Shared Transdiagnostic Neuroanatomical Signatures Across First-episode Patients with Major Psychiatric Diseases and Individuals at Familial Risk

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ABSTRACT

Background: Nowadays, increasing evidence has found transdiagnostic neuroimaging biomarkers across major psychiatric disorders (MPDs). However, it remains to be known whether this transdiagnostic pattern of abnormalities could also be seen in individuals at familial high-risk for MPDs (FHR). We aimed to examine shared neuroanatomical endophenotypes and protective biomarkers for MPDs.
Methods: This study examined brain grey matter volume (GMV) of individuals by voxel-based morphometry method. A total of 287 individuals were included, involving 100 first-episode medication-naive MPDs, 87 FHR, and 110 healthy controls (HC). They all underwent high-resolution structural magnetic resonance imaging (MRI).
Results: At the group level, we found MPDs were characterized by decreased GMV in the right fusiform gyrus, the right inferior occipital gyrus, and the left anterior and middle cingulate gyri compared to HC and FHR. Of note, the GMV of the left superior temporal gyrus was increased in FHR relative to MPDs and HC. At the subgroup level, the comparisons within the FHR group did not return any significant difference, and we found GMV difference among subgroups within the MPDs group only in the opercular part of the right inferior frontal gyrus.
Conclusion: Together, our findings uncover common structural disturbances across MPDs and substantial changes in grey matter that may relate to high hereditary risk across FHR, potentially underscoring the importance of a transdiagnostic way to explore the neurobiological mechanisms of major psychiatric disorders.

1. Introduction

Major depressive disorder (MDD), bipolar disorder (BD) and schizophrenia (SZ), three major psychiatric disorders (MPDs), are common causes of disease impairment and burden. Current operational diagnostic system is based on subjective descriptions of clinical symptoms and processes rather than objective measurement. What is intriguing is that although diagnostically diverse, symptom overlapping is quite common with a high rate of comorbidity and the long-term stability of the diagnoses is poor among these three disorders (Kessler et al., 2005; Plana-Ripoll et al., 2019). In addition, it has been found in

clinical practices that several atypical antipsychotics are effective not only in SZ but also in patients with MDD and BD, as monotherapy or adjuncts to antidepressants (Grinchii and Dremencov, 2020). These commonalities may be due to the limitation of the diagnostic criteria, on the one hand, and also implies the possible shared biological mechanisms behind these three diseases on the other.

Nowadays, different disciplines of studies have begun jumping out of the conventional diagnostic framework and tried to explore the shared signatures across MPDs from a biological perspective (Consortium, 2013; de Lange et al., 2019; Doucet et al., 2020; Huang et al., 2021; Yuan et al., 2019), which will help us deepen and broaden our understanding

of these three diseases. Specifically, several studies on neuroimaging by using magnetic resonance imaging (MRI) are at the frontier for its convenience and non-invasive advantages. They have found some shared abnormalities in functional connectivity (Baker et al., 2019, 2014; Huang et al., 2020; Li et al., 2021; Xia et al., 2019), regional brain activity (Zhang et al., 2021), and brain structure (Gong et al., 2019; Opel et al., 2020; Romer et al., 2021; Schaub et al., 2021) across MPDs. For example, Baker et al. found that disruptions in functional connectivity within the frontoparietal control network may be a shared biomarker across both affective psychosis and SZ, including portions of the lateral parietal cortex, posterior temporal cortex, dorsolateral and dorsomedial prefrontal cortex (Baker et al., 2019, Baker et al., 2014). In addition, a recent study reported that a common pattern of decreased neocortical thickness mirrors a feature of general psychopathology that crosses diagnoses (Romer et al., 2021).

Moreover, a lot of evidence suggests that MPDs are subject to strong familial predisposition implying that both genetic susceptibility and shared environmental exposures contribute significantly to the development of psychiatric disorders (Joseph, 2004; Sullivan et al., 2000). This effect can be seen even in the asymptomatic relatives with familial high risk (FHR) for MPDs. There is accumulating evidence for neuroanatomical endophenotypes with hereditary risk and growing evidence for protective biomarkers due to which FHR do not develop the diseases (Brosch et al., 2021; Hettwer et al., 2021; Lin et al., 2018). For instance, a follow-up study (Sugranyes et al., 2021) on young offspring of patients with BD and SZ found that smaller total surface area and grey matter volume (GMV) at baseline could predict the emergence of psychotic spectrum symptoms related to familial risk. And a review (Eaton et al., 2021) of neuroimaging studies on youth found greater GMV in frontal areas and hippocampus were linked to resilience. The conduction of "familial high-risk" research designs by structural neuroimaging has facilitated the exploration of possible biomarkers indicating both vulnerability and compensation for MPDs.

Besides ample evidence for familial co-aggregation of MPDs, it has shown that the transmission of diagnoses is not always a one-to-one mapping within a family under the current diagnostic system (Rasic et al., 2014; Reupert et al., 2013). The offspring of parents with MPDs have increased rates of not only the same disorder as their parents but also other types of disorders within MPDs (Cheng et al., 2018; Rasic et al., 2014). Though evidence is abundant, most of the previous studies have merely focused on the offspring of parents with one or two specific diagnoses of MPDs. When it comes to transdiagnostic findings, we only found one *meta*-analysis based on structural imaging studies exploring shared grey matter abnormalities of FHR (Zhang et al., 2020). Since it is unclear whether these risk or protective neuroimaging biomarkers remain when relatives with diverse familial risk profiles and patients are examined simultaneously, it is necessary to study them in one study directly.

Compared with functional MRI, the results of structural MRI may be more stable (Bennett and Miller, 2010), reflecting the trait rather than the state feature of the disease. The volume of grey matter can reflect histopathology-related changes in brain structure (Asan et al., 2021) and is closely related to genes controlling neurodevelopment and genetic predisposition to neuropsychiatric diseases (Giedd and Rapoport, 2010). Taken together, we conducted a voxel-based morphometry (VBM) study to examine GMV in healthy controls (HC), FHR, and first-episode medication-naive MPDs. The following hypotheses were proposed: (1) transdiagnostic GMV abnormalities that might indicate disease expression would exist across MPDs; (2) GMV abnormalities specific to FHR that might reflect effects of familial risk rather than established diseases would be discovered across FHR; and (3) FHR and MPDs might display GMV abnormalities in common that could represent structural neuroimaging endophenotype.

2. Materials and methods

2.1. Participants

A total of 300 subjects were initially enrolled, but 13 of them did not pass the data quality check, leaving 287 individuals finally included in this study: 35 first-episode medication-naive MPDs with MDD, 32 with BD, and 33 with SZ, as well as 29 FHR of MDD (FHR-MDD), 23 of BD (FHR-BD), and 35 of SZ (FHR-SZ), and 100 HC. Inclusion criteria were age (18–45 years) and right-handed. Diagnoses for patients were confirmed by professional psychiatrists and further validated by using the Structured Clinical Interview for DSM-IV (SCID). Exclusion criteria were MRI contraindications, poor image quality, substance/alcohol abuse or dependence, major medical disorders, pregnancy, history of head trauma with loss of consciousness for ≥ 5 min, or any neurological disorder. Additional exclusion criteria for HC and FHR were current or lifetime history of any Axis I or II disorders. FHR-MDD, FHR-BD, and FHR-SZ must have at least one parent diagnosed with MDD, BD, and SZ, respectively (FHR and MPDs are not from the same family in the present study); on the contrary, HC did not have any first-degree relatives with a current or history of Axis I or Axis II disorders.

All MPDs were outpatients in the First Affiliated Hospital of China Medical University or inpatients in Shenyang Mental Health Center, while HC and FHR were recruited from the local community by advertisement. Written informed consent was provided by all survey participants prior to their enrollment after a detailed explanation of the experiment. Approval from the clinical research ethics committee of the First Affiliated Hospital of China Medical University was received.

2.2. Demographic and clinical information

The severity of clinical symptoms was assessed by the Hamilton depression scale (HAMD) (Hamilton, 1960), Hamilton anxiety scale (HAMA) (Hamilton, 1959), Young mania rating scale (YMRS) (Young et al., 1978), and Brief psychiatric rating scale (BPRS) (Overall and Gorham, 1962) using Chinese versions of validated measurement tools. Cognitive function was assessed by the Wisconsin Card Sorting Test (WCST) (Kongs et al., 2000). Demographic and other clinical data were self-reported by the participants, including age, sex (male or female), years of education, and duration of illness. (see Table 1) All assessments were conducted by researchers previously well trained in their use.

2.3. MRI data acquisition

High-resolution, three-dimensional, T1-weighted images were collected using a General Electric Signa HDX 3 T scanner with a standard 8-channel head coil at the First Affiliated Hospital of China Medical University, Shenyang, China. A 3D fast spoiled gradient recalled (FSPGR) sequence was used with the following parameters: repetition time = 7.148 ms, echo time = 3.15 ms, flip angle = 13°, matrix size = 240 × 240, field of view = 240 × 240 mm^2, slice thickness = 1 mm, spacing between slices = 1 mm, voxel size = 1.0 × 0.9375 × 0.9375 mm^3. Earplugs and foam pads were used to minimize noise and head motion.

2.4. Voxel-based morphometry

Structural images detected visually with abnormalities and artifacts were excluded from this study. Others were then manually adjusted and reoriented to have orientation and origin similar to the Montreal Neurological Institute (MNI) template using the Display tool of Statistical Parametric Mapping (SPM12, https://www.fil.ion.ucl.ac.uk/spm/software/spm12, version 6686). This step reduces errors encountered and gets better alignment during processing. The VBM analysis was conducted using Computational Anatomy Toolbox 12 (CAT12, https://www.neuro.uni-jena.de/cat/, version r1900), a

Table 1
Demographic and clinical characteristics of participants.

Variable	MPDs			A		FHR			B		HC	C	
	MDD	BD	SZ	F/χ2	P	FHR-MDD	FHR-BD	FHR-SZ	F/χ2	P	(n = 100)	F/χ2	P
	(n = 35)	(n = 32)	(n = 33)			(n = 29)	(n = 23)	(n = 35)					
Age(years)	30.86 (8.47)	27.34 (7.79)	27.15 (7.96)	2.271	0.109	30.45 (7.10)	32.91 (8.25)	32.80 (6.04)	1.126	0.329	29.18 (7.32)	5.640	0.004
Female	20(57.1%)	18(56.3%)	20(60.6%)	0.143	0.931	14(48.3%)	8(34.8%)	13(37.1%)	1.203	0.548	59(59.0%)	8.143	0.017
Education (years)	13.21 (2.72)	13.23 (2.90)	10.30 (3.49)	10.085	<0.001	12.72 (3.55)	13.30 (3.96)	12.80 (3.89)	0.174	0.841	15.13 (3.27)	19.249	<0.001
Duration (months)	11.05 (13.14)	16.66 (18.13)	9.27 (18.32)	1.553	0.218	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
HAMD-17	23.91 (9.33)	7.63(5.97)	11.42 (8.94)	36.099	<0.001	1.83(2.63)	1.22(2.52)	2.89(3.71)	2.183	0.119	0.89(1.52)	127.21	<0.001
HAMA	19.60 (10.18)	7.34 (7.86)	11.21 (9.98)	14.922	<0.001	1.90(2.46)	1.57(2.86)	2.63(4.17)	0.786	0.459	1.10(1.96)	94.909	<0.001
BPRS	24.60 (5.66)	25.72 (6.52)	42.09 (13.01)	39.529	<0.001	18.93 (2.09)	18.61 (1.59)	19.38 (2.36)	0.986	0.377	18.29 (0.76)	92.347	<0.001
YMRS	0.54(1.48)	16.31 (8.90)	1.70(6.59)	62.583	<0.001	0.24(0.64)	0.17(0.83)	0.37(1.11)	0.362	0.697	0.22(0.77)	33.302	<0.001
WSCT_CR	22.89 (9.22)	24.38 (11.69)	17.39 (12.05)	3.657	0.029	29.52 (11.06)	29.26 (12.07)	27.59 (13.19)	0.230	0.795	29.48 (12.23)	12.898	<0.001
TIV	1469.82 (142.83)	1459.63 (144.46)	1409.06 (145.41)	1.702	0.188	1466.30 (150.17)	1504.11 (182.19)	1481.87 (124.71)	0.408	0.666	1442.65 (123.34)	2.277	0.105

Data are presented as the mean (standard deviation) or number (%).
Abbreviations: MPDs, major psychiatric disorders; MDD, major depressive disorder; BD, bipolar disorder; SZ, schizophrenia; FHR, individuals at familial high-risk for major psychiatric disorders; FHR-MDD, individuals at familial high-risk for major depressive disorder; FHR-BD, individuals at familial high-risk for bipolar disorder; FHR-SZ, individuals at familial high-risk for schizophrenia; HC, healthy controls; HAMD-17, Hamilton Depression Scale-17; HAMA, Hamilton Anxiety Scale; BPRS, Brief Psychiatric Rating Scale; YMRS, Young Mania Rating Scale; WSCT_CR, the number of correct responses of Wisconsin Card Sorting Test; TIV, Total Intracranial Volume; N/A, not applicable.
A: comparison among MDD, BD, and SZ groups by ANOVA test or χ2 test.
B: comparison among FHR-MDD, FHR-BD, and FHR-SZ groups by ANOVA test or χ2 test.
C: comparison among HC, FHR, and MPDs groups by ANOVA test or χ2 test.

toolbox that is implemented within SPM12 in Matlab (version R2017a), with the default settings. The processing steps involved segmentation of the images into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) probability maps; affine registration to the 'ICBM template-East Asian Brains' template; normalization to the MNI template using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL); resampling to $1.5 \times 1.5 \times 1.5$ mm^3 voxel size and nonlinear modulation of the normalized data to get grey matter volume (GMV). Then, the images were smoothed with an isotropic Gaussian kernel of 6 mm full width at half maximum (FMWH). The total intracranial volume (TIV) was calculated by combining the segmented GM, WM, and CSF images. Finally, all subjects underwent the visual quality inspection and the CAT12 automated data quality check procedures involving both the "Check sample homogeneity" tool and quality rating scale reports.

2.5. Analysis

The demographic and clinical results were analyzed using ANOVA and χ2 tests in IBM SPSS Statistics for Windows, Version 23.0 (SPSS23.0). A P-value less than 0.05 was set as significance. All GMV analyses were performed by the Data Processing & Analysis for Brain Imaging (DPABI, version 6.0) software (Yan et al., 2016) based on SPM12.

Given the heritability and symptom overlapping phenomenon across the three diseases as we mentioned before, we conducted the first step analysis on overall individuals at familial risk and patients (HC vs. FHR vs. MPDs). With the statistical module, ANCOVA (F-test) was first performed to identify overall group differences (HC vs. MPDs vs. FHR) in whole-brain GMV. Age, sex, years of education, and TIV variables were entered as covariates. Statistical maps were thresholded using the Gaussian random field (GRF) correction procedure (voxel level $p < 0.001$, cluster level $p < 0.05$). Brain clusters that showed significant statistical differences were saved as a mask. Whole-brain groupwise

comparisons were then conducted using Bonferroni adjusted post-hoc t-tests, as implemented in DPABI, with the same covariates. GRF correction for multivoxel comparisons (voxel level $p < 0.001$, cluster level $p < 0.05$, two-tailed) with the mask from ANCOVA analysis was also conducted. Additionally, the mean GMV of every subject was also extracted based on each cluster by the ROI Signal Extractor tool of DPABI for further correlation analyses between the abnormal cluster and clinical features. We then conducted secondary analyses among subgroups of FHR and MPDs respectively to further investigate the potential whole-brain GMV differences within FHR and MPDs groups (FHR-MDD vs. FHR-BD vs. FHR-SZ and MDD vs. BD vs. SZ). The detailed process for the secondary analyses is the same as the first step analysis above.

Potential relationships between GMV values of clusters and clinical features (HAMD −17, HAMA, YMRS, BPRS, and WCST scores) in the MDD, BD, and SZ subgroups were additionally analyzed by using partial correlation analysis controlling for age, sex, years of education, duration of illness, and TIV separately. Results were corrected using Bonferroni correction ($p < 0.05$, two-tailed).

3. Results

3.1. Demographic and clinical features

The demographic and clinical information of all subjects was displayed in Table 1. TIV was not significantly different among all groups and subgroups. No significant difference was observed among subgroups of MPDs in age, sex, and duration of illness and among subgroups of FHR in age and sex. However, there were significant differences among MPDs, FHR, and HC groups in age, sex, years of education, HAMD-17, HAMA, BPRS, YMRS, and WSCT ($p < 0.05$). Significant differences in years of education, HAMD-17, HAMA, BPRS, YMRS, and WSCT were noted among MDD, BD, and SZ ($p < 0.05$).

3.2. GMV values

Significant GMV differences among HC, FHR, and MPDs groups were detected in 4 clusters, mainly across five brain regions (see Table 2 and Fig. 1). Post-hoc analyses (Table 3 and Fig. 1) revealed that compared with MPDs, HC and FHR groups had greater GMVs in cluster A (the right fusiform gyrus and the right inferior occipital gyrus), cluster C (the left anterior cingulate gyrus), and cluster D (the left middle cingulate gyrus), while no differences were found between HC and FHR groups in these regions. On the contrary, compared with FHR, HC and MPDs groups had lower GMV in cluster B (the left superior temporal gyrus). There were no significant GMV differences among subgroups of FHR (FHR-MDD vs. FHR-BD vs. FHR-SZ). We found significant GMV differences among subgroups of MPDs only in the opercular part of the right inferior frontal gyrus (cluster size = 119; peak voxel: F value = 10.281, Cohen's f^2 = 0.221) and post-hoc analyses showed that patients with SZ had larger GMV than MDD in this region (cluster size = 215; peak voxel: z value = 10.281).

Additionally, we identified a positive correlation between the BPRS total scores and GMV values of cluster A (the right fusiform gyrus and the right inferior occipital gyrus) in patients with BD (r = 0.484, p = 0.017). The GMV values of cluster C (the left anterior cingulate gyrus) had a positive correlation with YMRS total scores (r = 0.445, p = 0.020), and the GMV values of the opercular part of the right inferior frontal gyrus also had a positive correlation with BPRS total scores in patients with SZ (r = 0.437, p = 0.033). However, none of them could pass the rigor of Bonferroni corrections.

4. Discussion

To the best of our knowledge, this is the first study to explore shared neuroanatomical biomarkers that may indicate effects of familial risk or disease expression across diagnoses by a direct comparison between MPDs and FHR in a single study. Meanwhile, the inclusion of first-episode drug-naive patients minimized the confounding effects of medication and course of the disease. We found that MPDs shared similar patterns of lower volume in the right fusiform gyrus, the right inferior occipital gyrus, and the left anterior and middle cingulate gyrus when compared to the HC and FHR groups, suggesting these may be altered regions related to the disease expression. Our findings also indicated a common possible signature that reflects effects of familial risk rather than established diseases across FHR: an increase in GMV of the left superior temporal gyrus relative to MPDs and HCs. In this study, no similar changes of GMV were detected both in MPDs and FHR yet, reflecting no endophenotypes were discovered.

Consistent with our first hypothesis, a concordance across MPDs in terms of grey matter abnormalities was identified in the right fusiform gyrus, the right inferior occipital gyrus, and the left anterior and middle cingulate gyrus. These changes were thought to be associated with the onset of MPDs (i.e., disease expression), because they presented in patients but not in high-risk individuals. This finding also supports previous studies (Chang et al., 2018; Goodkind et al., 2015; Li et al., 2020; Opel et al., 2020) showing that there are comprehensive, multi-focal,

shared structural changes across psychiatric disorders, especially in heteromodal association cortex and limbic regions. Interestingly, GMV across MPDs was found to change in the same pattern in our study. That is, they were lower than those of the HC. In MPDs, grey matter reduction is well documented (Goodkind et al., 2015). It is also part of the longitudinal pathological process termed "neuroprogression" (Kapczinski and Streb, 2014). However, it has recently been suggested that we should not ignore the bidirectional nature of neuroprogression (Moylan et al., 2013) with plastic adaptation to pathology (Pascual-Leone et al., 2005). Other studies observed that there is not only a loss of matter but also brain volume increases (Amad et al., 2020). Taken together, it is critical to consider the directionality of effects in order to understand mechanisms across diagnostic groups in the future (Barch, 2020). All the disrupted brain regions with transdiagnostic features in the present study match result from earlier studies based on disease-specific design (Beasley et al., 2006; Lee et al., 2002) and play an important role in the regulation of higher-level cognition, executive function, emotion, and decision making (Jung et al., 2021; Rolls, 2019; Tohid et al., 2015). They are all functions commonly impaired in MPDs (McTeague et al., 2016). This may partially reveal the neurobiological mechanisms underpinning the overlapping symptoms and comorbidity that appeared in MPDs. Moreover, it is worth noting that while the main aim of the present study was to examine similar neuroanatomical biomarkers, we cannot rule out disorder-specific biomarkers for MPDs.

Increased GMV in the left superior temporal gyrus was detected across FHR compared to HC and MPDs groups, which confirms our second hypothesis that this GMV abnormality specific to FHR may reflect effects of familial risk rather than established diseases. The superior temporal gyrus plays an important role in social cognition and perception of facial emotions (Saitovitch et al., 2012). Consistent with our findings, some meta-analyses also found increased GMV in the superior temporal gyrus within high-risk individuals with MPDs (Cattarinussi et al., 2019; Ding et al., 2019). However, in a meta-analysis (Zhang et al., 2020) of brain structural investigations in relatives of individuals with MDD, BD, and SZ, the sole hallmark shared by relatives was reduced right cerebellar GMV. This discrepancy may be attributed to the between-study heterogeneity such as methodological details, medications, and sample variability. Strikingly, we included FHR, HC as well as MPDs simultaneously from a transdiagnostic view in our study. When compared with the above and other studies, which only include high-risk individuals without patients as a contrast, this may allow for further speculation beyond familial risk as to which mechanism underlying MPDs may be associated with the brain abnormalities identified in FHR: vulnerability (i.e., endophenotypes) or resilience. Compensatory or resiliency mechanisms are present in unaffected high-risk individuals but not in affected patients, thus may prevent the onset of diseases (Cattarinussi et al., 2019). So, the greater GMV in the left superior temporal gyrus may most likely reflect compensatory or resiliency mechanisms against MPDs development since this abnormality was only detected in the FHR group with no change in the MPDs group, when compared to the HC group. However, it is still difficult to conclude an accurate answer as to which role this structural change plays in the mechanism of MPDs because of the inconsistencies between different

Table 2
GMV differences among HC, MPDs and FHR groups.

Clusters	Regions	Voxels	Peak MNI coordinates			F values	Effect size (Cohen's f^2)
			X	Y	Z		
A	Right fusiform gyrus	189	36	−73.5	−16.5	14.63*	0.104
	Right inferior occipital gyrus						
B	Left superior temporal gyrus	134	−52.5	−33	15	10.98*	0.078
C	Left anterior cingulate gyrus	206	−10.5	33	24	11.26*	0.080
D	Left middle cingulate gyrus	173	−2	7.5	42	10.31*	0.073

Abbreviations: L, left; R, right; MNI, Montreal Neurological Institute.
*: voxel level $p < 0.001$, cluster level $p < 0.05$, corrected by Gaussian random field correction.
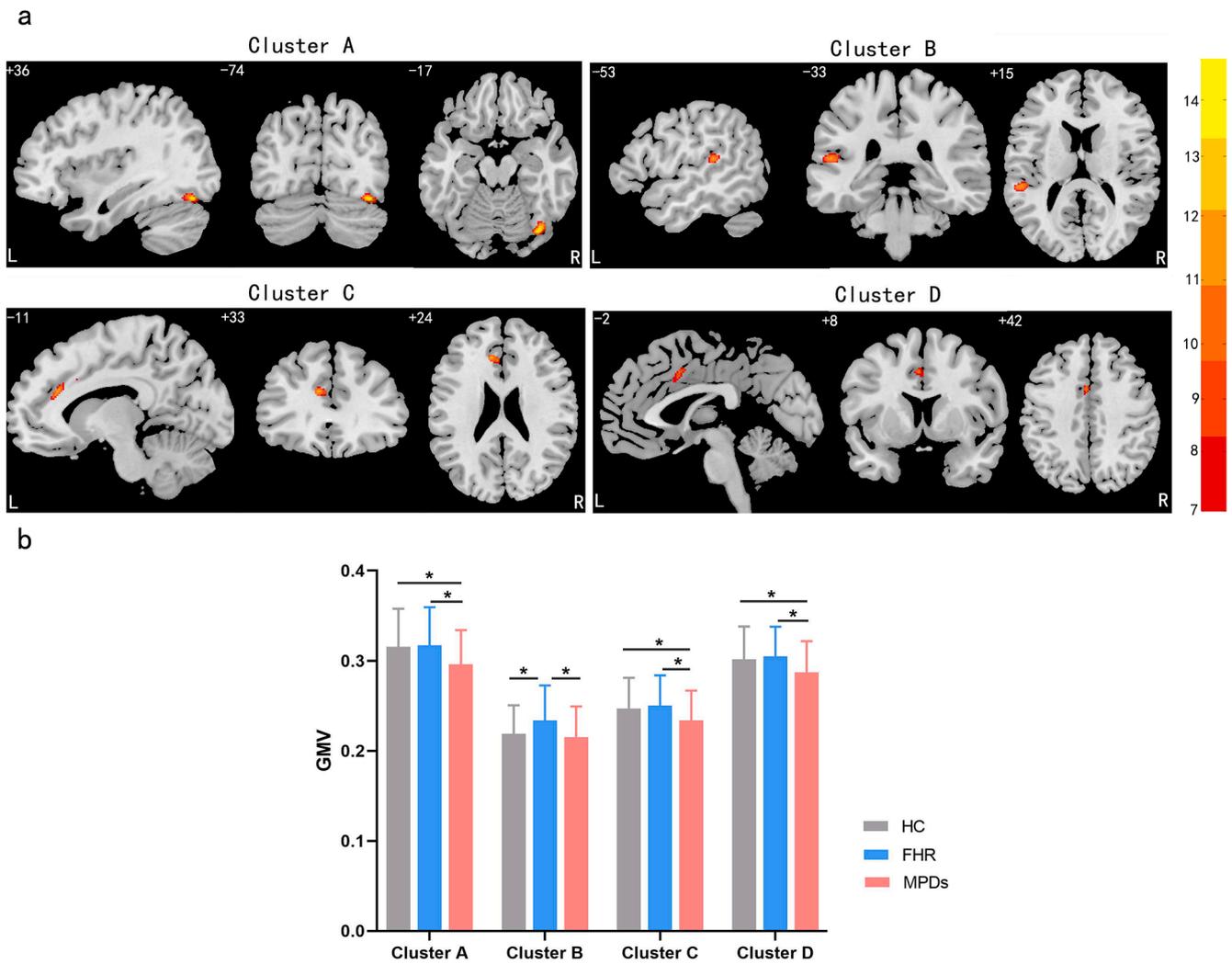
Fig. 1. Significant differences in GMV among HC, MPDs and FHR groups. (a) Regions with significantly different GMV (GRF correction, voxel level $p < 0.001$, cluster level $p < 0.05$) among groups: cluster A (the right fusiform gyrus and inferior occipital gyrus), cluster B (the left superior temporal gyrus), cluster C (the left anterior cingulate gyrus), and cluster D (the left middle cingulate gyrus). L: left, R: right. The color bar is the range of F values. Numbers in brain maps are Montreal Neurological Institute (MNI) coordinates. (b) Result of Post-hoc tests in 4 clusters. Error bar represents the standard deviation. * indicates $p < 0.05$, Bonferroni correction. HC, healthy controls; FHR, individuals at familial high-risk for major psychiatric disorders, MPDs, major psychiatric disorders. The values on the y-axis refer to gray matter volume (GMV) measured as cm^3.

Table 3
GMV differences of pairwise comparisons between HC, MPDs, and FHR groups.

Post-hoc Comparisons	Cluster	Cluster size(#voxels)	Peak MNI coordinates			Z values	Effect size (Cohen's f^2)
			X	Y	Z		
HC VS. FHR							
HC < FHR	Temporal_Sup_L	71	−55.5	−34.5	15	−4.034*	0.074
HC VS. MPDs							
HC > MPDs	Fusiform_R, Occipital_Inf_R	80	36	−73.5	−16.5	4.500*	0.126
	Cingulum_Ant_L	12	−12	34.5	22.5	3.457*	0.095
	Cingulum_Mid_L	2	−3	7.5	42	3.387*	0.075
FHR VS. MPDs							
FHR > MPDs	Fusiform_R, Occipital_Inf_R	141	36	−73.5	−16.5	4.821*	0.092
	Temporal_Sup_L	133	−52.5	−33	15	4.739*	0.101
	Cingulum_Ant_L	180	−9	31.5	25.5	4.157*	0.084
	Cingulum_Mid_L	136	−7.5	13.5	37.5	4.213*	0.089

Abbreviations: HC, healthy controls; MPDs, major psychiatric disorders; FHR, individuals at familial high-risk for major psychiatric disorders; Temporal_Sup_L, the Left superior temporal gyrus; Fusiform_R, the right fusiform gyrus; Occipital_Inf_R, the right inferior occipital gyrus; Cingulum_Ant_L, the left anterior cingulate gyrus; Cingulum_Mid_L, the left middle cingulate gyrus; Z values, the corrected Z values of post hoc comparison at peak voxel between each pair of group.
*: These findings correspond to a corrected voxel $p < 0.001$, cluster $p < 0.05$ after GRF correction (two-tailed).

studies and the absence of longitudinal design. Unlike results of unchanged GMV in patients in our and some previous studies (Keramatian et al., 2021), increased (Adler et al., 2007; Liu et al., 2021) or reduced (Bandeira et al., 2021; Chen et al., 2004; Cui et al., 2011; Qi et al., 2018) GMV value in the superior temporal gyrus has been frequently reported in patients with MPDs in other studies. Thus, the precise mechanism underlying this finding warrants further confirmation.

Contrary to our third hypothesis, no transdiagnostic endophenotype was detected in this study. One essential feature of an endophenotype is that it should exist in both patients and unaffected relatives. The absence of a comparable grey matter difference between patients and familial high-risk individuals, when compared to HC, is in accordance with some prior findings (Boos et al., 2012; van der Velde et al., 2015). However, similar grey matter abnormalities in unaffected familial high-risk individuals and patients have been found in other lower threshold studies, which may explain the positive findings in earlier meta-analyses (Zhang et al., 2020). Despite these previously reported positive findings, the inconsistent results in some distinct meta-analyses (Cooper et al., 2014; Fusar-Poli et al., 2014; Tomyshev et al., 2020) cast more doubts on the reliability of grey matter as an endophenotype for MPDs. One explanation could be that variations of GMV are associated with different psychiatric susceptibility genes and even different single nucleotide polymorphisms (Trost et al., 2013a, p. 1, Trost et al., 2013b, p. 1). For instance, while carriers of *CNNM2* allele have increased GMV in the anterior cingulate cortex (Rose et al., 2014), carriers of *DISC1* allele have decreased ones (Szeszko et al., 2008). The lack of shared findings between the FHR and MPDs, relative to the HC, may also be that neuroanatomical endophenotypes are rather specific to each disorder. Another explanation could be that the brain grey matter atrophy only occurs after the debut of illness, or it could be that brain grey matter atrophy in asymptomatic relatives is undetectable in macroscopic investigations. It is possible that only brain functional activities are changed in healthy relatives with just a reorganization of synaptic connections without decreased GMV.

GMV differences among subgroups of FHR and MPDs were not obvious in our study, with only a small enhanced GMV cluster in the opercular part of the right inferior frontal gyrus observed in patients with SZ. It is possible that we were underpowered to detect significant group differences because of inter-subject variability. The brain is a plastic system (Pascual-Leone et al., 2005) that is constantly shaped by subject-specific intrinsic (i.e., gene) and external factors (i.e., environment) (Seghier and Price, 2018), and can produce inter-subject variability in brain anatomy. We have minimized the intrinsic variability by matching subjects for demographic variables (e.g., age, sex, and handedness) among subgroups. We have also incorporated age, sex, years of education, and TIV into the analyses as covariates. However, the variability in brain GMV may also arise from other environmental factors such as stressful life events (Papagni et al., 2011) and living habits (Kokubun et al., 2021), which could not be better controlled in the present study. What we lack in homogeneity within the subgroups we may compensate for in greater sample sizes in the future. Additionally, meaningful differences between subgroups of FHR and MPDs may be hidden in complex spatial patterns across multiple voxels rather than simple alterations in individual voxels. Thus, in the future, we could also adopt the multivoxel pattern analysis (MVPA) method (Mahmoudi et al., 2012) other than the classical individual-voxel-based statistical tests to identify subtle anatomical patterns for diverse disease states and at-risk states, through which the conclusions drawn from the standard mean (central) group effects can be enriched by the characterization of inter-subject variability.

Our study still has some limitations. First, FHR and MPDs in our study are not from the same family. It's worth noting that many studies (Byun et al., 2012; Chang et al., 2016) also defined the unaffected individuals at familial risk as genetic high risk (GHR), considering that they have higher genetic loading than HC who have no relatives with psychiatric disorders. From this perspective, even if the FHR and MPDs

in the study did not come from the same family, they still could help us explore markers for genetic liability and understand the etiology of MPDs without confounding factors such as clinical and treatment histories. Though this is acceptable, it can be revised in the future. Second, this is just a cross-sectional study. In order to improve trajectories of diseases and the risk or resilience for diseases throughout the life course, we propose that longitudinal studies are needed. Third, since we did not measure genotypes of the participants, the interpretation of this negative result of risk biomarker in our present study is still limited. Future studies should be conducted to determine whether these genetic variants might explain the divergent findings of risk biomarkers for MPDs.

In conclusion, our study suggests that reduced grey matter in the right fusiform gyrus, inferior occipital gyrus, and left cingulate gyrus might represent a shared neuroanatomical signature for MDD, BD, and SZ. Individuals at familial high risk for MDD, BD, and SZ might exhibit a shared neuroanatomical biomarker indicating herediraty risk for MPDs. Our study provides evidence for the value of neuroimaging commonalities for finding the transdiagnostic neurobiological mechanisms for the onset and compensation of MPDs.

CRediT authorship contribution statement

Linna Jia: Conceptualization, Investigation, Formal analysis, Writing – original draft. **Xiaowei Jiang:** Methodology, Writing – review & editing. **Qikun Sun:** Investigation, Validation. **Jian zhou:** Investigation, Validation. **Linzi Liu:** Investigation, Validation. **Ting Sun:** Investigation, Validation. **Pengshuo Wang:** Investigation, Validation. **Yanqing Tang:** Resources, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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