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Frontostriatal functional connectivity and striatal dopamine synthesis capacity in schizophrenia in terms of antipsychotic responsiveness: an [^{18}F]DOPA PET and fMRI study

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Abstract

Background. Given that only a subgroup of patients with schizophrenia responds to first-line antipsychotic drugs, a key clinical question is what underlies treatment response. Observations that prefrontal activity correlates with striatal dopaminergic function, have led to the hypothesis that disrupted frontostriatal functional connectivity (FC) could be associated with altered dopaminergic function. Thus, the aim of this study was to investigate the relationship between frontostriatal FC and striatal dopamine synthesis capacity in patients with schizophrenia who had responded to first-line antipsychotic drug compared with those who had failed but responded to clozapine.

Methods. Twenty-four symptomatically stable patients with schizophrenia were recruited from Seoul National University Hospital, 12 of which responded to first-line antipsychotic drugs (first-line AP group) and 12 under clozapine (clozapine group), along with 12 matched healthy controls. All participants underwent resting-state functional magnetic resonance imaging and [^{18}F]DOPA PET scans.

Results. No significant difference was found in the total PANSS score between the patient groups. Voxel-based analysis showed a significant correlation between frontal FC to the associative striatum and the influx rate constant of [^{18}F]DOPA in the corresponding region in the first-line AP group. Region-of-interest analysis confirmed the result (control group: $R^2 = 0.019$, $p = 0.665$; first-line AP group: $R^2 = 0.675$, $p < 0.001$; clozapine group: $R^2 = 0.324$, $p = 0.054$) and the correlation coefficients were significantly different between the groups.

Conclusions. The relationship between striatal dopamine synthesis capacity and frontostriatal FC is different between responders to first-line treatment and clozapine treatment in schizophrenia, indicating that a different pathophysiology could underlie schizophrenia in patients who respond to first-line treatments relative to those who do not.

Introduction

Schizophrenia is thought to be a heterogeneous disorder in terms of underlying neurophysiological mechanisms (Brugger and Howes, 2017). In particular, it has been proposed that schizophrenia could be subclassified on the basis of dopamine dysfunction into a hyperdopaminergic form that responds well to first-line antipsychotics and a normodopaminergic form that shows limited response to these treatments (Howes and Kapur, 2014). Indeed, molecular imaging studies have reported that patients resistant to first-line antipsychotic drugs show lower striatal dopamine synthesis capacity compared with patients who have shown a good response to first-line treatment (Demjaha *et al.*, 2012; Kim *et al.*, 2017; Jauhar *et al.*, 2018). Further support for there being neurobiological differences between patients who are responsive and resistant to first-line treatment is reviewed in a recent systematic review (Gillespie *et al.*, 2017). Moreover, the differences in dopamine synthesis capacity were most marked in the part of the striatum functionally linked to dorsolateral prefrontal regions; termed the

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associative striatum, and consistent with prior findings in schizophrenia (Howes *et al.*, 2009*b*; Kegeles *et al.*, 2010) and its prodrome (Howes *et al.*, 2011; Mizrahi *et al.*, 2012).

Disrupted brain connectivity is one of the leading mechanisms proposed to contribute to the pathophysiology of schizophrenia (Friston, 1999). Among implicated regions, the frontal cortex is a major focus of this hypothesis (Fusar-Poli *et al.*, 2011; Zhou *et al.*, 2015) and frontostriatal dysconnectivity in schizophrenia is a well replicated finding from both structural and functional neuroimaging studies (Fornito *et al.*, 2013; Levitt *et al.*, 2017). Reduced frontostriatal structural connectivity in the associative loop was observed in chronic patients with schizophrenia using diffusion tensor imaging (Levitt *et al.*, 2017) and a voxel-wise analysis of functional magnetic resonance imaging (fMRI) showed widespread dysregulation of frontostriatal systems in first-episode psychosis patients (Fornito *et al.*, 2013). Furthermore, the pattern of striatal functional connectivity (FC) has been shown to predict response to antipsychotic treatment (Sarpal *et al.*, 2016) and treatment-responsive and treatment-resistant patients with schizophrenia exhibited different striatal FC patterns (White *et al.*, 2016). Along with differences in striatal dopamine synthesis capacity, this suggests neurophysiological divergence in the pathophysiology underlying schizophrenia linked to antipsychotic responsiveness.

The observation that interference with prefrontal efferents can disinhibit striatal dopamine function (Jaskiw *et al.*, 1990; Meyer-Lindenberg *et al.*, 2002) leads to the hypothesis that the disrupted frontostriatal FC could be related to altered dopaminergic function in schizophrenia (Howes *et al.*, 2015; Horga *et al.*, 2016). In line with this idea, rats treated with high doses of phencyclidine manifested frontostriatal functional dysconnectivity and increased dopamine levels, which was associated with locomotor hyperactivity (Paasonen *et al.*, 2017). The locomotor hyperactivity has been widely used in modeling the schizophrenia-like symptoms (Castellani and Adams, 1981; van den Buuse, 2010). This demonstrates the possibility that disrupted frontostriatal FC may be associated with altered dopaminergic activity, though this has yet to be tested in patients with schizophrenia.

The aim of this study thus was to determine the relationship between frontostriatal FC and striatal dopamine synthesis capacity and to compare the relationship between patients responsive to first-line antipsychotic drugs and patients with a history of treatment resistance to first-line drugs but who are currently stable following the clozapine treatment. For this, we measured FC and presynaptic dopamine synthesis capacity using resting-state fMRI (RS-fMRI) and [^{18}F]DOPA positron emission tomography (PET).

Method

The current study was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Participants

All subjects participated in the [^{18}F]DOPA PET study as described in Kim *et al.* (2017). They received a comprehensive description of the study and were provided with written informed consent to participate. Screening procedures included physical examination, checking vital signs, laboratory tests (hematology, blood chemistry, and urinalysis), and an electrocardiogram. Subjects with any significant medical condition, and/or psychiatric disease (except for schizophrenia in patient group) were excluded from the study.

The inclusion criteria for patient group were diagnosis of schizophrenia by Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria; total score of the Positive and Negative Syndrome Scale (PANSS) not above 80 which indicates illness of mild-moderate degree (Leucht *et al.*, 2005; Levine *et al.*, 2008) and score no more than 4 on any item on the PANSS positive subscale. Patients had to be symptomatically stable and have been maintained on their treatment regimen without change for at least 12 weeks at enrollment. Twelve patients were taking first-line antipsychotic drugs (first-line AP group), including risperidone, olanzapine, and paliperidone, and had to have no history of being refractory to first-line antipsychotic drugs or being given clozapine. Twelve patients on clozapine (clozapine group) had to have a history of no response to at least two different first-line antipsychotic drugs despite adequate dose and duration (Howes *et al.*, 2017).

Twelve age- and gender-matched healthy individuals were enrolled as controls (control group) for this study. The presence of DSM-IV axis I disorders was screened using the Structured Clinical Interview for DSM-IV Axis I Disorders, Non-Patient edition (SCID-I/NP) (First *et al.*, 2002).

Positron emission tomography

All patients except for one, who was on a long-acting injectable risperidone, were instructed to take their antipsychotic medications at 9 p.m. a day before the PET scan. All participants had to fast and abstain from smoking and drinking from at least midnight. The PET scan was conducted at 2 p.m., 1 h prior to which 150 mg carbidopa and 400 mg entacapone were orally administered to minimize the formation of radiolabeled metabolites, increasing brain PET signal-to-noise ratio (Wahl *et al.*, 1994). Head movement was monitored with a mark and minimized using a light head strap.

All PET scans were performed on a Biograph 40 Truepoint PET/CT scanner (Siemens, Knoxville, Tennessee, USA). Participants underwent a short computed tomography (CT) for attenuation correction and the emission scans over 95 min were performed following an intravenous bolus injection of approximately 370 MBq (10 mCi) of [^{18}F]DOPA with minimum specific activity of 1.30×10^7 Ci/mol. After proceeding with routine corrections for uniformity, decay, and attenuation, the PET imaging data acquired in a list mode were reconstructed with a filtered back-projection using a Gaussian filter. Images were collected in a three-dimensional mode with 148 axial slices, an image size of 256×256, a pixel size of 1.3364×1.3364 mm^2 and a slice thickness of 3 mm. The dynamic volumetric images were sequenced using the following framing: 2×30, 4×60, 3×120, 3×180, and 15×300 s.

Magnetic resonance imaging

MRIs were obtained using a 3T Trio MRI scanner (Siemens, Erlangen, Germany) within 1 h after the PET scans. RS-fMRI were obtained using a gradient-echo echo-planar imaging sequence in 35 axial slices: echo time (TE)/repetition time (TR)

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= 30 ms/3500 ms, flip angle (FA) = 90°, and voxel size = 1.9 × 1.9 × 3.5 mm^3. During a 6 min 53 s resting-state scan, participants were instructed to stay awake with their eyes closed. We also acquired *T*1-weighted magnetization-prepared rapid-gradient echo anatomical images: TE/TR = 1.89 ms/1670 ms, FA = 9°, 208 slices, and voxel size = 1.0 × 0.98 × 0.98 mm^3. The wakefulness of participants was inspected just after the scan and confirmed by asking sleepiness during the scan. Volumetric segmentation in each *T*1-weighted MRI was conducted using the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) (Fischl, 2012) to extract striatal volumes. All images were examined by an experienced neuroradiologist and no gross abnormalities were observed for any of the participants.

Image analysis

Kinetic analysis for PET data

PET image analysis was conducted as previously described (Bloomfield *et al*., 2014). Inter-frame correction for head movement during the scan was performed by denoising the non-attenuation-corrected dynamic images using a level 2, order 64 Battle–Lemarie wavelet filter. Frames were realigned to a single 'reference' frame, acquired 8 min post-injection, employing a mutual information algorithm (Turkheimer *et al*., 1999). The transformation parameters were then applied to the corresponding attenuated-corrected dynamic images, creating a movement-corrected dynamic image. Subsequently, the realigned images were spatially normalized by registering their summed image to the [^{18}F]DOPA template created in a previous study (McGowan *et al*., 2004). Region-of-interest (ROI) time-activity curves (TACs) were extracted using atlas maps for the whole striatum, and its associative, limbic, and sensorimotor subregions (Martinez *et al*., 2003). The cerebellum was used as the reference region as it is a region with minimal dopaminergic projections (Hammers *et al*., 2003). Finally, using the cerebellar TAC as a reference region input, the Gjedde–Patlak plot (Patlak and Blasberg, 1985) was applied at ROI level to derive the influx rate constants (k_i^{cer}) relative to the cerebellum. The analysis was performed using a combination of SPM5 package (http://www.fil.ion.ucl.ac.uk/spm) and in-house code based on Matlab2012b® (The Mathworks Inc., MA, USA). A previous test-retest study has found this approach to have high reliability for striatum (Egerton *et al*., 2010).

FC analysis for RS-fMRI data

Image analysis was done using SPM12 (http://www.fil.ion.ucl.ac.uk/spm) and the DPARSFA toolbox (http://rfmri.org/DPARSF) (Chao-Gan and Yu-Feng, 2010). After discarding the first four images, functional images were corrected for slice timing and head-motion. To eliminate spurious changes in FC due to head motion, the data were checked with a method used for reducing motion-related artifacts in RS-fMRI (Parkes *et al*., 2018). All data showed (i) spatial movement <1.5 mm in any direction or 1.5° in any rotation and (ii) mean framewise displacement (FD), derived with Jenkinson's relative root mean square algorithm (Jenkinson *et al*., 2002), <0.25 mm. Next, nuisance signal regression [including nine regressors (six head-motion parameters, white matter mean signal, cerebrospinal fluid mean signal, and global mean signal), their derivatives, the squares of both the original and derivative time series, spike regressors, and a linear detrending term] was performed to remove noise due to head motion and non-neural sources of physiological variance based on recent studies (Satterthwaite *et al*., 2013; Ciric *et al*., 2017; Parkes *et al*., 2018). For spike regression, a separate nuisance regressor was generated for each contaminated volume (i.e. FD > 0.25 mm) (Satterthwaite *et al*., 2013). Recent studies have suggested that 36-parameter model with censoring is effective for de-nosing (Satterthwaite *et al*., 2013; Ciric *et al*., 2017; Parkes *et al*., 2018). Then, the residual functional images were spatially normalized to standard MNI space, resampled to 3 mm^3 voxels, and smoothed with a 6 mm full-width at half-maximum Gaussian kernel. Finally, a temporal band-pass filter of 0.01–0.1 Hz was applied to the time series.

Striatal seeds were defined based on three functional subdivisions of the striatum (three for each hemisphere; the limbic, associative, and sensorimotor subregions) reflecting the topographic arrangement of corticostriatal projects, which is identical to the atlas used for the analysis of the PET data (Martinez *et al*., 2003). Seed-based FC maps were created for each seed and each subject by calculating the Pearson correlation coefficient between the mean time series of the seed region and the time series at each voxel. Then, individual correlation maps were converted using Fisher *r*-to-*z* transformation.

Analysis of the relationship between k_i^{cer} and FC

The *z*-transformed FC maps described above were used for a group-level regression analysis to determine the association between the FC to each striatal seed and k_i^{cer} value in the seed. We conducted regression analyses in each group and combined group, respectively.

Given that some analysis tools produce invalid cluster-wise inference with inflated levels of false positives for cluster-forming thresholds of $p < 0.01$ or 0.005 (Eklund *et al*., 2016), all statistical results were thresholded at a cluster-forming height threshold of $p < 0.001$, uncorrected, combined with a cluster-extent threshold of $p < 0.05$, false discovery rate (FDR) corrected for multiple comparisons (Chumbley and Friston, 2009). To validate our finding in the left associative subregion (the association between the left associative seed–ventromedial prefrontal cortex (PFC) FC and the k_i^{cer} value in the seed), we further conducted additional correlation analyses using the ventromedial PFC ROI defined from the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer *et al*., 2002).

Statistical analysis

After confirming the data were normally distributed by using the Kolmogorov–Smirnov test, we used independent *t* tests and analysis of variance to compare demographic variables between groups. Pearson's χ^2 test was used to test differences in the sex ratio between groups. A mixed effects model was implemented in a repeated measures analysis to test whether there was a group effect on k_i^{cer} with the ROI (Region; modeled as a dummy variable: 1 = associative, 2 = limbic, 3 = sensorimotor subregions) and the group (Group: modeled as a dummy variable: 1 = control group, 2 = first-line AP group, 3 = clozapine group) as fixed effects and subjects as random effects.

Result

Table 1 shows the demographic characteristics of participants. There were no significant differences in age and the gender distribution between the groups (age: $F = 0.05$, df = 2.33, $p = 0.951$;

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Table 1. Demographic characteristics of participants

	Control group, $n = 12$	First-line AP group, $n = 12$	Clozapine group, $n = 12$	p value
Age (year ± S.D.)	30.3 ± 8.4	31.1 ± 9.8	31.3 ± 8.1	0.951
Gender (male/female)	8/4	8/4	9/3	0.877
PANSS total score (±S.D.)	31.7 ± 1.1	50.3 ± 11.1	49.7 ± 7.9	<0.001
Positive scale	7.0 ± 0.3	10.8 ± 2.7	11.2 ± 2.3	<0.001
Negative scale	7.2 ± 0.5	13.2 ± 5.2	12.8 ± 2.8	<0.001
General psychopathology scale	17.3 ± 1.0	26.3 ± 6.0	25.5 ± 3.9	<0.001
Duration of illness (month ± S.D.)	–	111.3 ± 108.2	144.7 ± 77.8	0.394
Antipsychotics (*n*)	–	Risperidone (5) Paliperidone (3) Olanzapine (4)	Clozapine (12)	
Antipsychotic dose (mg ± S.D.)	–	Risperidone: 4.0 ± 1.5 Paliperidone: 8.0 ± 1.7 Olanzapine: 11.9 ± 12.1	282.3 ± 126.9	
Chlorpromazine equivalent dose (mg ± S.D.)	–	285.4 ± 153.2	261.4 ± 117.5	0.671
Duration of exposure to current antipsychotics (month ± S.D.)	–	64.1 ± 18.2	76.3 ± 12.4	0.584
Concomitant mediation (*n*)	–	None (6) SSRI (2) Benzodiazepine (3) Antiparkinsonian agent (4)	None (4) SSRI (4) Benzodiazepine (4) Antiparkinsonian agent (3)	

The chlorpromazine equivalent dose was calculated based on the formula from Andreasen *et al.* (2010).
One patient treated with risperidone was given long-acting injectable risperidone. The dose of long-acting injectable risperidone was converted to oral equivalent (Bai *et al.*, 2007).
SSRI includes escitalopram and fluoxetine in the first-line AP group and escitalopram, sertraline and fluoxetine in the clozapine group.
Benzodiazepine includes lorazepam and clonazepam in the first-line AP group and lorazepam, alprazolam, and clonazepam in the clozapine group.
Antiparkinsonian agent indicates medication for treating extrapyramidal symptoms including propranolol, benztropine, and trihexyphenidyl in both groups.

gender: $\chi^2 = 0.262$, df = 2, $p = 0.877$). There was a significant effect of group on PANSS scores ($F = 21.75$, df = 2.33, $p < 0.001$). Pairwise comparison using Bonferroni's correction revealed significantly lower scores in the control group than in the first-line AP group (mean difference = 18.67, S.E. = 3.21, df = 33, $p < 0.001$) and in the clozapine group (mean difference = 18.00, S.E. = 3.21, df = 33, $p < 0.001$), but no significant difference in the total PANSS score between the first-line AP group and the clozapine group (mean difference = 0.67, S.E. = 3.21, df = 33, $p = 1.000$). One smoking patient was enrolled in the clozapine group and there were no smoking patients in the first-line AP group and the control group.

The mean striatal volumes (±S.D.) were 21 953.6 ± 1896.3 mm^3 in the control group, 23 685.6 ± 2787.8 mm^3 in the first-line AP group, and 22 576.8 ± 2529.8 mm^3 in the clozapine group. There was no significant difference in the striatal volume between the groups ($F = 1.56$, df = 2.33, $p = 0.225$).

Table 2 shows the k_i^{cer} values in each subregion by group. The k_i^{cer} values were significantly different according to the group (Group: $F = 15.96$, df = 295.0, $p < 0.001$; Region: $F = 19.46$, df = 263.7, $p < 0.001$). In pairwise comparison, the clozapine group showed significantly lower k_i^{cer} value than the control group (mean difference = −0.00154, S.E. = 0.00028, df = 95.0, $p < 0.001$) and the first-line AP group (mean difference = −0.00110, S.E. = 0.00028, df = 95.0, $p < 0.001$). However, the k_i^{cer} value in the first-line AP group was not significantly different from that in the control group (mean difference = −0.00044, S.E. = 0.00028, df = 95.0, $p = 0.367$) (Kim *et al.*, 2017).

Table 3 demonstrates the result of the voxel-based regression analysis showing the association between the FC to each striatal seed and the k_i^{cer} value in the corresponding seed. The clusters showing the significant correlations in the first-line AP group were located in the ventromedial PFC and middle occipital cortex. In the clozapine group, a significant correlation was found in precentral gyrus. The combined group including the control group, the first-line AP group and the clozapine group showed a significant correlation in the putamen. Figure 1 shows a significant negative correlation between frontal FC to the left associative striatum and the k_i^{cer} in the corresponding region in the first-line AP group.

In order to validate our finding, the ventromedial PFC derived from the AAL atlas [including right superior orbital gyrus (AAL #6); right medial orbital gyrus (AAL #26); and right rectal gyrus (AAL #28)] was chosen for additional ROI analysis and a significant correlation between FC of the ROI to the left associative striatum and the k_i^{cer} in the region was found in the first-line AP group (control group: $R^2 = 0.019$, $p = 0.665$; first-line AP group: $R^2 = 0.675$, $p < 0.001$; clozapine group: $R^2 = 0.324$, $p = 0.054$) (Fig. 2). The correlation shown in the first-line AP group remained significant after applying Bonferroni's correction. The correlation coefficients calculated from ROI analysis were significantly different between the first-line AP group and the clozapine group (first-line AP group *v.* clozapine group: $z = -3.83$, $p < 0.001$; first-line AP group *v.* control group: $z = -2.16$, $p = 0.031$; clozapine group *v.* control group: $z = -1.67$, $p = 0.095$).

Discussion

To our knowledge, this is the first study to assess the relationship between striatal dopamine synthesis capacity and frontostriatal FC

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Table 2. The [^{18}F]DOPA influx rate constants (k_i^{cer}) (±S.D.) in the healthy controls (control group) and patients treated with first-line antipsychotic drugs (first-line AP group) or clozapine (clozapine group)

	k_i^{cer} (1/min)		
	Control group	First-line AP group	Clozapine group
Whole striatum	0.01521 ± 0.00121	0.01465 ± 0.00112	0.01351 ± 0.00135
Associative striatum	0.01483 ± 0.00131	0.01420 ± 0.00126	0.01318 ± 0.00136
Limbic striatum	0.01439 ± 0.00115	0.01411 ± 0.00076	0.01315 ± 0.00107
Sensorimotor striatum	0.01647 ± 0.00135	0.01596 ± 0.00132	0.01446 ± 0.00161

Table 3. Summary of voxel-based analysis in the whole brain

Group	Seed region	Direction of correlation	Correlated region	Montreal Neurological Institute coordinates	*T*/*Z* values	FDR corrected *p* value
Control group	No significant correlation					
First-line AP group	Left AST	Negative	Right medial orbitofrontal cortex	15, 33, −18	7.66/4.30	0.043
	Right AST	Negative	Left middle occipital cortex	−48, −78, 12	5.92/3.79	0.012
Clozapine group	Right SMST	Negative	Left precentral gyrus	−30, −24, 66	6.76/4.06	0.045
Patient group (first-line AP and clozapine group)	No significant correlation					
All groups	Right LST	Positive	Putamen	−21, 9, 3	4.56/4.00	0.006

Clusters showing significant correlations between FC to associative (AST), limbic (LST), and sensorimotor (SMST) subregions and the k_i^{cer} in the corresponding subregion. Statistical results are thresholded at a cluster-forming height threshold of $p < 0.001$, uncorrected, combined with a cluster-extent threshold of $p < 0.05$, FDR corrected for multiple comparisons.

according to antipsychotic responsiveness. Our study found a significant correlation between striatal dopamine synthesis capacity and frontostriatal FC in patients with schizophrenia responsive to first-line antipsychotic drugs, whilst the correlation was not found in patients who have responded to clozapine with the history of being resistant to first-line antipsychotic drug treatment. This result may extend previous findings suggesting different underlying neurobiology according to antipsychotic responsiveness (Demjaha *et al.*, 2012; Kim *et al.*, 2017; Jauhar *et al.*, 2018), though the effects of the differential therapeutic mechanism of action among antipsychotic drugs need to be taken into consideration.

The inverse correlation between striatal dopamine synthesis capacity and frontostriatal FC observed in the first-line AP group supports the hypothesis that disrupted brain connectivity may lead to dopaminergic abnormalities in schizophrenia (Gleich *et al.*, 2015). The finding is in line with the report by Horga *et al.* (2016), demonstrating the correlation of striatal connectivity patterns with dopamine D2 receptor binding potentials of [^{11}C]FBL457 in unmedicated patients with schizophrenia. It reported that abnormal corticostriatal circuitry related to lower binding potential of extrastriatal dopamine D2 receptor (Horga *et al.*, 2016).

Our results show significant correlation with ventromedial PFC. While dorsolateral PFC has drawn attention as a prominent area of abnormality in schizophrenia, frequently in relation to executive dysfunction (Minzenberg *et al.*, 2009), structural alterations in medial PFC such as reduction in gray matter volume (Glahn *et al.*, 2008; Fornito *et al.*, 2009; Pomarol-Clotet *et al.*, 2010), the abnormality of white matter connectivity (Ellison-Wright and Bullmore, 2009; Pomarol-Clotet *et al.*, 2010) has been reported. Moreover, dysfunction of medial PFC has been observed as in part of default mode network which was measured by RS-fMRI as in the current study (Pomarol-Clotet *et al.*, 2008; Whitfield-Gabrieli *et al.*, 2009; Pomarol-Clotet *et al.*, 2010). Such medial PFC is presumed to exert a top-down control over midbrain dopaminergic interaction with the striatum (Ferenczi *et al.*, 2016). Furthermore, the dysregulation of the interaction, consequently leading to abnormal dopamine signaling, is considered to be related with cognitive symptoms of schizophrenia (Simpson *et al.*, 2010). Together with the correlation found in first-line AP group of this study, it supports the idea that cortical dysregulation may result in altered brain dopaminergic transmission.

Our significant findings with associative striatum regarding dopamine capacity are consistent with a number of other reports identifying the associative striatum as a major locus of pathophysiology of schizophrenia (Howes *et al.*, 2009*b*; Kegeles *et al.*, 2010; Miyake *et al.*, 2011; McCutcheon *et al.*, 2018). Moreover, reduced structural connectivity in frontostriatal white matter tracts in the associative loop in chronic patients with schizophrenia has been reported (Levitt *et al.*, 2017). The correlation we observed was between the associative striatum and the orbitofrontal cortex. This is consistent with the known cortical input from orbitofrontal cortex to associative striatum (Eblen and Graybiel, 1995; Haber *et al.*, 2006), though the majority of corticostriatal projections are from dorsolateral PFC (Alexander *et al.*, 1986; Joel and Weiner, 2000).

To consider antipsychotic treatment responsiveness, we divided the patient group into the first-line AP group and the clozapine group, where lower dopamine synthesis capacity has been observed in the clozapine group (Kim *et al.*, 2017). Our finding of a group difference in the correlation pattern between striatal dopamine capacity and frontostriatal FC from this study adds to other evidence suggesting a distinct pathophysiologic mechanism in non-responders to first-line treatment relative to

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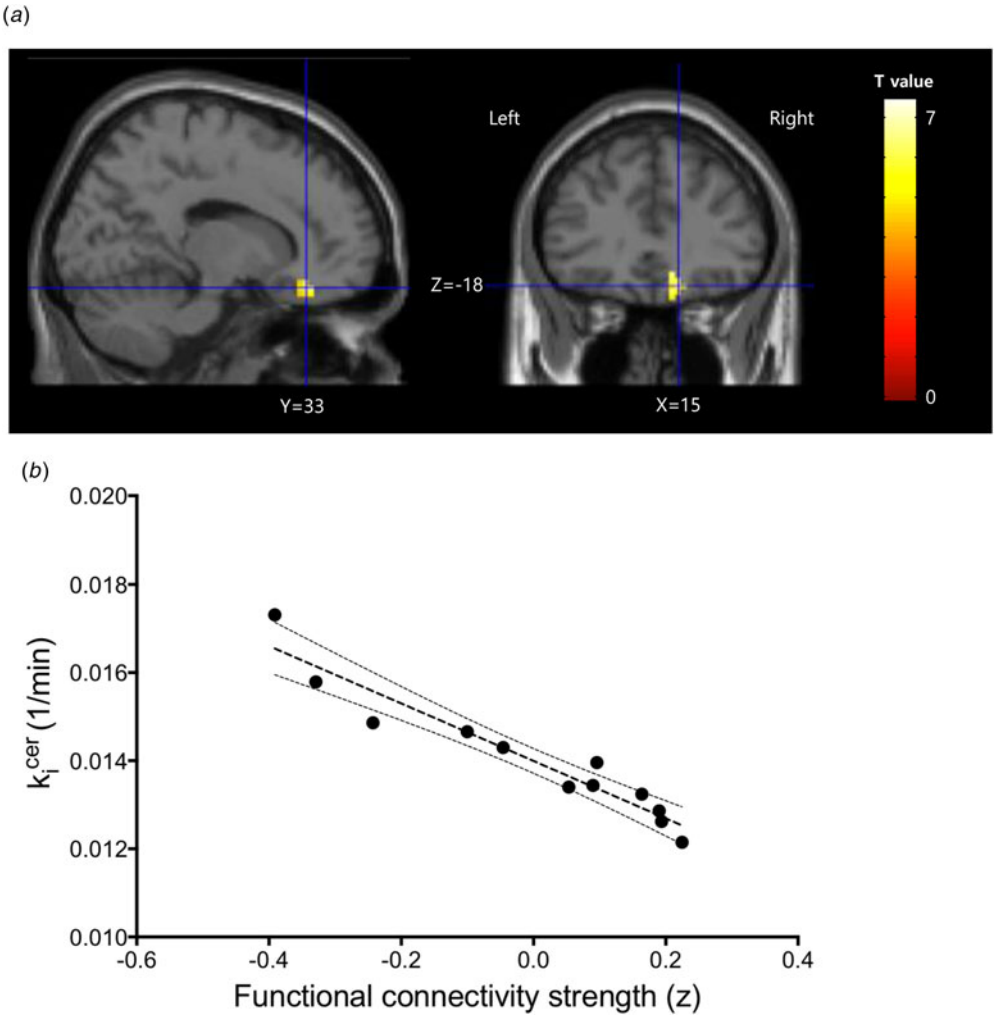

Fig. 1. Cluster showing a significant correlation between FC to the left associative striatal subregion (*a*) and correlation plot between FC strength of the cluster and the k_i^{cer} in the left associative striatal subregion in the first-line AP group ($R^2 = 0.919$, $p < 0.001$) (*b*). Statistical results are thresholded at a cluster-forming height threshold of $p < 0.001$, uncorrected, combined with a cluster-extent threshold of $p < 0.05$, FDR corrected for multiple comparisons. The dashed line and dotted lines indicate the means and 95% CIs, respectively.

first-line responders (Demjaha *et al.*, 2012; Selvaraj *et al.*, 2014; Mouchlianitis *et al.*, 2016).

About one-third of patients with schizophrenia is said to be resistant to first-line antipsychotic drugs (Lally *et al.*, 2016; Demjaha *et al.*, 2017) and a subgroup of these patients is known to respond to clozapine (Kane *et al.*, 1988; Siskind *et al.*, 2016), an atypical antipsychotic with relatively weak dopamine antagonism (Howes *et al.*, 2009*a*). The diverse response to antipsychotic treatment and the abnormalities in different neurotransmitter systems according to the antipsychotic responsiveness suggest a different underlying neurobiology in schizophrenia (Daskalakis and George, 2009; Howes and Kapur, 2014; Mouchlianitis *et al.*, 2016). The different relationship between dopamine synthesis capacity and frontostriatal FC in the clozapine group also supports this notion.

Limitations

Potential confounding effects of antipsychotic medication, under cross-sectional design of this study in particular, limit the interpretation and generalization of the results. The varied antipsychotic agents administered in the first-line AP group may have added noise to the reported relationships and the heterogeneity of the medication history in the clozapine group could have also influenced the relationship. Effects of antipsychotic drugs on dopamine synthesis capacity have been reported before. For example, subchronic haloperidol treatment was related with downregulation of dopamine synthesis capacity (Grunder *et al.*, 2003), while both increase and decrease in dopamine synthesis capacity were observed after aripiprazole and risperidone treatment (Ito *et al.*, 2009; Ito *et al.*, 2012). Furthermore, clozapine was reported to reduce extracellular dopamine level after chronic administration (Shilliam and Dawson, 2005), which might be associated with the lower k_i^{cer} value in the clozapine group. These results indicate antipsychotic agents may also have implications to correlation between frontostriatal FC and dopamine synthesis capacity in the absence of prospective research. We enrolled medicated patients in the study to control the symptomatic severity between the two patient groups. When interpreting the result, one should take it into consideration that the two patient groups are different in the pharmacology of the treatment, which could have

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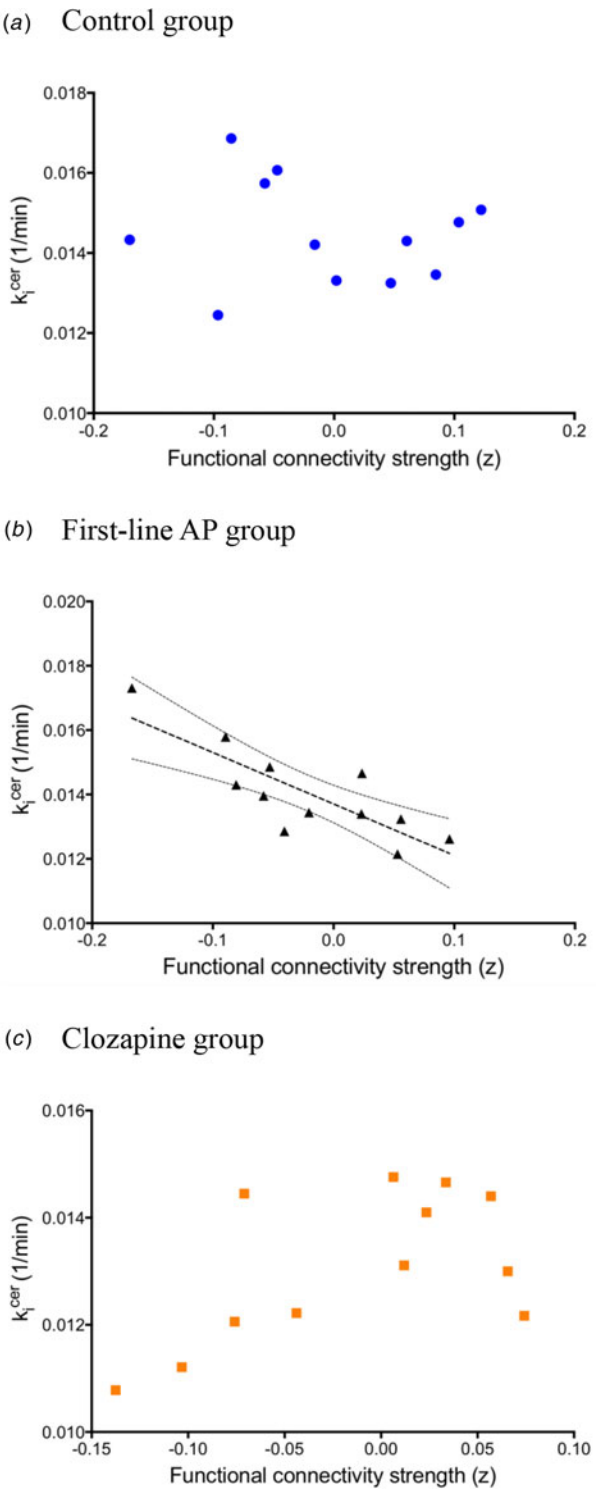

Fig. 2. Correlation between the FC strength of the ventromedial PFC defined from the Automated Anatomical Labeling atlas and the k_i^{cer} values in the control ($R^2 = 0.019$, $p = 0.665$), the first-line AP ($R^2 = 0.675$, $p < 0.001$) and the clozapine group ($R^2 = 0.324$, $p = 0.054$). The dashed line and dotted lines indicate the means and 95% CIs, respectively.

influenced the relationship between FC and dopamine synthesis capacity.

Nevertheless, patients participated in this study were through with acute psychotic phase and were all in stable status, especially with positive symptoms well-controlled under steady drug regimen at the point of the assessment. Prior studies have reported meaningful changes in FC after atypical antipsychotics treatment in patients with schizophrenia but mostly accompanied by changes in clinical symptom severity (Sambataro *et al.*, 2009; Lui *et al.*, 2010). In addition, Sarpal *et al.* (2015) reported a positive relationship between the reduction of psychotic symptom and increase in corticostriatal FC after antipsychotic treatment in patients with first-episode schizophrenia. This result suggests corticostriatal functional dysconnectivity is modulated by pharmacologic intervention, but in a manner that is linked with symptom reduction. Meanwhile, a longitudinal study describing abnormalities in large scale functional networks in patients with schizophrenia demonstrated that dysconnectivity modulated by antipsychotic medication is seen only to a certain extent (Kraguljac *et al.*, 2016), and a previous comparison of striatal FC between patients taking antipsychotics and those who were medication-free did not show significant differences (Fornito *et al.*, 2013). Accordingly, similar clinical symptom level regarding treatment groups in our study is also noteworthy, although mediated by antipsychotic medication.

Conclusion

Different patterns of relationship between striatal dopamine synthesis capacity and frontostriatal FC observed in this study indicate different pathophysiology underlying schizophrenia according to antipsychotics treatment-responsiveness. Results should be reconfirmed in prospective manner with larger sample size in future studies.

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Conflict of interest. None.

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