



## King's Research Portal

DOI:

[10.1038/s41380-019-0570-6](https://doi.org/10.1038/s41380-019-0570-6)

*Document Version*

Peer reviewed version

[Link to publication record in King's Research Portal](#)

*Citation for published version (APA):*

D'Ambrosio, E., Jauhar, S., Kim, S., Veronese, M., Rogdaki, M., Pepper, F., Bonoldi, I., Kotoula, V., Kempton, M. J., Turkheimer, F., Kwon, J. S., Kim, E., & Howes, O. D. (2021). The relationship between grey matter volume and striatal dopamine function in psychosis: a multimodal 18F-DOPA PET and voxel-based morphometry study. *Molecular Psychiatry*, 26(4), 1332–1345. <https://doi.org/10.1038/s41380-019-0570-6>

### **Citing this paper**

Please note that where the full-text provided on King's Research Portal is the Author Accepted Manuscript or Post-Print version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version for pagination, volume/issue, and date of publication details. And where the final published version is provided on the Research Portal, if citing you are again advised to check the publisher's website for any subsequent corrections.

### **General rights**

Copyright and moral rights for the publications made accessible in the Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognize and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the Research Portal

### **Take down policy**

If you believe that this document breaches copyright please contact [librarypure@kcl.ac.uk](mailto:librarypure@kcl.ac.uk) providing details, and we will remove access to the work immediately and investigate your claim.

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

Enrico D'Ambrosio<sup>1,2†</sup>, Sameer Jauhar<sup>1,3†</sup>, Seoyoung Kim<sup>4</sup>, Mattia Veronese<sup>5</sup>, Maria Rogdaki<sup>1,6</sup>, Fiona Pepper<sup>1</sup>, Ilaria Bonoldi<sup>1</sup>, Vasileia Kotoula<sup>1</sup>, Matthew J Kempton<sup>1</sup>, Federico Turkheimer<sup>5</sup>, Jun Soo Kwon<sup>7,8</sup>, Euitae Kim<sup>4,8\*</sup>, Oliver D Howes<sup>1,6\*</sup>

† These authors contributed equally to this work and are considered the first authors

\* Corresponding authors

<sup>1</sup>Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, SE5 8AF, UK

<sup>2</sup>Psychiatric Neuroscience Group, Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari "Aldo Moro", Bari, Italy

<sup>3</sup>Early Intervention Psychosis Clinical Academic Group, South London & Maudsley NHS Trust, London

<sup>4</sup>Department of Neuropsychiatry, Seoul National University Bundang Hospital, Gyeonggi-do, Republic of Korea

<sup>5</sup>Centre for Neuroimaging Sciences, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, SE5 8AF, UK

<sup>6</sup>Psychiatric Imaging Group MRC London Institute of Medical Sciences, Hammersmith Hospital, London, W12 0NN, UK

<sup>7</sup>Department of Brain & Cognitive Sciences, College of Natural Sciences, Seoul National University, Seoul, Republic of Korea

<sup>8</sup>Department of Psychiatry, Seoul National University College of Medicine, Seoul, Republic of Korea

## Corresponding Authors:

Professor Oliver D Howes

Box 67, Institute of Psychiatry, Camberwell, London, SE5 8AF, UK

Tel: +44 2083833446; email: oliver.howes@kcl.ac.uk

Professor Euitae Kim

Department of Neuropsychiatry, Seoul National University Bundang Hospital, Gyeonggi-do, Republic of Korea

Tel: +8231 787 7435; email: euitae.kim@snu.ac.kr

## 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 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  $^{18}\text{F}$ -DOPA PET scans to measure dopamine synthesis capacity (indexed as the influx rate constant  $K_i^{\text{cer}}$ ) 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  $K_i^{\text{cer}}$ . 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.

Key words: schizophrenia, treatment response, neurobiology, antipsychotics, imaging, resistant, biomarker, neurochemistry

## INTRODUCTION

Schizophrenia is a severe mental illness, affecting approximately 1% of the population<sup>1</sup> and ranks as a leading cause of disability and functional impairment.<sup>2</sup> Disability is compounded by the fact that approximately one third of patients with schizophrenia show limited or no response to first-line antipsychotic drugs.<sup>3-6</sup> It has recently been suggested that there may be two different subtypes of schizophrenia (hyperdopaminergic and normodopaminergic) with differing neurobiological mechanisms.<sup>7, 8</sup> 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 capacity<sup>9</sup>, and reduced grey matter volume in the prefrontal cortex.<sup>10-15</sup> 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<sup>16, 17</sup> and to increased release of subcortical dopamine evoked by drug challenges or stress<sup>18-20</sup>. These findings have led to the hypothesis that increased striatal dopaminergic transmission in schizophrenia may be a consequence of a primary prefrontal alteration.<sup>16, 21-24</sup>

Recent human studies showed an inverse correlation between frontal cortical thickness and d-amphetamine-induced striatal dopamine response in healthy subjects.<sup>25, 26</sup> Moreover, correlations between striatal dopaminergic function and prefrontal functional activation during cognitive tasks have been reported both in individuals at clinical high risk for psychosis<sup>27</sup> and in patients with

schizophrenia.<sup>28</sup> 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.<sup>29</sup> 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<sup>30-34</sup> and confirmed by meta-analysis<sup>35</sup>, 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. <sup>18</sup>F-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.<sup>8</sup> 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.<sup>7, 36, 37</sup> 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 criteria<sup>38</sup>; and within 5 years of the first onset of illness<sup>39</sup>. 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.<sup>40</sup>

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.<sup>41</sup> 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,<sup>42</sup> and measures of concordance used (antipsychotic blood monitoring, self-report and pharmacy records).<sup>43</sup> Chlorpromazine-equivalent dose-years<sup>44</sup> 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  $\geq 50\%$ .<sup>45</sup> Percentage change was adjusted for minimum scores ( $\% \text{ change in total PANSS} = \{[(\text{baseline score} - 30) - (\text{follow up score} - 30)] * 100\} / (\text{baseline score} - 30)$ )<sup>45</sup> 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).<sup>46</sup> 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.<sup>47, 48</sup> Based on this, we defined a treatment response as a CGI-I score of 1 or 2, and non-response as a rating of  $\geq 3$ . The other one was based on the remission criteria evaluated at 6 months.<sup>49</sup>

### *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  $\leq 80$  in the PANSS and no items with a score  $> 3$  on the positive subscale of the PANSS, as reported for this sample before).<sup>37</sup> Written informed consent was obtained from all subjects. Inclusion criteria: diagnosis of schizophrenia according to DSM-IV criteria<sup>50</sup> 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).<sup>46</sup> To be classified as treatment responders, patients were required to have a CGI-S score of  $\leq 3$ , a total score of  $\leq 80$  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.<sup>37</sup>

## ***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)<sup>51</sup> 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.<sup>52</sup>

### ***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.<sup>53</sup> All subjects received 400 mg entacapone, a peripheral catechol-o-methyltransferase 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.<sup>54, 55</sup> 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 <sup>18</sup>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  $^{18}\text{F}$ -DOPA (transaxial resolution of  $\sim 4.2$  mm full width at half maximum).<sup>37</sup> 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.<sup>56, 57</sup> 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 (18F-DOPA) template<sup>33, 58</sup> together with the striatal probabilistic brain atlas<sup>59</sup> 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.<sup>60</sup> Tracing and tractography studies have shown that the cortical projections to the striatum show a topographical distribution across the striatum.<sup>61-63</sup> 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 sub-divided into limbic, associative and sensorimotor sub-divisions respectively based on this topography. We sub-divided the striatum into these sub-regions as previously described.<sup>33, 59</sup> The striatal influx constant ( $K_i^{cer}$ , written as  $K_i$  in some previous publications)<sup>33</sup> was calculated relative to uptake in the reference region using a graphical approach adapted for a reference tissue input function.<sup>64</sup> 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.<sup>58</sup> Further details of the image analysis approach are given in Jauhar et al.<sup>65</sup> and Bloomfield et al.<sup>60</sup> The PET, but not MR, data have been reported for the discovery sample in Jauhar et al.<sup>7, 66</sup> and for the replication sample in Kim et al.<sup>37</sup>

### ***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-Atlas<sup>67</sup> with an ROI in the DLPFC identified as lateral BA9 and BA 46<sup>68, 69</sup> because of our a priori hypothesis based on the fact this brain region has been consistently implicated in the pathophysiology of schizophrenia<sup>70, 71</sup> and sends a large number of cortico-striatal projections<sup>63, 72</sup>. 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.<sup>35</sup> 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.<sup>73, 74</sup> The correlation between associative striatum  $K_i^{cer}$  and DLPFC (the corresponding cortical region)<sup>63</sup> 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).<sup>67</sup>

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.<sup>75, 76</sup>

For illustrative purposes, we computed effect sizes from the maximum T statistic obtained from the significant clusters<sup>77</sup> and meta-analysed them using Comprehensive Meta-Analysis Version 3.<sup>78</sup>

## RESULTS

Demographic ( $\pm$  SD) and  $K_i^{\text{cer}}$  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  $\geq 3$  (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:  $x= -40$ ,  $y= 36$ ,  $z= 38$ ;  $k= 158$ ,  $Z= 4.22$ ,  $p_{\text{FWE corrected}}= 0.017$ ) and right (BA 9:  $x= 32$ ,  $y= 54$ ,  $z= 33$ ;  $k= 163$ ,  $Z= 3.94$ ,  $p_{\text{FWE corrected}}= 0.042$ ) 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:  $37.9 \pm 20.4$  months; non-responders:  $40.2 \pm 19.9$  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:  $x= 20$ ,  $y= 46$ ,  $z= 38$ ;  $k= 57$ ,  $Z= 3.93$ ,  $p_{FWE\ corrected}= 0.031$ ) [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, pFWE 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.<sup>8</sup> Moreover, it has been observed that patients who respond to antipsychotics have higher striatal density of dopaminergic synapses<sup>79</sup> and higher striatal dopamine synthesis capacity<sup>7, 36, 37</sup> when compared with patients with treatment-resistant illness, whilst the latter show greater frontal cortical glutamate levels.<sup>80, 81</sup> 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.<sup>8</sup>

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 schizophrenia<sup>29</sup> and between prefrontal cortex functional activation and dopamine synthesis capacity in subjects with an at-risk mental state and patients with schizophrenia.<sup>28, 82, 83</sup> They are also consistent with evidence of direct and indirect anatomical connections between PFC and striatum<sup>84, 85</sup> 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,<sup>21-24</sup> 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.<sup>86</sup>

Projections from the prefrontal cortex act as a “brake” on the striatal dopaminergic system.<sup>87, 88</sup> 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,<sup>25, 26, 89-92</sup> 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,<sup>61, 93-96</sup> and extends previous studies that have localized dopaminergic dysfunction in schizophrenia to associative regions of the striatum,<sup>33-35</sup> 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.<sup>97</sup>

It is important to consider that treatment-resistant psychosis may be characterized by greater heterogeneity;<sup>98</sup> 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.<sup>99-101</sup> Nevertheless, given heterogeneity in structural volumes in schizophrenia,<sup>10</sup> 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.<sup>102, 103</sup> 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.<sup>104</sup> 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.<sup>105</sup> Moreover, elevated striatal dopamine synthesis and release capacity has been reported in people at risk of psychosis,<sup>31, 32, 106</sup> and to increase during the prodrome,<sup>107</sup> whilst frontal volume has been found to reduce during the

prodrome.<sup>108-110</sup> 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 studies is that one conducted in mice by Kim et al<sup>111</sup> 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.<sup>25, 26</sup> 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.<sup>112, 113</sup> 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.<sup>80,</sup>

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<sup>114-116</sup> and, potentially, on dopamine synthesis capacity.<sup>117, 118</sup> 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 <sup>18</sup>F-DOPA. However, the administered dose in both samples are within the standard range used in imaging studies.<sup>33, 65, 119-122</sup> Doses within the standard imaging range are not thought to lead to appreciable differences in signal to noise ratio.<sup>123</sup> 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.<sup>106</sup>

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.<sup>124</sup>

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.<sup>125</sup> 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,<sup>66</sup> 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,<sup>118</sup> although it may be altered by following treatment with first-generation antipsychotic.<sup>117</sup>

## **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.

## **Acknowledgments**

This research was supported by Medical Research Council (grant MC-A656-5QD30), Maudsley Charity (grant 666), the US Brain & Behavior Research Foundation, Wellcome Trust (grant 094849/Z/10/Z to Professor Howes), the National Institute for Health Research Biomedical Research Centre at South London and Maudsley National Health Service Foundation Trust, King's College London, the Seoul National University Bundang Hospital (SNUBH) research Fund (grant 02-2013-010), the National Research Foundation of Korea (grants NRF-2019R1A2C2005500, NRF-2019M3C7A1032472 and 2017M3C7A1029610). Dr Jauhar is supported by a Sim Fellowship, from the Royal College of Physicians, Edinburgh. Dr Veronese is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London.

## **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.

Supplementary information is available at MP's website.

## REFERENCES

1. Perälä J, Suvisaari J, Saarni SI, Kuoppasalmi K, Isometsä E, Pirkola S *et al.* Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry* 2007; **64**(1): 19-28.
2. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE *et al.* Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. *Lancet* 2013; **382**(9904): 1575-1586.
3. Lindenmayer JP. Treatment refractory schizophrenia. *Psychiatr Q* 2000; **71**(4): 373-384.
4. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO *et al.* Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med* 2005; **353**(12): 1209-1223.
5. Howes OD, McCutcheon R, Agid O, de Bartolomeis A, van Beveren NJ, Birnbaum ML *et al.* Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *Am J Psychiatry* 2017; **174**(3): 216-229.
6. Demjaha A, Lappin JM, Stahl D, Patel MX, MacCabe JH, Howes OD *et al.* Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and predictors. *Psychol Med* 2017; **47**(11): 1981-1989.
7. Jauhar S, Veronese M, Nour MM, Rogdaki M, Hathway P, Turkheimer FE *et al.* Determinants of treatment response in first-episode psychosis: an 18F-DOPA PET study. *Mol Psychiatry* 2018.
8. Howes OD, Kapur S. A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic). *Br J Psychiatry* 2014; **205**(1): 1-3.
9. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A *et al.* The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry* 2012; **69**(8): 776-786.
10. Brugger SP, Howes OD. Heterogeneity and Homogeneity of Regional Brain Structure in Schizophrenia: A Meta-analysis. *JAMA Psychiatry* 2017; **74**(11): 1104-1111.

11. Gong Q, Lui S, Sweeney JA. A Selective Review of Cerebral Abnormalities in Patients With First-Episode Schizophrenia Before and After Treatment. *Am J Psychiatry* 2016; **173**(3): 232-243.
12. Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK *et al.* Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry* 2001; **50**(11): 825-844.
13. Bora E, Fornito A, Yücel M, Pantelis C. The effects of gender on grey matter abnormalities in major psychoses: a comparative voxelwise meta-analysis of schizophrenia and bipolar disorder. *Psychol Med* 2012; **42**(2): 295-307.
14. Selemon LD, Kleinman JE, Herman MM, Goldman-Rakic PS. Smaller frontal gray matter volume in postmortem schizophrenic brains. *Am J Psychiatry* 2002; **159**(12): 1983-1991.
15. Hirayasu Y, Tanaka S, Shenton ME, Salisbury DF, DeSantis MA, Levitt JJ *et al.* Prefrontal gray matter volume reduction in first episode schizophrenia. *Cereb Cortex* 2001; **11**(4): 374-381.
16. Jaskiw GE, Karoum FK, Weinberger DR. Persistent elevations in dopamine and its metabolites in the nucleus accumbens after mild subchronic stress in rats with ibotenic acid lesions of the medial prefrontal cortex. *Brain Res* 1990; **534**(1-2): 321-323.
17. Pycock CJ, Kerwin RW, Carter CJ. Effect of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. *Nature* 1980; **286**(5768): 74-76.
18. Braun AR, Jaskiw GE, Vladar K, Sexton RH, Kolachana BS, Weinberger DR. Effects of ibotenic acid lesion of the medial prefrontal cortex on dopamine agonist-related behaviors in the rat. *Pharmacol Biochem Behav* 1993; **46**(1): 51-60.
19. Flores G, Wood GK, Liang JJ, Quirion R, Srivastava LK. Enhanced amphetamine sensitivity and increased expression of dopamine D2 receptors in postpubertal rats after neonatal excitotoxic lesions of the medial prefrontal cortex. *J Neurosci* 1996; **16**(22): 7366-7375.
20. Roberts AC, De Salvia MA, Wilkinson LS, Collins P, Muir JL, Everitt BJ *et al.* 6-Hydroxydopamine lesions of the prefrontal cortex in monkeys enhance performance on an analog of the Wisconsin Card Sort Test: possible interactions with subcortical dopamine. *J Neurosci* 1994; **14**(5 Pt 1): 2531-2544.
21. Deutch AY. The regulation of subcortical dopamine systems by the prefrontal cortex: interactions of central dopamine systems and the pathogenesis of schizophrenia. *J Neural Transm Suppl* 1992; **36**: 61-89.
22. Grace AA. Cortical regulation of subcortical dopamine systems and its possible relevance to schizophrenia. *J Neural Transm Gen Sect* 1993; **91**(2-3): 111-134.

23. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 1987; **44**(7): 660-669.
24. Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry* 1991; **148**(11): 1474-1486.
25. Casey KF, Cherkasova MV, Larcher K, Evans AC, Baker GB, Dagher A *et al.* Individual differences in frontal cortical thickness correlate with the d-amphetamine-induced striatal dopamine response in humans. *J Neurosci* 2013; **33**(38): 15285-15294.
26. Jaworska N, Cox SM, Casey KF, Boileau I, Cherkasova M, Larcher K *et al.* Is there a relation between novelty seeking, striatal dopamine release and frontal cortical thickness? *PLoS One* 2017; **12**(3): e0174219.
27. Fusar-Poli P, Howes OD, Allen P, Broome M, Valli I, Asselin MC *et al.* Abnormal prefrontal activation directly related to pre-synaptic striatal dopamine dysfunction in people at clinical high risk for psychosis. *Mol Psychiatry* 2011; **16**(1): 67-75.
28. Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M *et al.* Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. *Nat Neurosci* 2002; **5**(3): 267-271.
29. Bertolino A, Breier A, Callicott JH, Adler C, Mattay VS, Shapiro M *et al.* The relationship between dorsolateral prefrontal neuronal N-acetylaspartate and evoked release of striatal dopamine in schizophrenia. *Neuropsychopharmacology* 2000; **22**(2): 125-132.
30. Howes OD, Williams M, Ibrahim K, Leung G, Egerton A, McGuire PK *et al.* Midbrain dopamine function in schizophrenia and depression: a post-mortem and positron emission tomographic imaging study. *Brain* 2013; **136**(Pt 11): 3242-3251.
31. Mizrahi R, Addington J, Rusjan PM, Suridjan I, Ng A, Boileau I *et al.* Increased stress-induced dopamine release in psychosis. *Biol Psychiatry* 2012; **71**(6): 561-567.
32. Howes OD, Bose SK, Turkheimer F, Valli I, Egerton A, Valmaggia LR *et al.* Dopamine synthesis capacity before onset of psychosis: a prospective [18F]-DOPA PET imaging study. *Am J Psychiatry* 2011; **168**(12): 1311-1317.
33. Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P *et al.* Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch Gen Psychiatry* 2009; **66**(1): 13-20.
34. Kegeles LS, Abi-Dargham A, Frankle WG, Gil R, Cooper TB, Slifstein M *et al.* Increased synaptic dopamine function in associative regions of the striatum in schizophrenia. *Arch Gen Psychiatry* 2010; **67**(3): 231-239.

35. McCutcheon R, Beck K, Jauhar S, Howes OD. Defining the Locus of Dopaminergic Dysfunction in Schizophrenia: A Meta-analysis and Test of the Mesolimbic Hypothesis. *Schizophr Bull* 2018; **44**(6): 1301-1311.
36. Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am J Psychiatry* 2012; **169**(11): 1203-1210.
37. Kim E, Howes OD, Veronese M, Beck K, Seo S, Park JW *et al*. Presynaptic Dopamine Capacity in Patients with Treatment-Resistant Schizophrenia Taking Clozapine: An [18F]DOPA PET Study. *Neuropsychopharmacology* 2017; **42**(4): 941-950.
38. Organization WH. *The ICD-10 classification of mental and behavioural disorders: Diagnostic criteria for research*, vol. 2. World Health Organization 1993.
39. Breitborde NJ, Srihari VH, Woods SW. Review of the operational definition for first-episode psychosis. *Early Interv Psychiatry* 2009; **3**(4): 259-265.
40. Leucht S, Winter-van Rossum I, Heres S, Arango C, Fleischhacker WW, Glenthøj B *et al*. The optimization of treatment and management of schizophrenia in Europe (OPTiMiSE) trial: rationale for its methodology and a review of the effectiveness of switching antipsychotics. *Schizophr Bull* 2015; **41**(3): 549-558.
41. Kahn RS, Winter van Rossum I, Leucht S, McGuire P, Lewis SW, Leboyer M *et al*. Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): a three-phase switching study. *Lancet Psychiatry* 2018; **5**(10): 797-807.
42. Taylor DM, Paton C, Kapur S. *The Maudsley Prescribing Guidelines in Psychiatry*. 12th edn, 2015.
43. Sajatovic M, Velligan DI, Weiden PJ, Valenstein MA, Ogedegbe G. Measurement of psychiatric treatment adherence. *J Psychosom Res* 2010; **69**(6): 591-599.
44. Andreasen NC, Pressler M, Nopoulos P, Miller D, Ho BC. Antipsychotic dose equivalents and dose-years: a standardized method for comparing exposure to different drugs. *Biol Psychiatry* 2010; **67**(3): 255-262.
45. Leucht S, Davis JM, Engel RR, Kane JM, Wagenpfeil S. Defining 'response' in antipsychotic drug trials: recommendations for the use of scale-derived cutoffs. *Neuropsychopharmacology* 2007; **32**(9): 1903-1910.
46. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)* 2007; **4**(7): 28-37.

47. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry* 2000; **157**(4): 514-520.
48. Leucht S, Kane JM, Kissling W, Hamann J, Etschel E, Engel RR. What does the PANSS mean? *Schizophr Res* 2005; **79**(2-3): 231-238.
49. Andreasen NC, Carpenter WT, Kane JM, Lasser RA, Marder SR, Weinberger DR. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry* 2005; **162**(3): 441-449.
50. First M, Gibbon M, Spitzer R, Williams J. User's guide for the structured clinical interview for DSM-IV axis I Disorders—Research version. *New York: Biometrics Research Department, New York State Psychiatric Institute* 1996.
51. Ashburner J. A fast diffeomorphic image registration algorithm. *Neuroimage* 2007; **38**(1): 95-113.
52. Malone IB, Leung KK, Clegg S, Barnes J, Whitwell JL, Ashburner J *et al*. Accurate automatic estimation of total intracranial volume: a nuisance variable with less nuisance. *Neuroimage* 2015; **104**: 366-372.
53. Association NEM. NEMA standards publication NU 2-2007: performance measurements of positron emission tomographs. *Rosslyn, VA: National Electrical Manufacturers Association* 2007.
54. Cumming P, Léger GC, Kuwabara H, Gjedde A. Pharmacokinetics of plasma 6-[18F]fluoro-L-3,4-dihydroxyphenylalanine ([18F]Fdopa) in humans. *J Cereb Blood Flow Metab* 1993; **13**(4): 668-675.
55. Guttman M, Léger G, Reches A, Evans A, Kuwabara H, Cedarbaum JM *et al*. Administration of the new COMT inhibitor OR-611 increases striatal uptake of fluorodopa. *Mov Disord* 1993; **8**(3): 298-304.
56. Studholme C, Hill DL, Hawkes DJ. Automated 3-D registration of MR and CT images of the head. *Med Image Anal* 1996; **1**(2): 163-175.
57. Turkheimer FE, Brett M, Visvikis D, Cunningham VJ. Multiresolution analysis of emission tomography images in the wavelet domain. *J Cereb Blood Flow Metab* 1999; **19**(11): 1189-1208.
58. Egerton A, Demjaha A, McGuire P, Mehta MA, Howes OD. The test-retest reliability of 18F-DOPA PET in assessing striatal and extrastriatal presynaptic dopaminergic function. *Neuroimage* 2010; **50**(2): 524-531.

59. Martinez D, Slifstein M, Broft A, Mawlawi O, Hwang DR, Huang Y *et al.* Imaging human mesolimbic dopamine transmission with positron emission tomography. Part II: amphetamine-induced dopamine release in the functional subdivisions of the striatum. *J Cereb Blood Flow Metab* 2003; **23**(3): 285-300.
60. Bloomfield MA, Pepper F, Egerton A, Demjaha A, Tomasi G, Mouchlianitis E *et al.* Dopamine function in cigarette smokers: an [<sup>18</sup>F]-DOPA PET study. *Neuropsychopharmacology* 2014; **39**(10): 2397-2404.
61. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 1986; **9**: 357-381.
62. Tziortzi AC, Haber SN, Searle GE, Tsoumpas C, Long CJ, Shotbolt P *et al.* Connectivity-based functional analysis of dopamine release in the striatum using diffusion-weighted MRI and positron emission tomography. *Cereb Cortex* 2014; **24**(5): 1165-1177.
63. Haber SN. Corticostriatal circuitry. *Dialogues Clin Neurosci* 2016; **18**(1): 7-21.
64. Kumakura Y, Cumming P. PET studies of cerebral levodopa metabolism: a review of clinical findings and modeling approaches. *Neuroscientist* 2009; **15**(6): 635-650.
65. Jauhar S, Veronese M, Rogdaki M, Bloomfield M, Natesan S, Turkheimer F *et al.* Regulation of dopaminergic function: an [18F]-DOPA PET apomorphine challenge study in humans. *Transl Psychiatry* 2017; **7**(2): e1027.
66. Jauhar S, Nour MM, Veronese M, Rogdaki M, Bonoldi I, Azis M *et al.* A Test of the Transdiagnostic Dopamine Hypothesis of Psychosis Using Positron Emission Tomographic Imaging in Bipolar Affective Disorder and Schizophrenia. *JAMA Psychiatry* 2017; **74**(12): 1206-1213.
67. Maldjian JA, Laurienti PJ, Kraft RA, Burdette JH. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage* 2003; **19**(3): 1233-1239.
68. Colantuoni C, Lipska BK, Ye T, Hyde TM, Tao R, Leek JT *et al.* Temporal dynamics and genetic control of transcription in the human prefrontal cortex. *Nature* 2011; **478**(7370): 519-523.
69. Rajkowska G, Goldman-Rakic PS. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. *Cereb Cortex* 1995; **5**(4): 307-322.
70. Guillozet-Bongaarts AL, Hyde TM, Dalley RA, Hawrylycz MJ, Henry A, Hof PR *et al.* Altered gene expression in the dorsolateral prefrontal cortex of individuals with schizophrenia. *Mol Psychiatry* 2014; **19**(4): 478-485.

71. Selemon LD, Zecevic N. Schizophrenia: a tale of two critical periods for prefrontal cortical development. *Transl Psychiatry* 2015; **5**: e623.
72. Haber SN. The place of dopamine in the cortico-basal ganglia circuit. *Neuroscience* 2014; **282**: 248-257.
73. Draganski B, Kherif F, Klöppel S, Cook PA, Alexander DC, Parker GJ *et al*. Evidence for segregated and integrative connectivity patterns in the human Basal Ganglia. *J Neurosci* 2008; **28**(28): 7143-7152.
74. Di Martino A, Scheres A, Margulies DS, Kelly AM, Uddin LQ, Shehzad Z *et al*. Functional connectivity of human striatum: a resting state FMRI study. *Cereb Cortex* 2008; **18**(12): 2735-2747.
75. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. *Neuroimage* 2000; **11**(6 Pt 1): 805-821.
76. Barnes J, Ridgway GR, Bartlett J, Henley SM, Lehmann M, Hobbs N *et al*. Head size, age and gender adjustment in MRI studies: a necessary nuisance? *Neuroimage* 2010; **53**(4): 1244-1255.
77. Cullen AE, De Brito SA, Gregory SL, Murray RM, Williams SC, Hodgins S *et al*. Temporal lobe volume abnormalities precede the prodrome: a study of children presenting antecedents of schizophrenia. *Schizophr Bull* 2013; **39**(6): 1318-1327.
78. Borenstein M, Hedges L, Higgins J, Rothstein H. Comprehensive Meta-Analysis Version 3. Biostat: Englewood, NJ, 2013.
79. Roberts RC, Roche JK, Conley RR, Lahti AC. Dopaminergic synapses in the caudate of subjects with schizophrenia: relationship to treatment response. *Synapse* 2009; **63**(6): 520-530.
80. Mouchlianitis E, Bloomfield MA, Law V, Beck K, Selvaraj S, Rasquinha N *et al*. Treatment-Resistant Schizophrenia Patients Show Elevated Anterior Cingulate Cortex Glutamate Compared to Treatment-Responsive. *Schizophr Bull* 2016; **42**(3): 744-752.
81. Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM *et al*. Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. *Biol Psychiatry* 2014; **75**(5): e11-13.
82. Fusar-Poli P, Howes OD, Allen P, Broome M, Valli I, Asselin MC *et al*. Abnormal frontostriatal interactions in people with prodromal signs of psychosis: a multimodal imaging study. *Arch Gen Psychiatry* 2010; **67**(7): 683-691.
83. Allen P, Luigjes J, Howes OD, Egerton A, Hirao K, Valli I *et al*. Transition to psychosis associated with prefrontal and subcortical dysfunction in ultra high-risk individuals. *Schizophr Bull* 2012; **38**(6): 1268-1276.

84. Nakano K, Kayahara T, Tsutsumi T, Ushiro H. Neural circuits and functional organization of the striatum. *J Neurol* 2000; **247 Suppl 5**: V1-15.
85. Carr DB, Sesack SR. Projections from the rat prefrontal cortex to the ventral tegmental area: target specificity in the synaptic associations with mesoaccumbens and mesocortical neurons. *J Neurosci* 2000; **20**(10): 3864-3873.
86. Sarpal DK, Robinson DG, Lencz T, Argyelan M, Ikuta T, Karlsgodt K *et al.* Antipsychotic treatment and functional connectivity of the striatum in first-episode schizophrenia. *JAMA Psychiatry* 2015; **72**(1): 5-13.
87. Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML. Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annu Rev Pharmacol Toxicol* 2001; **41**: 237-260.
88. Kegeles LS, Abi-Dargham A, Zea-Ponce Y, Rodenhiser-Hill J, Mann JJ, Van Heertum RL *et al.* Modulation of amphetamine-induced striatal dopamine release by ketamine in humans: implications for schizophrenia. *Biol Psychiatry* 2000; **48**(7): 627-640.
89. Caravaggio F, Ku Chung J, Plitman E, Boileau I, Gerretsen P, Kim J *et al.* The relationship between subcortical brain volume and striatal dopamine D2/3 receptor availability in healthy humans assessed with [11 C]-raclopride and [11 C]-(+)-PHNO PET. *Hum Brain Mapp* 2017; **38**(11): 5519-5534.
90. Morales AM, Kohno M, Robertson CL, Dean AC, Mandelkern MA, London ED. Gray-matter volume, midbrain dopamine D2/D3 receptors and drug craving in methamphetamine users. *Mol Psychiatry* 2015; **20**(6): 764-771.
91. Werhahn KJ, Landvogt C, Klimpe S, Buchholz HG, Yakushev I, Siessmeier T *et al.* Decreased dopamine D2/D3-receptor binding in temporal lobe epilepsy: an [18F]fallypride PET study. *Epilepsia* 2006; **47**(8): 1392-1396.
92. Woodward ND, Zald DH, Ding Z, Riccardi P, Ansari MS, Baldwin RM *et al.* Cerebral morphology and dopamine D2/D3 receptor distribution in humans: a combined [18F]fallypride and voxel-based morphometry study. *Neuroimage* 2009; **46**(1): 31-38.
93. Hoover JE, Strick PL. Multiple output channels in the basal ganglia. *Science* 1993; **259**(5096): 819-821.
94. Ferry AT, Ongür D, An X, Price JL. Prefrontal cortical projections to the striatum in macaque monkeys: evidence for an organization related to prefrontal networks. *J Comp Neurol* 2000; **425**(3): 447-470.
95. Joel D, Weiner I. The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. *Neuroscience* 2000; **96**(3): 451-474.

96. Parent A, Hazrati LN. Functional anatomy of the basal ganglia. I. The cortico-basal ganglia-thalamo-cortical loop. *Brain Res Brain Res Rev* 1995; **20**(1): 91-127.
97. van Erp TGM, Walton E, Hibar DP, Schmaal L, Jiang W, Glahn DC *et al.* Cortical Brain Abnormalities in 4474 Individuals With Schizophrenia and 5098 Control Subjects via the Enhancing Neuro Imaging Genetics Through Meta Analysis (ENIGMA) Consortium. *Biol Psychiatry* 2018; **84**(9): 644-654.
98. Kinon BJ. The Group of Treatment Resistant Schizophrenias. Heterogeneity in Treatment Resistant Schizophrenia (TRS). *Front Psychiatry* 2018; **9**: 757.
99. Goldstein ME, Anderson VM, Pillai A, Kydd RR, Russell BR. Glutamatergic neurometabolites in clozapine-responsive and -resistant schizophrenia. *Int J Neuropsychopharmacol* 2015; **18**(6).
100. Frank J, Lang M, Witt SH, Strohmaier J, Rujescu D, Cichon S *et al.* Identification of increased genetic risk scores for schizophrenia in treatment-resistant patients. *Mol Psychiatry* 2015; **20**(7): 913.
101. Lin CC, Wang YC, Chen JY, Liou YJ, Bai YM, Lai IC *et al.* Artificial neural network prediction of clozapine response with combined pharmacogenetic and clinical data. *Comput Methods Programs Biomed* 2008; **91**(2): 91-99.
102. Chklovskii DB, Schikorski T, Stevens CF. Wiring optimization in cortical circuits. *Neuron* 2002; **34**(3): 341-347.
103. Stepanyants A, Hof PR, Chklovskii DB. Geometry and structural plasticity of synaptic connectivity. *Neuron* 2002; **34**(2): 275-288.
104. Modinos G, Allen P, Grace AA, McGuire P. Translating the MAM model of psychosis to humans. *Trends Neurosci* 2015; **38**(3): 129-138.
105. Kellendonk C, Simpson EH, Polan HJ, Malleret G, Vronskaya S, Winiger V *et al.* Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron* 2006; **49**(4): 603-615.
106. Egerton A, Chaddock CA, Winton-Brown TT, Bloomfield MA, Bhattacharyya S, Allen P *et al.* Presynaptic striatal dopamine dysfunction in people at ultra-high risk for psychosis: findings in a second cohort. *Biol Psychiatry* 2013; **74**(2): 106-112.
107. Howes O, Bose S, Turkheimer F, Valli I, Egerton A, Stahl D *et al.* Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. *Mol Psychiatry* 2011; **16**(9): 885-886.

108. Cannon TD, Chung Y, He G, Sun D, Jacobson A, van Erp TG *et al.* Progressive reduction in cortical thickness as psychosis develops: a multisite longitudinal neuroimaging study of youth at elevated clinical risk. *Biol Psychiatry* 2015; **77**(2): 147-157.
109. Sun D, Phillips L, Velakoulis D, Yung A, McGorry PD, Wood SJ *et al.* Progressive brain structural changes mapped as psychosis develops in 'at risk' individuals. *Schizophr Res* 2009; **108**(1-3): 85-92.
110. Borgwardt SJ, McGuire PK, Aston J, Gschwandtner U, Pflüger MO, Stieglitz RD *et al.* Reductions in frontal, temporal and parietal volume associated with the onset of psychosis. *Schizophr Res* 2008; **106**(2-3): 108-114.
111. Kim IH, Rossi MA, Aryal DK, Racz B, Kim N, Uezu A *et al.* Spine pruning drives antipsychotic-sensitive locomotion via circuit control of striatal dopamine. *Nat Neurosci* 2015; **18**(6): 883-891.
112. Plitman E, Patel R, Chung JK, Pipitone J, Chavez S, Reyes-Madrigal F *et al.* Glutamatergic Metabolites, Volume and Cortical Thickness in Antipsychotic-Naive Patients with First-Episode Psychosis: Implications for Excitotoxicity. *Neuropsychopharmacology* 2016; **41**(10): 2606-2613.
113. Kraguljac NV, White DM, Reid MA, Lahti AC. Increased hippocampal glutamate and volumetric deficits in unmedicated patients with schizophrenia. *JAMA Psychiatry* 2013; **70**(12): 1294-1302.
114. Fusar-Poli P, Smieskova R, Kempton MJ, Ho BC, Andreasen NC, Borgwardt S. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neurosci Biobehav Rev* 2013; **37**(8): 1680-1691.
115. Torres US, Duran FL, Schaufelberger MS, Crippa JA, Louzã MR, Sallet PC *et al.* Patterns of regional gray matter loss at different stages of schizophrenia: A multisite, cross-sectional VBM study in first-episode and chronic illness. *Neuroimage Clin* 2016; **12**: 1-15.
116. Vita A, De Peri L, Deste G, Sacchetti E. Progressive loss of cortical gray matter in schizophrenia: a meta-analysis and meta-regression of longitudinal MRI studies. *Transl Psychiatry* 2012; **2**: e190.
117. Gründer G, Vernaleken I, Müller MJ, Davids E, Heydari N, Buchholz HG *et al.* Subchronic haloperidol downregulates dopamine synthesis capacity in the brain of schizophrenic patients in vivo. *Neuropsychopharmacology* 2003; **28**(4): 787-794.
118. Jauhar S, Veronese M, Nour MM, Rogdaki M, Hathway P, Natesan S *et al.* The Effects of Antipsychotic Treatment on Presynaptic Dopamine Synthesis Capacity in First-Episode Psychosis: A Positron Emission Tomography Study. *Biol Psychiatry* 2019; **85**(1): 79-87.

119. Stokes PR, Shotbolt P, Mehta MA, Turkheimer E, Benecke A, Copeland C *et al.* Nature or nurture? Determining the heritability of human striatal dopamine function: an [18F]-DOPA PET study. *Neuropsychopharmacology* 2013; **38**(3): 485-491.
120. Guttman M, Burkholder J, Kish SJ, Hussey D, Wilson A, DaSilva J *et al.* [11C]RTI-32 PET studies of the dopamine transporter in early dopa-naive Parkinson's disease: implications for the symptomatic threshold. *Neurology* 1997; **48**(6): 1578-1583.
121. Alessandrini M, Micarelli A, Chiaravalloti A, Candidi M, Bruno E, Di Pietro B *et al.* Cortico-subcortical metabolic correlates of olfactory processing in healthy resting subjects. *Sci Rep* 2014; **4**: 5146.
122. Avram M, Brandl F, Cabello J, Leucht C, Scherr M, Mustafa M *et al.* Reduced striatal dopamine synthesis capacity in patients with schizophrenia during remission of positive symptoms. *Brain* 2019; **142**(6): 1813-1826.
123. Carson RE. Tracer kinetic modeling in PET. *Positron Emission Tomography*. Springer 2005, pp 127-159.
124. Reddan MC, Lindquist MA, Wager TD. Effect Size Estimation in Neuroimaging. *JAMA Psychiatry* 2017; **74**(3): 207-208.
125. Heslin M, Lomas B, Lappin JM, Donoghue K, Reininghaus U, Onyejiaka A *et al.* Diagnostic change 10 years after a first episode of psychosis. *Psychol Med* 2015; **45**(13): 2757-2769.

## FIGURE LEGENDS

### 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  $K_i^{cer}$  x treatment response (replication sample)**

Colour bar represents T score values.

## TABLE LEGENDS

### Table 1

#### Demographic characteristics of the sample

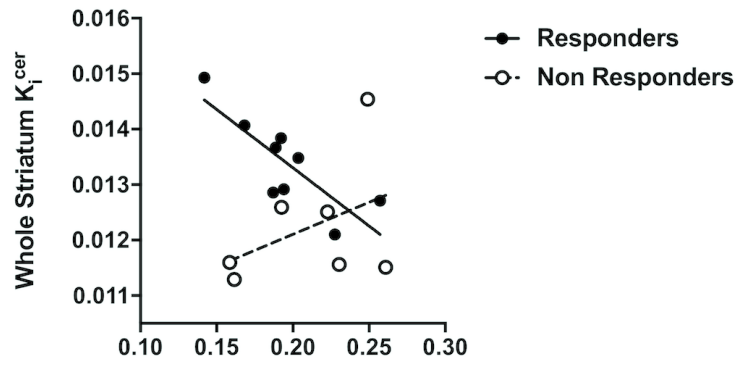
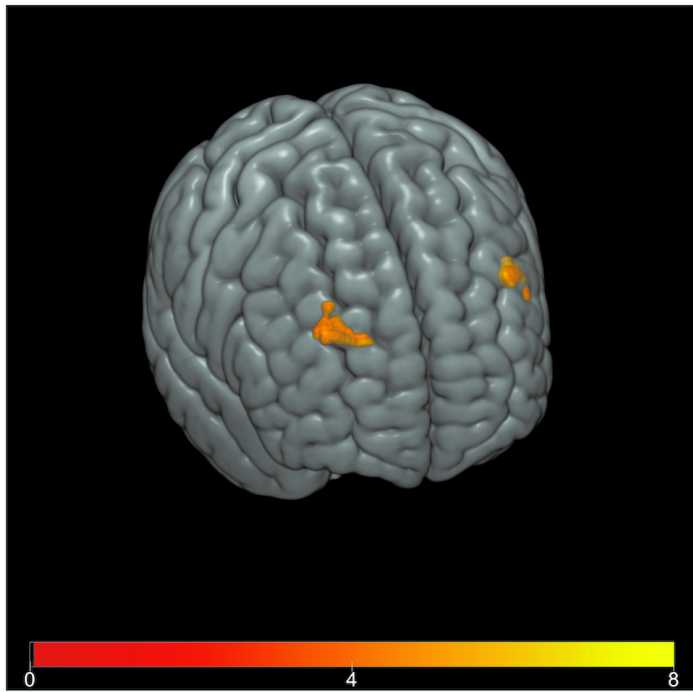
Medication status classification: antipsychotic naïve, antipsychotic free (prior oral antipsychotic medication but free of treatment for at least 6 weeks (oral) or 6 months (depot, if relevant)) or minimally treated (taking antipsychotic medication for two weeks or less).

### Table 2

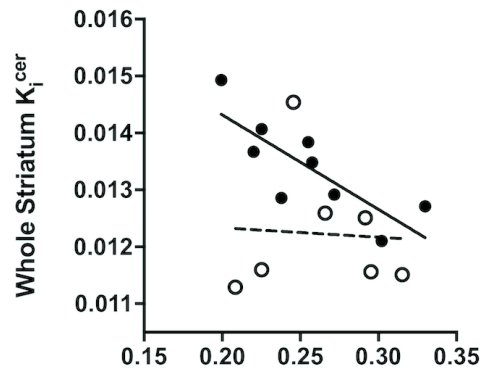
#### Interaction GM volume in PFC x striatal $K_i^{cer}$ x treatment response (discovery sample)

### Table 3

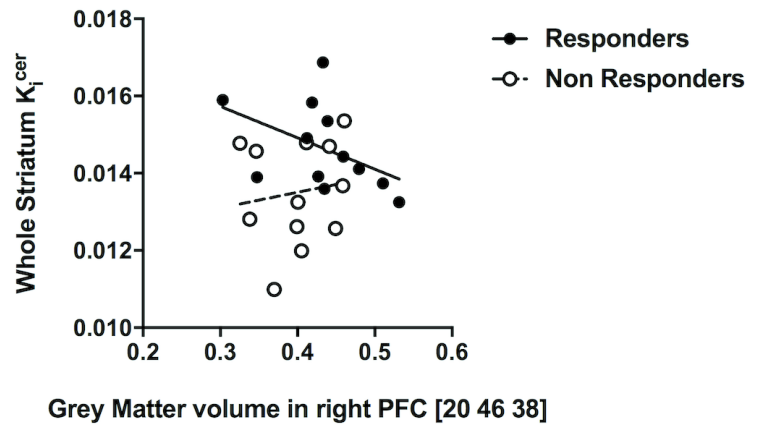
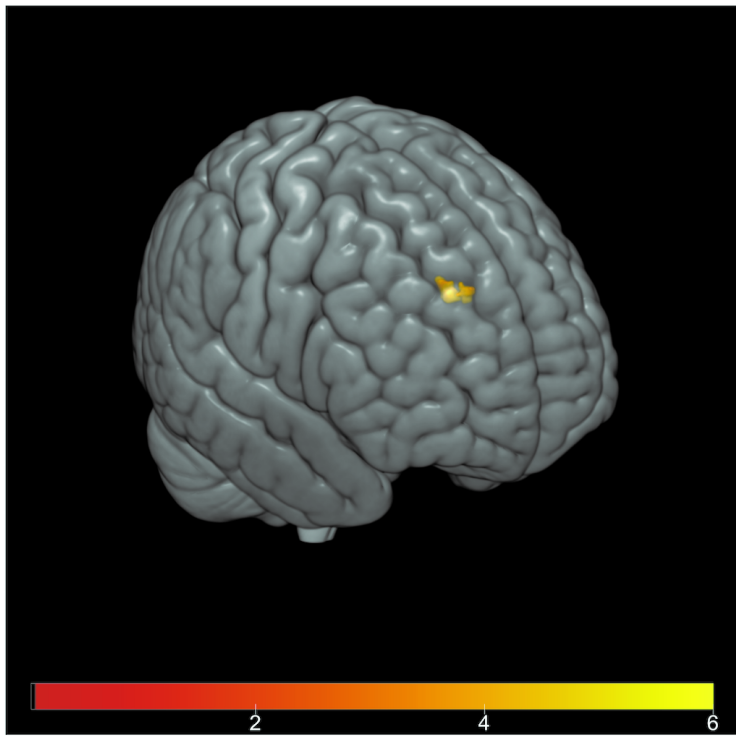
#### Interaction GM volume in PFC x striatal $K_i^{cer}$ x treatment response (replication sample)



Grey Matter volume in right PFC [32 54 33]



Grey Matter volume in left PFC [-40 36 38]



**Table 1**

	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
<b>n</b>	9	7	-	12	12	-
<b>Age (yr ± SD)</b>	24.8 ± 3.5	25.6 ± 3.9	0.675	31.1 ± 9.8	31.3 ± 8.1	0.946
<b>Gender (male/female)</b>	7/2	7/0	0.475	8/4	9/3	0.65
<b>PANSS total score (± SD) [baseline]</b>	74.2 ± 19.8	76.7 ± 17.4	0.796	50.3 ± 11.1	49.7 ± 7.9	0.867
<b>PANSS positive score (± SD) [baseline]</b>	19.7 ± 8.0	20.4 ± 4.4	0.824	10.8 ± 2.7	11.3 ± 2.4	0.635
<b>PANSS negative (± SD) [baseline]</b>	18.4 ± 4.1	17.4 ± 7.4	0.730	13.3 ± 5.2	12.8 ± 2.9	0.809
<b>PANSS general score (± SD) [baseline]</b>	36.1 ± 10.1	38.9 ± 8.4	0.571	26.3 ± 6.1	25.6 ± 3.9	0.722
<b>PANSS total score (± SD) [follow-up]</b>	41.7 ± 8.8	78.6 ± 22.7	0.001*	NA	NA	-

PANSS positive ( $\pm$ SD) [follow-up]	9.6 $\pm$ 2.6	19.1 $\pm$ 5.4	0.0001*		NA	NA	-
PANSS negative ( $\pm$ SD) [follow-up]	10.1 $\pm$ 3.1	19.1 $\pm$ 6.9	0.003*		NA	NA	-
PANSS general ( $\pm$ SD) [follow-up]	22.0 $\pm$ 4.4	40.3 $\pm$ 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 ( $\pm$ SD)	8.77 $\pm$ 1.01	9.08 $\pm$ 1.37	0.606		7.88 $\pm$ 0.96	7.57 $\pm$ 0.93	0.429
$K_i^{cer}$ (1/min) Whole Striatum ( $\pm$ SD)	0.013398 $\pm$ 0.000848	0.012229 $\pm$ 0.001140	0.033*		0.014651 $\pm$ 0.001119	0.013509 $\pm$ 0.001353	0.035*
$K_i^{cer}$ (1/min) Associative Striatum ( $\pm$ SD)	0.013410 $\pm$ 0.000861	0.012064 $\pm$ 0.001169	0.019*		0.014201 $\pm$ 0.001255	0.013178 $\pm$ 0.001365	0.069
$K_i^{cer}$ (1/min) Limbic Striatum ( $\pm$ SD)	0.012927 $\pm$ 0.000796	0.012346 $\pm$ 0.001124	0.245		0.014105 $\pm$ 0.000762	0.013150 $\pm$ 0.001074	0.020*

<b>SD)</b>									
<b>K<sub>l</sub><sup>cer</sup> (1/min) Sensorimotor Striatum (± SD)</b>	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.
<b>whole striatum</b> $K_i^{cer}$	-40 36 38	Left Sup Frontal Gyrus	9	158	4.22	<b>0.017*</b>
	32 54 33	Right Sup Frontal Gyrus	9	163	3.94	<b>0.042*</b>

**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.
<b>whole striatum <math>K_i^{cer}</math></b>	20 46 38	Right Sup Frontal Gyrus	9	57	3.93	<b>0.031*</b>

## **SUPPLEMENTARY INFORMATION**

### **Supplementary Table 1**

**Psychotropic medication**

### **Supplementary Table 2**

**Exploratory analyses - Interaction GM volume in PFC x  $K_i^{cer}$  (striatal subdivisions) x treatment response**

### **Supplementary Figure 1**

**Exploratory analysis - Interaction GM volume in PFC x associative striatum  $K_i^{cer}$  x treatment response (discovery sample)**

Colour bar represents T score values.

### **Supplementary Figure 2**

**Exploratory analysis - Interaction GM volume in PFC x sensorimotor striatum  $K_i^{cer}$  x treatment response (discovery sample)**

Colour bar represents T score values.

### **Supplementary Figure 3**

**Exploratory analysis - Interaction GM volume in PFC x sensorimotor striatum  $K_i^{cer}$  x treatment response (replication sample)**

Colour bar represents T score values.

**Supplementary Table 1**

**Psychotropic medication**

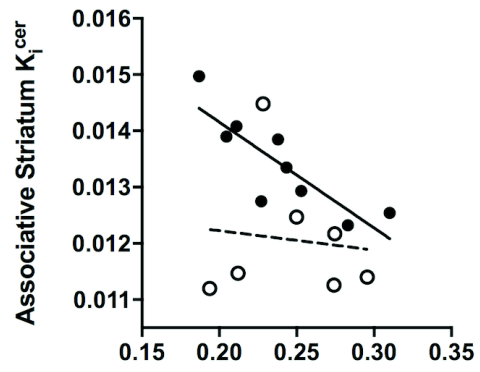
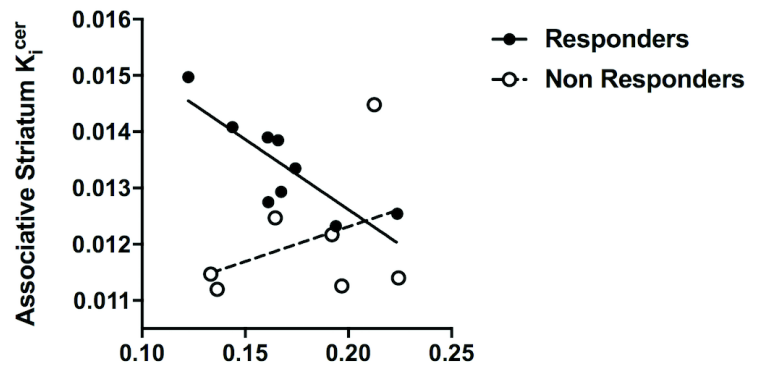
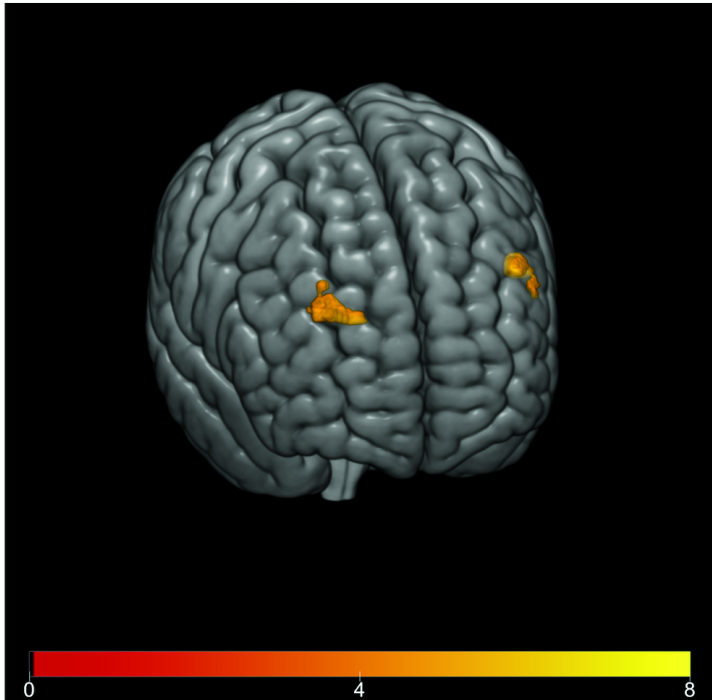
	Analysis in the discovery sample		
	Responders	Non-responders	p-value
<b>Chlorpromazine equivalents (dose years) between scan and follow-up clinical assessment (mean <math>\pm</math> SD)</b>	0.40 $\pm$ 0.31	0.43 $\pm$ 0.28	0.85

	Analysis in the replication sample		
	Responders (first-line AP group)	Non-responders (clozapine group)	p-value
<b>Chlorpromazine equivalents (mg/day) (mean <math>\pm</math> SD)</b>	285.4 $\pm$ 153.2	261.4 $\pm$ 117.5	0.67
<b>Duration of exposure to current antipsychotics (months) (mean <math>\pm</math> SD)</b>	64.1 $\pm$ 18.2	76.3 $\pm$ 12.4	0.58

**Supplementary Table 2**

**Exploratory analyses - Interaction GM volume in PFC x  $K_i^{cer}$  (striatal subdivisions) x treatment response**

Correlation with	MNI coordinates	Subregion	BA	cluster size (k)	Z	pFWE corr.	Sample
<b>associative striatum <math>K_i^{cer}</math></b>	-42 34 38	Sup Frontal Gyrus	9	166	4.30	0.013*	discovery
<b>limbic <math>K_i^{cer}</math></b>	32 54 34	Sup Frontal Gyrus	9	138	3.92	0.046*	discovery
	<i>no clusters surviving correction</i>						
<b>sensorimotor <math>K_i^{cer}</math></b>	34 50 34	Sup Frontal Gyrus	9	190	3.93	0.043*	discovery
<b>associative <math>K_i^{cer}</math></b>	<i>no clusters surviving correction</i>						
<b>limbic <math>K_i^{cer}</math></b>	<i>no clusters surviving correction</i>						
<b>sensorimotor <math>K_i^{cer}</math></b>	18 48 38	Sup Frontal Gyrus	9	46	3.89	0.034*	replication



Grey Matter volume in left PFC [-42 34 38]

