Effects of dopamine-based genetic risk score on dynamic low-frequency fluctuations in patients with first-episode drug-naïve schizophrenia

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Research Article

Keywords: dynamic amplitude of low-frequency fluctuation, schizophrenia, dopamine genetic risk score, functional magnetic resonance imaging, single nucleotide polymorphism

Posted Date: November 9th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2237212/v1

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Abstract

Alterations in dynamic intrinsic brain activity and neurotransmitter signaling, such as dopamine, have been independently detected in schizophrenia patients. Yet, it remains unclear whether the dopamine genetic risk variants have additive effects on brain intrinsic activity. We aimed to investigate the schizophrenia-specific dynamic amplitude of low frequency fluctuation (dALFF) altered pattern, and its association with dopamine genetic risk score in first-episode drug-naïve schizophrenia (FES). Fifty-five FES and 53 healthy controls were included. A sliding-window method based on the dALFF was adopted to estimate the dynamic alterations in intrinsic brain activity. Subjects were genotyped, and a genetic risk score (GRS), which combined the additive effects of ten risk genotypes from five dopamine-related genes, was calculated. We used the voxel-wised correlation analysis to assess the effects of dopamine-GRS on dALFF. FES showed significantly increased dALFF in the left medial prefrontal cortex and significantly decreased dALFF in the right posterior cingulate cortex compared with healthy controls. Greater dopamine GRS in FES was associated with higher dALFF in the left middle frontal gyrus and left inferior parietal gyrus. Our findings indicate that cumulative dopamine genetic risk is associated with a known imaging phenotype for schizophrenia.

1. Introduction

Schizophrenia (SZ), which is characterized by positive symptoms, negative symptoms, and cognitive deficits, is a devastating psychiatric illness (Tandon et al., 2013). The estimated heritability for SZ is 65–80% (Hilker et al., 2018). Although the impact of genetic factors on brain function in SZ has repeatedly been reported (Romme et al., 2017), the neurobiological mechanisms of dopamine risk genotypes remain unclear.

Resting-state brain activity evaluated by the blood oxygen level-dependent (BOLD) signal could reflect the intrinsic characteristics of brain fluctuations. Intrinsic brain activity is crucial for understanding the neuropathology and neurophysiology of mental disease; for example, abnormal energy consumption in a region may suggest decreased or excessive resting-state metabolic rates or concentrations of neuromodulators (Fox and Raichle, 2007). The amplitude of low frequency fluctuation (ALFF) is an established method for characterizing spontaneous neural activity and effectively exploring the potential pathophysiological mechanisms of psychiatric disorders (Yang et al., 2007). Recently, ALFF has been conducted to investigate abnormal neural activity in first-episode drug-naïve schizophrenia (FES), reporting increased ALFF in the middle temporal gyrus and precuneus regions, as well as decreased ALFF in the precentral gyrus and cerebellar regions (Guo et al., 2018; Wu et al., 2018). However, previous studies rely on the implicit assumption that brain activity remains stationary during typical resting functional magnetic resonance imaging (fMRI) scanning. This assumption may neglect the dynamic and time-varying changes in brain activity. An accumulating number of studies have reported that the human brain inherently rapidly changes neural interactions over time with nonstationary brain activity (Buzsáki and Freeman, 2015; Hutchison et al., 2013). In fact, human neural activity is highly dynamic over time (Calhoun et al., 2014; Li et al., 2019). Therefore, static or time-averaged ALFF may provide limited
information on the functional activity of the brain in association with the pathophysiology of psychiatric disease (Calhoun et al., 2014). Combining the ALFF with ‘sliding-window’ methods, the dynamic ALFF (dALFF) provides a new avenue to measure the temporal variability of intrinsic brain activity. Several studies have reported that dALFF is a more stable and sensitive indicator than static ALFF (Ma et al., 2020; Tang et al., 2018). Cui et al. discovered that compared with static ALFF abnormalities, dALFF contributes more than static ALFF in differentiating between generalized anxiety disorder and healthy controls (HCs) (Cui et al., 2020). The conduct of dALFF will probably provide a more accurate assessment of brain activity, enabling us to more cleanly capture information related to the disease.

Considering the high heritability of SZ, a considerable effort has been made to discover the causative genetic factors, candidate gene studies have been a major approach in this area. Selecting candidate genes based on prevailing theories of the etiology in SZ, such as the dopamine hypothesis or/and antipsychotic pharmacology, is an important strategy in identifying genetic variation. The dopamine hypothesis has been one of the most enduring ideas in SZ. This hypothesis has one major implication for clinical treatment methods (Howes and Kapur, 2009). Existing first and second generation antipsychotic drugs for SZ act via the dopamine system (Horacek et al., 2006). Therefore, dopamine-related genes have traditionally been prime candidates for genetic studies of SZ. Because the list of genes relating to dopaminergic function is potentially long, we involved five frequently studied genes, including catechol-O-methyltransferase (COMT), dopamine receptor D1 (DRD1), dopamine receptor D2 (DRD2), dopamine receptor D3 (DRD3), and ankyrin repeat and kinase domain containing 1 (ANKK1) genes. COMT is involved in the catabolic clearance of dopamine. Two meta-analyses report an association between rs4680 polymorphism and SZ, with the G allele may be a reliable risk factor for SZ (Glatt et al., 2003; Lohmueller et al., 2003). Recent association studies have investigated several other single nucleotide polymorphism (SNPs) of the COMT gene. A large sample study revealed a highly significant association between rs165599 and rs737865 and SZ, with SZ displaying an excess of G/G genotype in these two SNPs (Shifman et al., 2002). Wang et.al reported the rs4633 T allele was associated with susceptibility to SZ (Wang et al., 2009). Zhu et.al found the T allele of rs686 of DRD1 gene was associated with a higher risk of SZ (Zhu et al., 2011). The DRD2 is a logical target for association studies because of the effect of therapeutic agents. One large case-control study detected a significant association between the G allele of rs6277 and SZ (Betcheva et al., 2009), a result that has been confirmed by a meta-analysis including 12 articles involving 3079 SZ and 3851 HCs (Liu et al., 2014). The association between the A allele of rs6275 (Lawford et al., 2016) and the A allele of rs1076560 (Cohen et al., 2016) with SZ was also reported. Numerous studies have sought association at DRD3, and most have focused on rs6280. Lochman et.al reported the T allele of rs6280 is likely to be a risk factor for SZ (Lochman et al., 2013). A case-control study, followed by a 108 trios family-based association analysis for replication, reported an association between the ANKK1 rs1800497 G allele and SZ (Dubertret et al., 2010).

Dopamine is an important neuromodulator that influences oscillatory information processing (Zaldivar et al., 2018). Dysregulated dopaminergic modulation of brain activity is fundamental to many studies that attempt to explain the mechanisms underlying the clinical symptoms of SZ (Howes and Kapur, 2009; Kraguljac et al., 2021). Multiple imaging genetic studies have observed an association between single-
nucleotide polymorphisms (SNPs) of dopamine candidate genes and functionally or structurally derived brain imaging phenotypes. Vink et al. found that compared with noncarriers of DRD2 rs2514218 in SZ, risk genotype carriers exhibit a diminished striatal response to increasing proactive inhibitory control demands (Vink et al., 2016). Vercammen et al. found that an increased number of risk alleles of COMT rs4680 and DRD2 rs2283265 predict decreased prefrontal activation during response inhibition in healthy adults (Vercammen et al., 2014). This study suggested a significant genotype effect of dopamine risk alleles on prefrontal activation in healthy subjects. SZ has a polygenic architecture in which hundreds or even thousands of risk genotypes collectively contribute to risk (Foley et al., 2017). The collective effects of the dopamine SNP should result in greater statistical sensitivity than that of studies using a single locus (Arslan, 2018). Thus, there remains a dearth of knowledge about whether and how dopamine-related risk genetic variations combine to affect dALFF in FES.

In the present study, we aimed to determine the extent to which ten dopamine-related SNPs from the COMT, DRD1, DRD2, DRD3 and ANKK1 genes combine to influence dALFF in FES patients and HCs. New evidence regarding the action of the dopamine gene on brain activity will help us elucidate the pathological mechanisms underlying SZ to facilitate more effective therapeutic development.

2. Materials And Methods

2.1 Subjects

The study was approved by the Ethics Committee of Shanghai Mental Health Center. Written informed consent was obtained from all subjects before participating in the study.

A total of 108 individuals were recruited from Shanghai Mental Health Center, including 55 FES patients and 53 HCs. The diagnoses of SZ were determined by the Structured Clinical Interview for DSM-IV Patient version (SCID-I/P). Inclusion criteria for patients were as follows: (1) DSM-IV criteria for SZ (Diagnostic and Statistical Manual of Mental Disorders, fourth edition); (2) first episode illness and antipsychotic-naïve; and (3) age between 16 and 40 years. Exclusion criteria for patients included the following: (1) major medical or neurological illness; (2) current pregnancy; (3) a history of suicide risk; and (4) alcohol or drug abuse. HCs were recruited via local media advertisements and were administered by the SCID, Non-Patient Edition (SCID-I/NP). None of the HCs had a history of major mental health problems, acquired brain injury, or intellectual disability. The exclusion criteria for HCs were the same as those for patients.

2.2 Functional MRI data acquisition

Resting-state BOLD functional magnetic resonance imaging fMRI was obtained with a 3.0-T Siemens Verio scanner (Erlangen Germany) using an echo planar imaging [EPI] sequence at the Shanghai Mental Health Center in Shanghai, China. For each subject, functional images were acquired with the following parameters: 170 volumes; repetition time [TR] = 3000 ms; echo time [TE] = 30 ms; slice thickness = 3 mm;
sagittal slices = 45; field of view [FOV] = 216 × 216 mm²; FOV phase = 100%; data matrix size = 64 × 64; voxel size = 3.0 mm × 3.0 mm × 3.0 mm.

2.3 Functional MRI data preprocessing

The fMRI data were preprocessed using the date processing assistant for resting state fMRI (DPARSF) implemented in MATLAB 2016b (Yan and Zang, 2010). A standard pipeline was used as described in our previous study (Kang et al., 2020). The first five slices were removed to minimize the nonequilibrium effects of magnetization and allow subjects to acclimate to the scanning environment. The following processing steps include slice timing, realignment, and spatial normalization to the standard Montreal Neurological Institute (MNI 152) space. The head motion parameters were calculated using the Friston 24 model (Balachandrasekaran et al., 2022). Regression of covariates, included head motion parameters, white matter, and cerebrospinal fluid signal. The global signal was not regressed out as has been recently suggested when processing fMRI data of SZ (Yang et al., 2017). The time coursed were filtered with 0.01–0.08 Hz to reduce low-frequency drifts and high-frequency noise. Smoothing was performed with a 6 mm full width-half maximum (FWHM) Gaussian kernel. Motion scrubbing was conducted to remove participants with more than 3 maximum head motions or 3 degrees of rotation in any direction (3 FES patients and 2 HCs were removed). Previous studies have shown that resting-state functional connectivity analysis is sensitive to head motion (Power et al., 2012; Van Dijk et al., 2012). Scrubbing was used to interpolate bad time points with cubic spline interpolation. Framewise displacement (FD), which represents the volume to volume changes in head position, is much larger in FES patients compared with HCs (p = 0.039). FD was considered a nuisance covariate in the subsequent statistical analyses.

2.4 Calculation of dALFF

The procedure for calculating the dALFF has been described in previous studies (Dong et al., 2015). Firstly, the filtered time series of all voxels in brain, except for the cerebellum, was transformed to the frequency domain with a fast Fourier transform (FFT). Then, the square root was calculated at each frequency of the power spectrum and the averaged square root was obtained across 0.01–0.08 Hz at each voxel, which was considered as ALFF values. The sliding window method was conducted to evaluate the dALFF for each subject using the Dynamic BC toolbox (Liao et al., 2014). The window length is an open but important parameter in resting state dynamics calculations. The window size should be short enough to capture reliable estimates of brain activity and long enough to achieve reliable estimates of brain activity. Based on this notion and according to previous studies, we selected a window length of 50 TRs and a window overlap of 60% (20 TRs) to calculate the dALFF of each subject (Zheng et al., 2021). Specifically, the ALFF maps for each subject were calculated within each window, and the variance of the ALFF maps across all windows was calculated to measure the dynamics of brain activity. To enhance data normality, the dALFF variability of all subjects was transformed into standardized z scores by subtracting the mean and dividing by the standard deviation across each voxel. We also calculated dALFF using different window lengths and different step sizes (30 TRs, 60% overlap; 50 TRs, 80% overlap; 80 TRs, 60% overlap).
It is noted that we also examined the static ALFF (sALFF) of each subject. For standardization purposes, the ALFF values of all voxels were divided by the global mean ALFF value with a brain mask.

### 2.5 Construction of the dopamine genetic risk score

All participants underwent blood draws. Blood samples were stored at -80°C for SNP analysis. Ten dopamine-related SNPs were genotyped: rs4633, rs165599, rs4680, and rs737865 of the COMT gene; rs686 of the DRD1 gene; rs1076560, rs6275, and rs6277 of the DRD2 gene; rs6280 of the DRD3 gene; and rs1800497 of the ANKK1 gene. For each subject, genomic DNA was extracted using the Flexi Gene DNA Kit. The extracted DNA was quantified using a Nano Drop™ 2000 (Thermo Fisher Scientific™, Waltham, MA, USA). SNP analysis was performed using the Kompetitive Allele Specific PCR genotyping system (KASP). All SNPs were in Hardy-Weinberg equilibrium. Details about these SNPs are shown in supplemental materials Table S1.

The cumulative genetic risk score (GRS) was generated as a count of the risk alleles for each of these ten SNPs, specifically, 0 for the absence of risk allele, 1 for one risk allele, and 2 for two risk alleles for each SNP, for total scores ranging from 0 to 20 (0 score means carrying zero risk alleles and 20 score means carrying 20 risk alleles).

### 2.6 Statistical analysis

Group differences in continuous and dichotomous demographic and clinical variables were examined using independent group \( t \) tests and chi-square tests, respectively. Two-sample \( t \) tests were performed to investigate the group difference in dALFF between the FES and HCs with age, sex, years of education, and mean FD as covariates. We explored the effect of dopamine GRS on dALFF using voxel-wised correlation analysis, controlling for age, sex, years of education, and mean FD. Multiple comparisons were corrected using the Gaussian random field (GRF) method with a statistical height threshold of \( p < 0.01 \) at the voxel level and \( p < 0.05 \) at the cluster level.

### 3. Results

#### 3.1 Demographic and clinical characteristics

The demographic information and clinical characteristics of all the subjects were presented in Table 1. No significant differences in age, sex, years of education, or GRS were found between FES patients and HCs \((p > 0.05)\).
Table 1
Demographic and clinical characteristics of FES and HCs

<table>
<thead>
<tr>
<th></th>
<th>FES (N = 52)</th>
<th>HCs (N = 51)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/Female</td>
<td>20/32</td>
<td>22/29</td>
<td>0.629</td>
</tr>
<tr>
<td>Age(years)</td>
<td>26 ± 6.88</td>
<td>26 ± 6.51</td>
<td>0.798</td>
</tr>
<tr>
<td>Education(years)</td>
<td>12.6 ± 2.99</td>
<td>13 ± 2.81</td>
<td>0.626</td>
</tr>
<tr>
<td>GRS</td>
<td>11.7 ± 1.23</td>
<td>11.7 ± 1.27</td>
<td>0.954</td>
</tr>
</tbody>
</table>

FES, first-episode schizophrenia; HCs, healthy controls; SD, standard deviation; GRS: genetic risk score

3.2 Alterations of sALFF and dALFF in FES

FES exhibited significantly decreased sALFF mainly in the right precentral gyrus (PCG) compared with HCs (Fig. 1A, Table 2, GRF corrected). The main results were based on the dALFF analysis using 50 TRs as the window length and window overlap of 60%. Compared with HCs, the FES patients showed significantly increased dALFF in the left medial prefrontal cortex (MPFC) and significantly decreased dALFF in the right posterior cingulate cortex (PCC) (Fig. 1B: 50 TRs with 60% overlap; Table 2, GRF corrected, p < 0.01 at the voxel level and p < 0.05 at the cluster level).
Table 2
Regions showing significant differences in dALFF between FES patients and HCs

<table>
<thead>
<tr>
<th>MNI coordinates</th>
<th>cluster size (voxel)</th>
<th>Peak T values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>sALFF</td>
<td>PCG</td>
<td>12</td>
</tr>
<tr>
<td>dALFF 50 TR with 60% overlap</td>
<td>PCC</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>MPFC</td>
<td>0</td>
</tr>
<tr>
<td>dALFF 30 TR with 60% overlap</td>
<td>PCC</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>MPFC</td>
<td>-12</td>
</tr>
<tr>
<td>dALFF 50 TR with 80% overlap</td>
<td>PCC</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>MPFC</td>
<td>-12</td>
</tr>
<tr>
<td>dALFF 80 TR with 60% overlap</td>
<td>PCC</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>MPFC</td>
<td>3</td>
</tr>
<tr>
<td>mTG</td>
<td>-39</td>
<td>-78</td>
</tr>
</tbody>
</table>

PCG: precentral gyrus; PCC: posterior cingulate cortex; MPFC: medial prefrontal cortex; mTG: middle temporal gyrus

We validated dALFF results using different sliding window lengths and step sizes. We found significantly increased dALFF in the left MPFC and significantly decreased dALFF in the right PCC in the FES group compared with HCs (Fig. 1C: 30 TRs with 60% overlap; Fig. 1D: 50 TRs with 80% overlap; and Fig. 1E: 80 TRs with 60% overlap; Table 2, GRF corrected, $p < 0.01$ at the voxel level and $p < 0.05$ at the cluster level).

### 3.3 Correlation results between dopamine GRS and dALFF

We found that higher GRS for FES was significantly associated with increased dALFF in the left middle frontal gyrus (MFG) (Fig. 2, Table 3, GRF corrected, $p < 0.05$ at the voxel level and $p < 0.05$ at the cluster level) and left inferior parietal gyrus (IPG) (Fig. 2, Table 3, GRF corrected, $p < 0.01$ at the voxel level and $p < 0.05$ at the cluster level). There was no correlation between GRS and dALFF in HC, and sALFF in both groups. Notable is, the association between GRS and dALFF in MFG did not survive correction for GRF at $p < 0.01$ at the voxel level and $p < 0.05$ at the cluster level, we used the $p < 0.05$ at the voxel level and $p < 0.05$ at the cluster level.
Table 3
Brian regions showing significant correlation with dopamine GRS in FES

<table>
<thead>
<tr>
<th>MNI coordinates</th>
<th>cluster size (voxel)</th>
<th>Peak r values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>x</td>
<td>y</td>
</tr>
<tr>
<td>50 TR with 60% overlap</td>
<td>MFG</td>
<td>-21</td>
</tr>
<tr>
<td></td>
<td>IPG</td>
<td>-39</td>
</tr>
<tr>
<td>30 TR with 60% overlap</td>
<td>MFG</td>
<td>-30</td>
</tr>
<tr>
<td></td>
<td>IPG</td>
<td>-39</td>
</tr>
<tr>
<td>50 TR with 80% overlap</td>
<td>MFG</td>
<td>-48</td>
</tr>
<tr>
<td></td>
<td>IPG</td>
<td>-39</td>
</tr>
<tr>
<td>80 TR with 60% overlap</td>
<td>MFG</td>
<td>-36</td>
</tr>
<tr>
<td></td>
<td>SFG</td>
<td>-18</td>
</tr>
</tbody>
</table>

MFG: middle frontal gyrus; IPG: inferior parietal gyrus; SFG: superior frontal gyrus

This finding was validated using different sliding window lengths and step sizes. We also found that dopamine GRS for FES was significantly positively correlated with dALFF in the MFG and IPG with parameters of 30 TRs with 60% overlap, 50 TRs with 80% overlap, and 80 TRs with 60% overlap (Fig. 2, Table 3, GRF corrected, \( p < 0.01 \) at the voxel level and \( p < 0.05 \) at the cluster level). Results about no correlation between GRS and dALFF in HC, and sALFF of both groups were also validated.

4. Discussion

4.1 Summary of findings

We investigated the sALFF and dALFF altered pattern in FES, and its association with dopamine genetic risk score. We found significantly higher dALFF in the left MPFC and significantly lower dALFF in the right PCC, and significantly lower sALFF in PCG in FES, compared with HCs. We also found dopamine GRS positively correlated with temporal variability of regional brain activity in the left MFG and left IPG in FES, and this association disappeared in HC. No association between GRS and sALFF was found in both groups. These findings indicate that dopamine-related risk genotypes influence frontal and parietal intrinsic activity through small but additive effects.

Consistent with previous studies (Hoptman et al., 2010; Yu et al., 2019), we found significantly stronger sALFF in the PCG in FES. This finding provides additional evidence about abnormalities of low-frequency oscillations in SZ. However, sALFF only generates a static estimate of brain intrinsic activity. The dALFF evaluates the temporal changes in energy consumption reflected by the level of oxygen content in
intrinsic brain activity, which reflects the adaptability of neural activity to various mental processes (Fu et al., 2018). We found significantly increased dALFF in the left MPFC and significantly decreased dALFF in the right PCC in FES. MPFC and PCC are key nodes in the default mode network that participates in self-referential processing and emotion, abnormalities in these core brain regions in SZ are often reported in previous studies. Reduction of PCC volume (Calabrese et al., 2008), and abnormalities in its white matter connections in SZ patients have been reported (Joo et al., 2018). The abnormal functional activities in MPFC have been reported by analyses of local regional homogeneity and functional connectivity (Chai et al., 2011; Xu et al., 2015). MPFC is associated with self-directed thoughts, dysregulation of this region may lead to the confusion of external and internal stimuli sources, which may be a neurophysiological basis for hallucinations (Euston et al., 2012). The PCC has an important role in supporting internally directed cognition (Leech and Sharp, 2014). Increased and decreased dALFF variability of FES patients found in this study is more likely to represent the irregular change of intrinsic brain activity rather than adaptive activities as that in HCs. The abnormal dALFF in these regions may be associated with disrupted cognitive and emotional functions in SZ.

Explaining the total amount of several risk variants of dopamine genes may extend traditional case-control studies (Purcell et al., 2009). By calculating the GRS score, we were able to detect the additive effects of dopamine system risk genotypes on resting state intrinsic brain activity. Previous studies have suggested a role of the additive influence of risk genotype in SZ susceptibility (Agerbo et al., 2015; Power et al., 2015), the potential effects of this cumulative risk on brain activity remain unclear. The main result of the present study suggests that dALFF in the left MFG and left IPG had a significant positive correlation with dopamine-related GRS in FES. Dopamine is synthesized by dedicated neurons in the midbrain. When these neurons fire, the neuromodulator dopamine is broadly released into neural tissue to affect cortex regions, such as frontal and parietal neurons (Ott and Nieder, 2019). Previous studies have found that dopamine-related genes influence frontal and parietal activity. Our previous study demonstrated an association between COMT genotype and frontal-related functional connectivity in FES (Kang et al., 2019). Wu et al. found that the interaction of COMT genotype and sex might regulate synaptic dopaminergic concentrations and influence the intrinsic functional connectivity in the left IPG (Wu et al., 2020). J. Tang et al. found inverted U-shaped modulation of COMT haplotypes on functional connectivity density in the IPG in healthy young subjects (Tang et al., 2019). The prefrontal lobe has been suggested to be a core region in emotional impairment in SZ. The IPG has been previously shown to be involved in social cognition, working memory, and executive function (Palaniyappan and Liddle, 2012). Various clinical symptoms such as passivity phenomenon, thought disorder, and disorganization in SZ indicate a role of frontal and parietal dysfunction (Müller et al., 2013). The correlation between dopamine GRS and dALFF in left MFG and left IPG suggests that the cumulative effect of dopamine risk genotypes has an effect on intrinsic brain activity in these regions in FES. The result in the present study is in line with previous studies demonstrating associations between dopamine genetic risk variants and frontal and parietal activity in SZ, and supports an additive genetic risk model for a polygenic phenotype.

4.2 Limitations
This research has several limitations. This is limited research based on a few genotypes that have been well studied previously. Considering the list of genes relating to dopaminergic function is potentially long, it is difficult to include all dopamine genes in this study. In addition, it should be noted that our risk genetic model was additive assuming a linear increase in disease susceptibility due to a lack of complete understanding of gene-gene interaction effects and molecular pathways. Moreover, considering the small sample size of this study, we used the GRF method for multiple comparison correction, which is not the most powerful correction method, and more rigorous methods will be necessary for future studies. Finally, when comparing FES patients and HCs, we did not find significant differences in GRS. This finding could be due to a lack of power because the GRS was derived from a small number of SNPs, and the sample size was comparatively small in this study. Considering that frontal and parietal dysfunction is a well-validated endophenotype and that the GRS was derived from SZ-associated dopamine risk genes, the imaging genetics results of our study reveal an important association with SZ that should be further investigated.

4.3. Conclusions

We derived a dopamine GRS, which combined the additive effects of 10 genetic risk variants of dopamine-related genes, and demonstrated that this score has a significantly positive correlation with dALFF in left MFG and left IPG in FES patients. This finding provides an empirically based standpoint linking dopamine GRS and brain activity alterations in FES patients. This result supports an additive genetic risk model for a polygenic phenotype in SZ. Our work sheds lights on potential mechanisms that might underlie the known relationship between dopamine risk genes and SZ.

Declarations

Funding This study was supported in part by China Postdoctoral Science Foundation (Grant/Award No. 2021M692007), Natural Science Foundation (Youth Science Foundation Project) of Shaanxi Province (Grant/Award No. 2022JQ-875), the National Natural Science Foundation of China (Grant/Award No. 82001784), and Natural Science Foundation (Youth Science Foundation Project) of Hunan Province (Grant/Award No. 2021JJ41054).

Data availability The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions Yafei Kang conceived of the study and drafted the manuscript. Youming Zhang, Kexin Huang and Zhenhong Wang helped to revise the manuscript.

Ethics approval The study was approved by the Ethics Committee of Shanghai Mental Health Center.

Consent to participate Before they participated in the study, all subjects provided their informed consent.

Consent to publish This article has not been published elsewhere in whole or in part. All authors have read and approved the content, and agree to submit for consideration for publication in the journal.
Competing interests None of the authors have any conflicts of interest to declare.

References


Figures
Figure 1

Different sALFF (A) and dALFF values (B, C, D, E) between two groups (GRF corrected).

Blue and red denote decreased and increased sALFF/dALFF values in FES group, respectively.

PCG: precentral gyrus; PCC: posterior cingulate cortex; MPFC: medial prefrontal cortex
Figure 2

Brain regions showing significant correlation with dopamine GRS in FES (GRF corrected).

MFG: middle frontal gyrus; IPG: inferior parietal gyrus; SFG: superior frontal gyrus

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterials.docx