Our main finding is an inverse correlation between grey matter volume in the DLPFC and dopamine synthesis capacity in the whole striatum in patients with psychosis who respond to treatment, but no relationship in patients who do not respond to first-line treatment. Specifically, in patients who had responded to first-line antipsychotics, lower prefrontal grey matter volume was associated with increased dopamine synthesis capacity in the whole striatum. We replicated this finding in an independent sample of patients with chronic schizophrenia.

As predicted, the two subgroups of patients (responders and non-responders) showed differences in correlations between the measures examined. These results lend further evidence to the theory that the neurobiology underlying treatment-resistant psychosis is different from that seen in treatment-responsive schizophrenia.⁸ Moreover, it has been observed that patients who respond to antipsychotics have higher striatal density of dopaminergic synapses⁷⁹ and higher striatal dopamine synthesis capacity^{7, 36, 37} when compared with patients with treatment-resistant illness, whilst the latter show greater frontal cortical glutamate levels.^{80, 81} This has led to speculation that only those patients whose

illness is characterized by dopaminergic dysfunction will show a good response to dopamine-blocking antipsychotics.⁸

The results of this study are consistent with previous findings of a correlation between measures of neuronal integrity and evoked release of striatal dopamine in patients with schizophrenia²⁹ and between prefrontal cortex functional activation and dopamine synthesis capacity in subjects with an at-risk mental state and patients with schizophrenia.^{28, 82, 83} They are also consistent with evidence of direct and indirect anatomical connections between PFC and striatum^{84, 85} and with the pre-clinical lesions studies and the long-standing hypothesis of dysregulation of the striatal dopaminergic system being secondary to prefrontal cortex pathology in schizophrenia,^{21–24} but critically also extend the hypothesis to indicate it can be applied to treatment-responsive schizophrenia only. This is in line with recent evidence of a relationship between treatment response and cortico-striatal connectivity in schizophrenia.⁸⁶

Projections from the prefrontal cortex act as a “brake” on the striatal dopaminergic system.^{87, 88} Thus, if lower PFC volume reflects fewer or disrupted inhibitory projections from the PFC, then this could lead to a relative disinhibition of striatal dopamine function, which would explain the negative relationship we observed in the treatment responders. However, further work is required to test whether lower PFC volume is associated with disrupted projections.

Although there have been prior investigations of the relationship between dopaminergic function and cerebral morphology in healthy volunteers,^{25, 26, 89–92} to the best of our knowledge this is the first study investigating this relationship in patients with psychosis.

The exploratory analyses performed in the discovery sample with the different striatal subdivisions showed statistically significant relationships between bilateral prefrontal cortex and dopamine synthesis capacity in the associative striatum subdivision. This is consistent with the evidence that the associative subdivision of the striatum receives a large number of inputs from the DLPFC,^{61, 93–96} and extends previous studies that have localized dopaminergic dysfunction in schizophrenia to associative regions of the striatum,^{33–35} to indicate that striatal dopaminergic dysfunction is linked to structural alterations in the disorder. However, the specificity of the involvement of the associative striatum was not confirmed by the exploratory analyses in the replication sample. Differences in segmentation or normalisation can lead to variations in the analyses of small areas such as the striatal subdivisions; therefore, further studies are needed to explore the involvement of the specific loci within the striatum.

We did not find any statistically significant differences in grey matter volumes between responders and non-responders. This may reflect the fact that the present study was not powered to detect grey matter volume differences, which are expected to be small in terms of effect size.⁹⁷

It is important to consider that treatment-resistant psychosis may be characterized by greater heterogeneity;⁹⁸ thus, non-responders might have more variability in imaging measures leading to overall non-significant correlations. However, it should be noted that the findings

were replicated in a sample of non-responders to first-line antipsychotics but homogeneous in terms of response to clozapine and, therefore, likely to be neurobiologically similar.^{99–101} Nevertheless, given heterogeneity in structural volumes in schizophrenia,¹⁰ further work would be useful to exclude variability as an explanation of our findings.

Interpretation and Limitations

Grey matter volume reflects a number of aspects of tissue composition, including the number of projection neurons and interneurons, and synaptic density.^{102, 103} Thus, further work is required to determine if it is lower density of projection neurons to the striatum that underlies the association we see. It should also be noted that we used an ROI approach and that the family-wise error correction that we applied is relatively conservative and thus there may be a risk of a type II error for other regions that could be linked to striatal dopaminergic dysfunction.¹⁰⁴ Nevertheless, the application of family-wise error correction gives confidence in the association between prefrontal cortex and associative striatal dopaminergic function.

However, it is important to recognise that association does not necessarily imply causality, and it should be recognised that some preclinical models also indicate that selective increases in striatal dopaminergic neurotransmission can affect frontal cortical function.¹⁰⁵ Moreover, elevated striatal dopamine synthesis and release capacity has been reported in people at risk of psychosis,^{31, 32, 106} and to increase during the prodrome,¹⁰⁷ whilst frontal volume has been found to reduce during the prodrome.^{108–110} Longitudinal multimodal studies and pre-clinical studies are necessary to clarify the timing of these alterations and determine which is primary. An example of such a preclinical study is that one conducted in mice by Kim et al¹¹¹ where it has been shown that cortical spine density influences striatal dopamine release via monosynaptic control of dopaminergic neurons; specifically spine loss in prefrontal cortex led to increased striatal dopamine release and hyperactivity which was normalised by haloperidol.

Two recent studies have examined the relationship between striatal dopamine release and frontal cortical thickness in healthy controls.^{25, 26} We would hypothesise a similar negative relationship between prefrontal cortical volume and striatal dopaminergic function in healthy volunteers, in keeping with our findings in people with psychosis who have good clinical response. It would be useful to test this in a further study.

Previous studies have demonstrated a correlation between glutamatergic neurometabolites and cerebral structural measures in schizophrenia.^{112, 113} It would be interesting to explore if this relationship is different in treatment responders and non-responders, especially in the context of the putative role of the glutamatergic system in the neurobiology of treatment-resistant schizophrenia.^{80, 81}

Understanding the underlying neurobiology of schizophrenia is essential for the rationale development of new treatments. Our study provides further evidence that schizophrenia should be recognised as a condition with at least two neurobiologically different subtypes.

A potential limitation is that some clinical and demographic variables differ between the discovery and replication samples. Specifically, the duration of antipsychotic treatment and duration of illness differ, and either may have effects on GM volume^{114–116} and, potentially, on dopamine synthesis capacity.^{117, 118} Despite this, effects were seen separately in each sample, suggesting the relationship between prefrontal cortical volume and striatal dopamine synthesis capacity in responders is a trait factor underlying the neurobiology of psychosis.

The subjects in the replication sample received a higher dose of ¹⁸F-DOPA. However, the administered dose in both samples are within the standard range used in imaging studies.^{33, 65, 119–122} Doses within the standard imaging range are not thought to lead to appreciable differences in signal to noise ratio.¹²³ Moreover, because of the quantification approach, the activity in the striatum (target region) is normalised to the one in the cerebellum (reference region). For this reason, differences in the injected dose are not expected to influence the K_i^{cer} values.

Whilst the K_i^{cer} values appear higher in the replication sample relative to the discovery sample, this could be due to scanner and other methodological differences.¹⁰⁶

The summary effect size was large. However, it should be considered that traditional neuroimaging studies are not optimized to estimate effect sizes and post hoc effect sizes calculated from imaging studies can be inflated.¹²⁴

Even though the findings were replicated in an independent sample, we should consider the relatively low sample size as a limitation. Therefore, future studies in larger samples are needed.

The discovery sample was in subjects with a diagnosis of first episode psychosis. It is important to recognise that first episode samples generally include patients who subsequently receive a diagnosis of bipolar affective disorder as well as schizophrenia. Indeed diagnoses often change in the first few years of a psychotic illness.¹²⁵ In view of this, it is important to appreciate that the findings in the discovery sample may not be specific to schizophrenia. However, in the replication sample we had a sample with an established diagnosis of schizophrenia. As the replication sample confirmed the findings in the discovery sample, this indicates that the findings are relevant for schizophrenia but, as we did not have a replication sample with bipolar or other psychotic disorders, we cannot comment on the specificity of our findings in the discovery sample to schizophrenia or psychotic disorders in general. In view of recent evidence that striatal dopaminergic dysfunction also underlies psychosis in bipolar disorder,⁶⁶ future studies investigating this would be useful.

Another potential limitation is that in the discovery sample there was a difference in medication status between responders and non-responders. However, the findings were replicated in a sample homogeneous in terms of medication status. Moreover, dopamine synthesis capacity has been recently demonstrated to be unaltered by second-generation antipsychotic treatment at doses commonly used in first episode patients,¹¹⁸ although it may be altered by following treatment with first-generation antipsychotic.¹¹⁷

Conclusions

To our knowledge, the present study is the first to test the relationship between frontal cortical volume and striatal dopamine function in patients, finding *in vivo* evidence for an inverse correlation between prefrontal grey matter volume and striatal dopamine synthesis capacity in patients with psychosis. Moreover, the fact that treatment-resistant patients do not show this correlation suggests that different mechanisms underlie the pathophysiology of treatment-responsive and treatment-resistant psychosis. Future studies are needed to clarify the pathoetiology responsible for these two potentially neurobiologically different forms of psychotic disorder.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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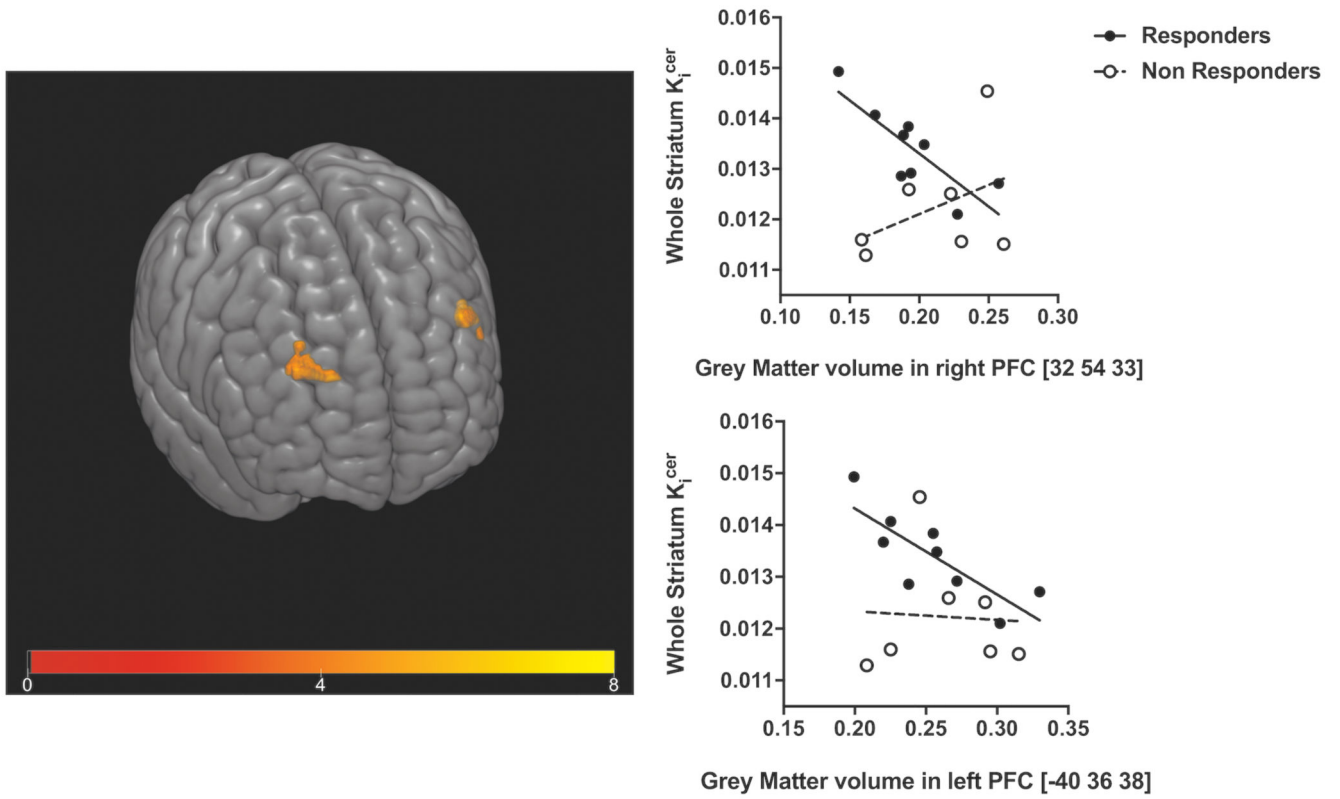


Figure 1. Interaction GM volume in PFC x whole striatum K_i^{cer} x treatment response (discovery sample)

Colour bar represents T score values.

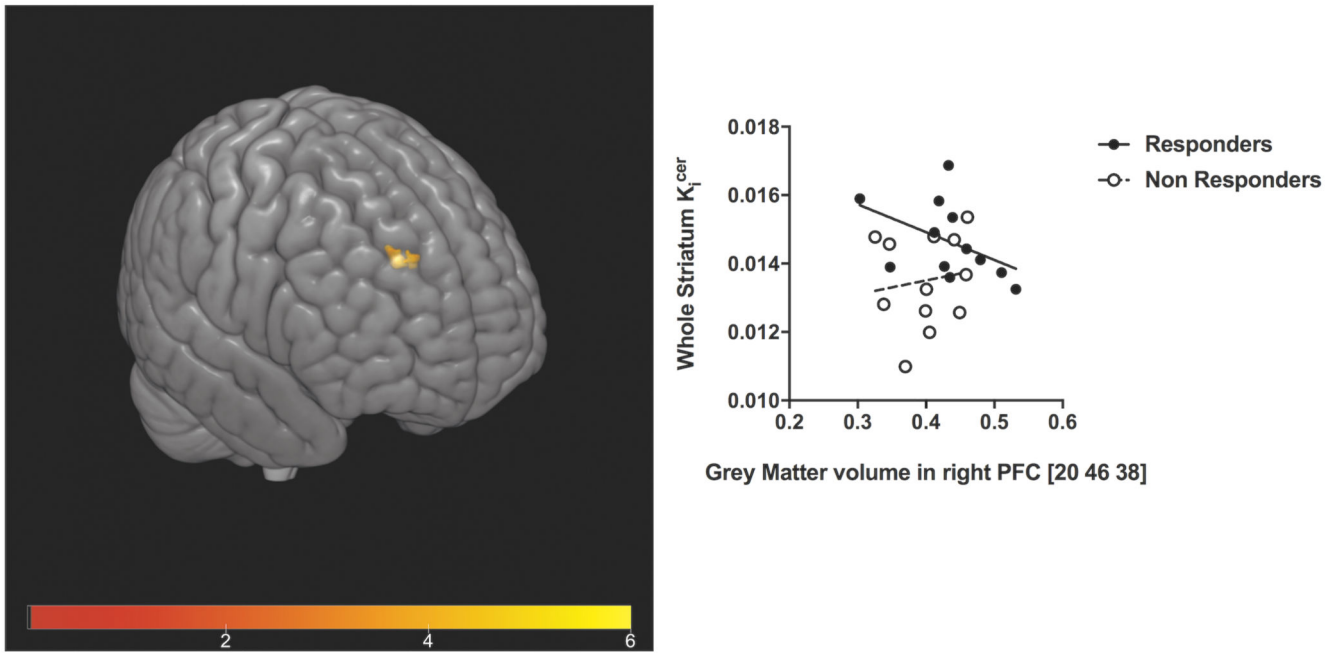


Figure 2. Interaction GM volume in PFC x whole striatum K_1^{cer} x treatment response (replication sample)
Colour bar represents T score values.

Table 1
Demographic characteristics of the sample

Medication status classification: antipsychotic naïve, antipsychotic free (prior oral antipsychotic medication but free of treatment for at least 6 weeks (oral) or 6 months (depot, if relevant)) or minimally treated (taking antipsychotic medication for two weeks or less).

	Analysis in the discovery sample			Analysis in the replication sample		
	Responders	Non-responders	p-value	Responders (first-line AP group)	Non-responders (clozapine group)	p-value
n	9	7	-	12	12	-
Age (yr ± SD)	24.8 ± 3.5	25.6 ± 3.9	0.675	31.1 ± 9.8	31.3 ± 8.1	0.946
Gender (male/female)	7/2	7/0	0.475	8/4	9/3	0.65
PANSS total score (± SD) [baseline]	74.2 ± 19.8	76.7 ± 17.4	0.796	50.3 ± 11.1	49.7 ± 7.9	0.867
PANSS positive score (± SD) [baseline]	19.7 ± 8.0	20.4 ± 4.4	0.824	10.8 ± 2.7	11.3 ± 2.4	0.635
PANSS negative (± SD) [baseline]	18.4 ± 4.1	17.4 ± 7.4	0.730	13.3 ± 5.2	12.8 ± 2.9	0.809
PANSS general score (± SD) [baseline]	36.1 ± 10.1	38.9 ± 8.4	0.571	26.3 ± 6.1	25.6 ± 3.9	0.722
PANSS total score (± SD) [follow-up]	41.7 ± 8.8	78.6 ± 22.7	0.001*	NA	NA	-
PANSS positive (± SD) [follow-up]	9.6 ± 2.6	19.1 ± 5.4	0.0001*	NA	NA	-
PANSS negative (± SD) [follow-up]	10.1 ± 3.1	19.1 ± 6.9	0.003*	NA	NA	-
PANSS general (± SD) [follow-up]	22.0 ± 4.4	40.3 ± 14.1	0.002*	NA	NA	-
Medication status until scan	7 antipsychotic-naïve, 1 minimally treated, 1 antipsychotic-free	2 antipsychotic-naïve, 2 minimally treated, 3 antipsychotic-free	0.14	medicated	medicated	-
GM volume (ml) in DLPFC (± SD)	8.77 ± 1.01	9.08 ± 1.37	0.606	7.88 ± 0.96	7.57 ± 0.93	0.429
K_i^{cer} (1/min) Whole Striatum (± SD)	0.013398 ± 0.000848	0.012229 ± 0.001140	0.033*	0.014651 ± 0.001119	0.013509 ± 0.001353	0.035*
K_i^{cer} (1/min) Associative Striatum (± SD)	0.013410 ± 0.000861	0.012064 ± 0.001169	0.019*	0.014201 ± 0.001255	0.013178 ± 0.001365	0.069
K_i^{cer} (1/min) Limbic Striatum (± SD)	0.012927 ± 0.000796	0.012346 ± 0.001124	0.245	0.014105 ± 0.000762	0.013150 ± 0.001074	0.020*
K_i^{cer} (1/min) Sensorimotor Striatum (± SD)	0.013579 ± 0.001047	0.012556 ± 0.001148	0.084	0.015962 ± 0.001324	0.014456 ± 0.001609	0.020*

Table 2
Interaction GM volume in PFC x striatal K_i^{cer} x treatment response (discovery sample)

Correlation with	MNI coordinates	Subregion	BA	cluster size (k)	Z	pFWE corr.
whole striatum K_i^{cer}	-40 36 38	left Sup Frontal Gyrus	9	158	4.22	0.017*
	32 54 33	Right Sup Frontal Gyrus	9	163	3.94	0.042*

Table 3
Interaction GM volume in PFC x striatal K_i^{cer} x treatment response (replication sample)

Correlation with	MNI coordinates	Subregion	BA	cluster size (k)	Z	p FWE corr.
whole striatum K_i^{cer}	20 46 38	Right Sup Frontal Gyrus	9	57	3.93	0.031*