Breakdown of the striatal-default mode network loop in schizophrenia

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Abstract

The striatum has been shown to be a core region in schizophrenia with functional and structural deficits. Previous studies have confirmed the schizophrenia-related functional connectivity between the striatal and cortical regions. However, among these, few studies have attempted to determine the directional flow of the influence. In the present study, we used resting-state fMRI to explore the directed connectivity between the striatum and the default mode network (DMN) in schizophrenia. Furthermore, the reciprocal influence of the DMN on the striatum was also significantly reduced. These findings provide compelling evidence for a breakdown of the striatum–DMN loop in schizophrenia. This abnormal connectivity could be related to clinical variables. In conclusion, our study suggests that abnormally directed influences between the striatum and the DMN might be a biomarker of schizophrenia and also reveals a potential target for treatment.

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1. Introduction

In recent years, neuroimaging studies concerning the neural substrates of schizophrenia have documented the dysfunction of several brain regions (Anticevic et al., 2011; Eisenberg and Berman, 2010), such as the dorsolateral prefrontal cortex (DLPFC). In particular, the striatum is important because this region is the primary target for anti-psychotic drugs and manifests several anomalies in schizophrenia. A number of imaging studies have found morphological changes in the putamen or caudate, both of which are key nodes of the striatum, indicating that this anatomical abnormality may be a core feature of the illness (Brandt and Bonelli, 2008; Mamah et al., 2007). Moreover, a recent study demonstrated increased intrinsic activity in the striatum in patients with schizophrenia, which was modulated by the disorder states and correlated with symptom dimensions (Sorg et al., 2013). These data suggest that the striatum is a key site of the functional and structural deficits in schizophrenia.

Previous studies have documented that the striatum may be connected to cortical regions within separate striatal–cortical circuitries. For instance, emerging evidence has suggested that the striatum functions in line with the prefrontal cortex (especially the DLPFC) to mediate working memory (Lewis et al., 2004) and executive control (Hazy et al., 2005) and inhibitory control (Rubia et al., 2001). One hypothesis assumed that the activity of the striatum was under the control of the prefrontal cortex (Flores et al., 1996), with one example of indirect evidence suggesting that the exaggerated striatal dopaminergic function could be predicted by reduced prefrontal activity (Meyer-Lindenberg et al., 2002). However, this assumption remains to be tested. Nevertheless, studies concerning the functions of the default mode network (DMN) have elucidated the existence of a striatal–DMN loop (Braskie et al., 2011; Lim et al., 2011). One study reported that the dopamine transporters in the striatum could modulate neural activity in the DMN (Tomasi et al., 2009). Furthermore, reduced functional connectivity between the striatum and the DMN has been observed in schizophrenia (Orliac et al., 2013).

Although multiple studies have established the schizophrenic anomalies of the striatal–cortical circuitries, most of these studies focused on the pharmacological effects or the functional connectivity patterns, which do not demonstrate the effective connectivity relationship between systems. Because schizophrenia has been conceptualized as a network-based disease (Andreasen et al., 1998), determining the directionality of the influence between separate regions could provide novel information toward understanding the underlying neural mechanisms of this disease. A recent study has demonstrated that schizophrenia is accompanied by a failure to coordinate directed influences between networks, which could be correlated with the clinical expression of psychosis (Palaniyappan et al., 2013). To date, no studies have examined the effective connectivity patterns between the striatum and the cortical regions.
To investigate the effective connectivity patterns within the corticostriatal loop, the present study employed a Granger causality (GC) analysis (GCA) of resting-state fMRI scans. GCA is an effective connectivity method based on autoregressive (VAR) modeling (Bressler and Seth, 2011). Defined as a measurement of the directed connectivity that a region (X) exerts over another (Y), this method has the advantage of revealing both the direction and the strength of the information flow between interacting brain regions. Using this method, Palaniyappan et al. (2013) observed a breakdown of the directed influences within the salience-execution loop in schizophrenia. We hypothesized that the effective connectivity patterns between certain cortical regions and the striatum would be abnormal in patients with schizophrenia compared with healthy controls. First, bivariate GC was calculated to explore the brain regions that exhibit abnormal effective connectivity with the striatum. We then took a further step to correlate the GC coefficients with clinical measurements.

2. Materials and methods

2.1. Subjects

Fifty-nine participants were recruited in the present study, including 23 patients with schizophrenia and 36 healthy controls. The patients were selected according to the DSM-IV criteria for schizophrenia, and diagnoses were conducted in the 2nd People’s Hospital of Beibei, Chongqing, China, via standardized clinical interviews. For each patient, we collected Positive and Negative Syndrome Scale (PANSS) scores that were assessed by psychiatrists. All of the patients were in a stable phase of illness, and the average duration of illness was 8.39 ± 6.10 years. Healthy controls were recruited from the local community. None of the controls had been diagnosed with any mental illness, and they met none of the DSM-IV criteria for schizophrenia. In addition, the controls had no family history of psychiatric disorders among first-degree relatives.

Both the patients and the controls were excluded if they had the following: (1) any history of amphetamine, cocaine, or marijuana dependence; (2) any history of substance abuse or dependence; or (3) a history of brain/head injury with a loss of consciousness for more than 5 min.

The demographic information of the participants is summarized in Table 1, and the patient treatment information is listed in Table S1. There were no differences regarding gender, age, or years of education between the patients and healthy controls. This study was approved by the institutional review board (IRB) at the Key Laboratory of Cognition and Personality in Southwest University, China. All of the participants gave written informed consent.

2.2. fMRI data acquisition and preprocessing

A detailed description of the fMRI data acquisition and preprocessing is presented in the Supplemental methods.

### Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group; mean (SD)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls (n = 36)</td>
<td>Patients (n = 23)</td>
</tr>
<tr>
<td>Age (year)</td>
<td>31.17 (9.27)</td>
<td>34.04 (8.96)</td>
</tr>
<tr>
<td>Gender (male: female)</td>
<td>20:16</td>
<td>14:9</td>
</tr>
<tr>
<td>Education (year)</td>
<td>13.17 (3.29)</td>
<td>12.09 (3.30)</td>
</tr>
<tr>
<td>Duration of illness (year)</td>
<td>–</td>
<td>8.39 (6.10)</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>–</td>
<td>10.39 (2.68)</td>
</tr>
<tr>
<td>PANSS-N</td>
<td>–</td>
<td>12.78 (4.06)</td>
</tr>
<tr>
<td>PANSS-G</td>
<td>–</td>
<td>22.69 (3.23)</td>
</tr>
<tr>
<td>PANSS-total</td>
<td>–</td>
<td>45.26 (7.71)</td>
</tr>
</tbody>
</table>

2.3. Voxel-wise GCA

To identify whether the striatum displayed functional deficits, we analyzed the amplitude of low-frequency fluctuation (ALFF). The details of the ALFF calculation are described in the Supplemental Methods 1.3. Because the ALFF values in the left striatum (x = −15, y = 9, z = −3, MNI coordinates) exhibited significant between-group differences, we defined the left striatum as a region of interest (ROI) with a 6 mm radius and estimated (1) the X-to-Y effects, the influence of the left striatum (X) on every other voxel in the brain (Y), and (2) the Y-to-X effects, the influence of every other voxel in the brain on the left striatum. The time lag order in this analysis was set to 1 (1 TR, 2.5 s) as the default.

The present study employed signed-path coefficients (Chen et al., 2009) to infer the probable positive or negative effects of the directed Granger influence. According to Palaniyappan et al. (2013), a path coefficient of +1 from region X to Y suggests that the activity of region X would positively predict the subsequent activity of region Y, which is referred to as an excitatory influence, whereas a path coefficient of −1 from region X to Y suggests that the activity of region X would negatively predict the subsequent activity of region Y, which is referred to as an inhibitory influence. In contrast to the multivariate residual-based GC model, bivariate coefficient-based GCA enables the simultaneous detection of bidirectional influences of opposite effects and allows for a parametric statistical analysis for group-level inference (Hamilton et al., 2011). An analysis of voxel-wise GC was performed within the gray mask using REST (http://www.restfmri.net). A Fisher transform was then applied to the resulting coefficients to produce z maps.

Between-group differences were analyzed using separate two-sample t-tests. For the regions with significant group differences, follow-up one sample t-tests were performed to investigate the direction of the influence in each group separately. All of these analyses were performed after controlling for age, gender and years of education.

2.4. GC coefficients and clinical variables

A stepwise regression analysis was performed to correlate the GC coefficients with the illness duration and the PANSS scores. The coefficients were extracted among the striatum and the other regions that had significant X-to-Y effects and/or Y-to-X effects in the bivariate GCA; for a detailed list, see Table S2. The final GC coefficient was computed as \([x\text{-to-}y] − (y\text{-to-}x)]\ (coefficients), which represents the net directed influences.

3. Results

3.1. Granger causality analysis

As displayed in Fig. 1 and Table 2, the two-sample t-test revealed significant between-group differences in the outflow from the left striatum to the DMN (including the bilateral frontal cortex, the posterior cingulate cortex (PCC), the bilateral angular gyrus and the ventral medial prefrontal cortex (vmPFC), and to the bilateral postcentral gyrus \((p < 0.05, \text{FDR corrected})\). In the controls, the striatum exerted inhibitory influences on these regions \((p < 0.05, \text{FDR corrected})\), whereas in the patients, no influence was observed, even at a threshold of \(p < 0.05, \text{uncorrected}\). Furthermore, the reciprocal influence from the DMN to the left striatum also revealed between-group differences (see Fig. 2). The controls displayed a significant excitatory influence from the DMN to the left striatum \((p < 0.05, \text{FDR corrected})\), whereas this influence was not observed in the patients \((p > 0.05, \text{uncorrected})\). To characterize our results, a mask was applied to match the regions in the DMN; see Supplemental Methods 1.4.

To confirm our results, we investigated the influence of the DMN on the rest of the brain. A voxel-wise GCA was performed using a 6 mm spherical ROI placed in the PCC \((x = 3, y = −2, z = 36)\). Significant group differences were observed regarding the effect of the PCC on
Fig. 1. Between-group differences of the directed outflow from the left striatum. A, B present the directed outflow exerted by the left striatum on the rest of the brain in controls (A) and patients (B). C presents regions that showed significant between-group differences (controls > patients).

Table 2
Two-sample t-test of the directed influences from and to the left striatum between controls and patients.

<table>
<thead>
<tr>
<th>Regions</th>
<th>MNI coordinate</th>
<th>GC coefficient</th>
<th>T value</th>
<th>Cluster size (k)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Causal outflow from the left putamen (x-to-y coefficients)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temporal pole</td>
<td>57</td>
<td>−2.13</td>
<td>2.41</td>
<td>−4.01</td>
</tr>
<tr>
<td>Middle temporal gyrus</td>
<td>−63</td>
<td>−4.84</td>
<td>1.08</td>
<td>−4.22</td>
</tr>
<tr>
<td>Superior temporal gyrus</td>
<td>−45</td>
<td>−4.64</td>
<td>1.68</td>
<td>−4.60</td>
</tr>
<tr>
<td>Medial frontal gyrus</td>
<td>−6</td>
<td>−5.17</td>
<td>2.05</td>
<td>−4.97</td>
</tr>
<tr>
<td>Medial frontal gyrus</td>
<td>−15</td>
<td>−3.00</td>
<td>3.52</td>
<td>−4.77</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>21</td>
<td>−1.29</td>
<td>3.32</td>
<td>−5.40</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>21</td>
<td>−3.54</td>
<td>3.15</td>
<td>−4.82</td>
</tr>
<tr>
<td>Superior frontal gyrus</td>
<td>18</td>
<td>−2.65</td>
<td>3.22</td>
<td>−4.62</td>
</tr>
<tr>
<td>Cingulate gyrus/precuneus</td>
<td>3</td>
<td>−4.46</td>
<td>3.33</td>
<td>−5.27</td>
</tr>
<tr>
<td>Precuneus</td>
<td>−36</td>
<td>−6.12</td>
<td>1.37</td>
<td>−4.46</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>−54</td>
<td>−3.79</td>
<td>2.65</td>
<td>−4.74</td>
</tr>
<tr>
<td>Postcentral gyrus</td>
<td>−54</td>
<td>−3.27</td>
<td>3.53</td>
<td>−4.37</td>
</tr>
</tbody>
</table>

| **Causal inflow to the left putamen (y-to-x coefficients)** |                |                |         |                 |
| Temporal pole                  | 51             | 3.98           | −1.40   | 4.13            | 77               |
| Middle temporal gyrus          | −45            | 3.68           | −1.38   | 3.64            | 42               |
| Middle temporal gyrus          | 60             | 3.41           | −1.92   | 4.24            | 95               |
| Middle temporal gyrus          | −42            | 3.85           | −1.58   | 3.77            | 27               |
| Medial frontal gyrus           | 45             | 3.35           | −1.26   | 3.74            | 59               |
| Medial frontal gyrus           | 6              | 3.23           | −1.96   | 4.05            | 114              |
| Medial frontal gyrus           | 15             | 4.12           | −2.26   | 4.61            | 53               |
| Superior frontal gyrus         | 15             | 3.35           | −2.09   | 3.83            | 28               |
| Lingual gyrus                  | −15            | 3.87           | −1.31   | 4.18            | 89               |
| Cingulate/lingual gyrus        | 15             | 2.80           | −1.95   | 3.45            | 29               |

Note: the significant level of the results was set at p < 0.05 (AlphaSim corrected).
the bilateral striatum ($p < 0.05$, AlphaSim corrected). In the controls, the PCC exerted an excitatory influence, whereas in the patients, the PCC exerted an inhibitory influence. In addition, there was a group difference in the effect of the bilateral striatum on the PCC ($p < 0.05$, AlphaSim corrected); the controls exhibited an inhibitory influence, whereas the patients exhibited an excitatory influence. These results are displayed in Fig. 3 and Table 3. Moreover, the results from another seed region, the vmPFC ($x = −6, y = 45, z = −12$), were consistent with the observation described above; see Fig. S3 for details.

To rule out the possibility that head motion might affect the results, we performed another procedure to correct for movement artifacts using the ArtRepair in DPARSF. Then, we performed the same GCAs with the resulting data. Our results of the seed region (the left striatum) corresponded with the findings described above. For details, see Figs. S4 and S5.

### 3.2. GC coefficients and clinical variables

The correlation between the GC coefficients and clinical variables is presented in Fig. 4. Regarding the net directed influences, the stepwise regression revealed two pathways within the striatum–DMN loop that could account for the illness duration, including a net influence from the temporal pole to the right superior temporal gyrus (rSTG) and a net influence from the medial temporal gyrus (meTG) to the rSTG. These two pathways accounted for 60% of the variance of the illness duration with a significance level of $p < 0.001$.

The scores on the positive scale of the PANSS (PANSS-P) could be predicted by the influences of the vmPFC on the superior frontal gyrus, of the inferior parietal lobule (IPL) on the meTG, and of the left superior temporal gyrus on the IPL. Overall, these pathways accounted for 56.4% of the variances of the PANSS-P ($p < 0.001$). Furthermore, the net influences of the PCC on the rSTG, the vmPFC and the lingual gyrus could predict the scores on the negative scale of the PANSS (PANSS-N) ($R^2 = 0.59, p < 0.001$).

### 3.3. Relationship to treatment with medication

To confirm whether our results were influenced by the treatment status of the patients, we performed further analysis to explore a possible relationship between our results and the medication doses (in chlorpromazine equivalents). Four out of the 23 patients were excluded from this analysis because there is no chlorpromazine equivalent for the paliperidone they received. Bivariate correlations were employed to examine the influence of medication on the ALFF and the GC coefficients within the clusters that had significant between-group differences. The results revealed no surviving voxels at the uncorrected level of $p < 0.05$.

### 4. Discussion

In the present study, we calculated bivariate GC with the left striatum as a seed region to explore the brain voxels that display an abnormal effective connectivity with the striatum in schizophrenia. We observed a failure of the inhibitory influence of the left striatum on the DMN in patients compared with healthy controls. Regarding the reciprocal pathway, the patients also had a reduction of the excitatory influence that the DMN exerted on the striatum. Further analyses were performed to correlate the GC coefficients with clinical variables.

Using ALFF values, we observed functional hyper-activation of the bilateral striatum in schizophrenia. Converging evidence from imaging studies has revealed schizophrenic functional and structural

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**Table 3**

Two-sample $t$-test of the directed causal influences from and to the posterior cingulate cortex between controls and patients.

<table>
<thead>
<tr>
<th>Regions</th>
<th>MNI coordinate x/y/z</th>
<th>GC coefficients</th>
<th>T value</th>
<th>Cluster size (k)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causal outflow from the posterior cingulate cortex (x-to-y coefficients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Striatum (left)</td>
<td>−24 0 −3</td>
<td>1.98</td>
<td>−6.34</td>
<td>631</td>
</tr>
<tr>
<td>Striatum (right)</td>
<td>18 6 −3</td>
<td>0.97</td>
<td>−6.77</td>
<td>5.53</td>
</tr>
<tr>
<td>Causal inflow to the posterior cingulate cortex (y-to-x coefficients)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Striatum (left)</td>
<td>−24 3 −3</td>
<td>−4.36</td>
<td>1.83</td>
<td>−4.28</td>
</tr>
<tr>
<td>Striatum (right)</td>
<td>24 6 0</td>
<td>−4.12</td>
<td>3.10</td>
<td>−4.95</td>
</tr>
</tbody>
</table>

Note: the significant level of the results was set at $p < 0.05$ (AlphaSim corrected).
abnormalities of the striatum (Shenton et al., 2001; Simpson et al., 2010). Several pooled analyses have illustrated that cognitive deficits are accompanied by disrupted activation of the striatum in inhibitory control (Rubia et al., 2001) and working memory (Koch et al., 2008). Furthermore, an elevated striatal dopamine signal was confirmed in a number of neuropathological studies (Breier et al., 1997; Kegeles et al., 2010). Therefore, our data, together with existing studies, suggest that striatal dysfunction might be an inherent biomarker of schizophrenia.

In the present study, a striatal anomaly was associated with a systematic dysregulation of the relationship of the striatum to the DMN, which includes the vmPFC, the PCC, the angular gyrus, and the medial temporal lobe (Andrews-Hanna et al., 2010). Because resting-state fMRI minimizes potentially confounding effects of between-group performance differences, we thus regarded our observations as intrinsic disconnectivity in schizophrenia. The predominantly reported hypothesis is that the DMN is involved in internally directed cognition (Andrews-Hanna, 2012) and self-related processing (Gusnard et al., 2001). Additionally, a growing number of fMRI studies have confirmed the deactivation of the DMN in goal-directed tasks in response to external stimuli (Daselaar et al., 2004), which is related to successful performance. However, in schizophrenia, this deactivation of the DMN is compromised (Anticevic et al., 2011), suggesting a failure to suppress certain internal activity and, in this case, impaired cognitive performance (Whitfield-Gabrieli et al., 2009). These abnormalities in the DMN have been identified with multimodal imaging studies (Bluhm et al., 2007; Pomarol-Clozet et al., 2010). DMN dysfunction is also correlated with psychopathology (Camchong et al., 2011), poor social cognition (Holt et al., 2011) or even auditory verbal hallucinations (Northoff and Qin, 2011). Taken together, the present study suggests that schizophrenic DMN anomalies might correspond to endogenous disorders of this illness.

In the patients with schizophrenia, the inhibitory influence of the striatum on the DMN was reduced. This result suggested that the often observed DMN suppression might stem from the inhibitory control exerted by the striatum. In return, there was a reciprocal reduction of the excitatory influence of the DMN on the striatum, indicating a breakdown of the striatal-DMN loop. A functional correlation of the striatum and the DMN has been observed in several studies (Orliac et al., 2013; Sambataro et al., 2013), which is in accordance with the basal ganglia–cortical tracts (Haber et al., 1995). The striatum is thought to play critical roles in modulating decision making (Graybiel, 2008) and working memory (together with the prefrontal cortex) (Voorn et al., 2004), as well as reward processing (Northoff and Hayes, 2011).

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*Fig. 3.* Between-group differences of Granger directed flow from and to the PCC. A, B present the between group differences of the directed influences from (A) and to (B) the PCC (controls > patients). PCC = posterior cingulate cortex. The results were AlphaSim corrected at the level of \( p < 0.05 \).

*Fig. 4.* The correlation between Granger causal coefficients and the clinical variables. The GC coefficients are indexed as the net influences between regions (calculated as \( [x \to y] - [y \to x] \)) coefficients. The PANSS-N means the negative scale of the Positive and Negative Syndrome Scale (PANSS), and the PANSS-P means the positive scale of the PANSS. PCC = posterior cingulate cortex, temPol = temporal pole, rSTG = right superior temporal cortex, meTG = medial temporal cortex, vmPFC = ventromedial prefrontal cortex, lingual = the lingual gyrus, and IPL = inferior parietal lobule, SFG = superior frontal cortex.
Although further evidence is required to test this hypothesis, the observation of the failure of both of the bidirectional influences between the striatum and the DMN implies that schizophrenic patients have deficits in modulating cognitive-affective control and/or switching between external and internal information processing. In addition, the impairments of the directed influences within the striatum and the DMN loop could predict clinical variables, suggesting that these abnormalities are core features of schizophrenia.

Evidence from pharmacological neuroimaging studies might further elucidate the mechanism underlying the striatal-DMN loop. The level of dopamine in the striatum could modulate the activity of the DMN and its coupling with a set of brain systems (Dang et al., 2012; Kelly et al., 2009). Sambataro et al. (2013) found that the dopamine D2 receptor gene type is associated with DMN connectivity and striatal dopamine signaling. Thus, the disturbed dopamine signal of the striatum observed in schizophrenia might be accompanied by hyperfunction of the DMN. Meanwhile, the medium spiny neurons located in the striatum release gamma-aminobutyric acid (GABA) (Huot and Parent, 2007), a chief inhibitory neurotransmitter in the central nervous system, which could modulate the activity of the cortex. In schizophrenia, abnormalities of this GABA-modulation could lead to reduced deactivation of the DMN (Menzies et al., 2007). Furthermore, cortical disinhibition with dysfunction of the N-methyl-D-aspartic acid (NMDA) pathway in turn produces corticocortical hyperactivity (including within the striatum) (Del Arco et al., 2011). In fact, the interactions among different neurotransmitters serve as a corticostriatal negative feedback loop to limit cortical hyperstimulation in the brain (Tekin and Cummings, 2002). Therefore, our observation of dysfunction of the striatal-DMN circuit might correspond to a disturbance of the excitation/inhibitory balance in information processing (Vizhhar et al., 2011).

To our knowledge, this is the first study to explore the effective connectivity between the striatum and the DMN. The reduced inhibitory influence of the striatum on the DMN provides a possible explanation for the failure to deactivate the DMN. In addition, there was a parallel failure of the excitatory influence of the DMN exerted onto the striatum, which highlighted a breakdown of the striatal-DMN loop. This breakdown might reflect deficits in modulating internal–external information processing with an underlying disturbed excitation/inhibitory balance. Therefore, our findings provide new insights into the study of schizophrenia from the perspective of interactions between large-scale networks.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2015.07.027.

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Contributors
Author Xiangpeng Wang designed the study, managed the statistical analysis, literature search and the writing/editing of the manuscript. Author Fenghua Li collected data from subjects and aided in statistical analysis. Author Hanfeng Zheng, Weihong Wang and Zhaoping Liu helped collect data. Author Wenwen Zhang and Yujing Sun aided in data entry and literature searching. Author Raymond C. K. Chan directed data collection, helped in collecting data. Author Antao Chen designed the study, wrote the protocol, obtained grant funding, directed data collection, and edited the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest
All authors declare that they have no conflicts of interest regarding this manuscript.

Acknowledgment
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