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# A neuroimaging biomarker for striatal dysfunction in schizophrenia

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# SUPPLEMENTAL FIGURES AND TABLES

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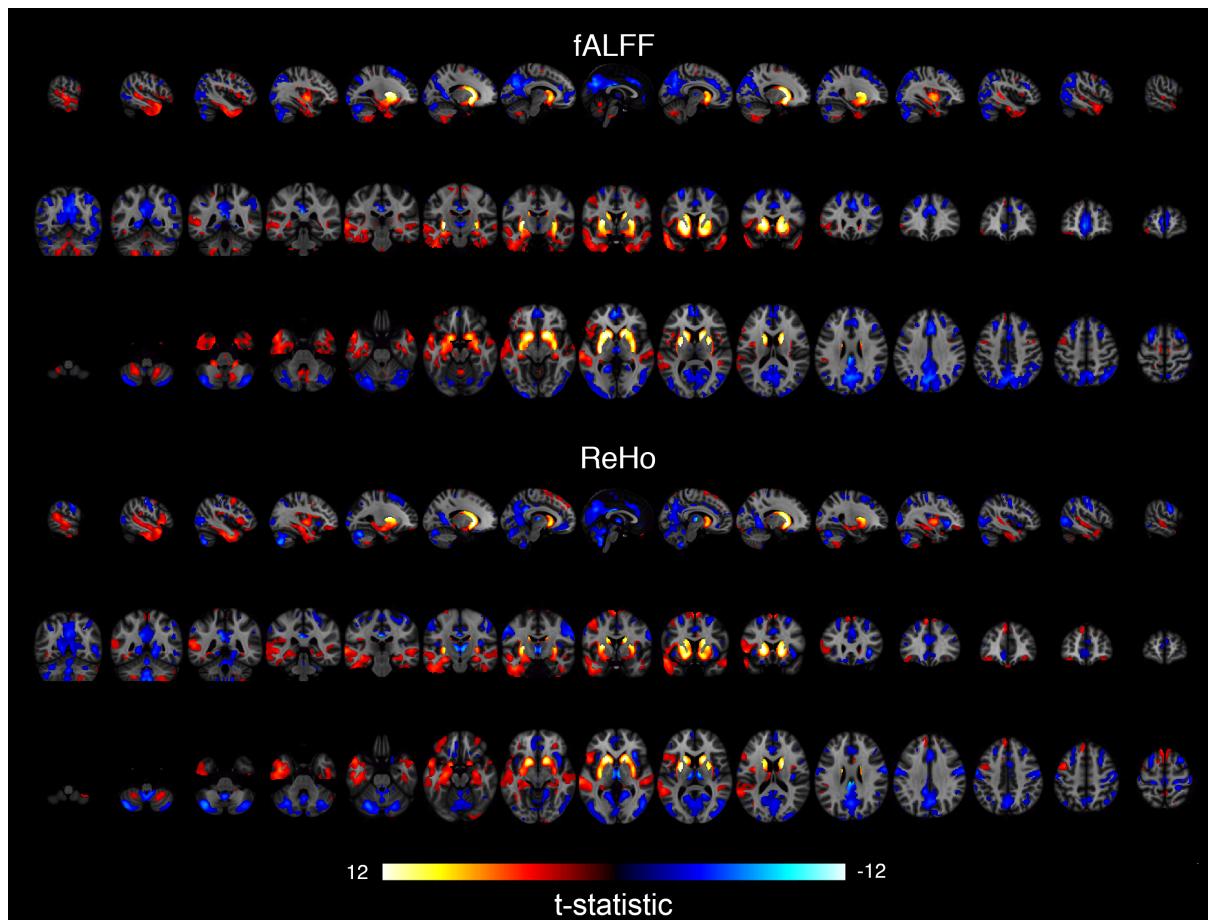
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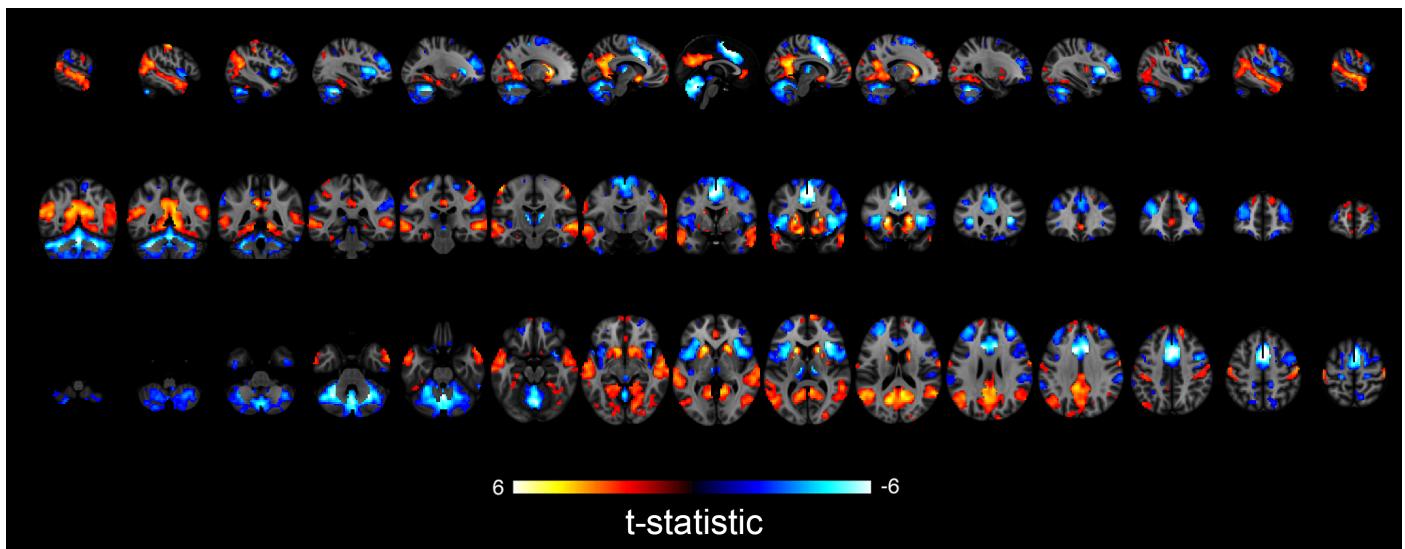
- **Supplementary Fig. 1** – Alterations in fALFF and ReHo across the brain in schizophrenia.
- **Supplementary Fig. 2** – Alterations in extra-striatal FC across the brain in schizophrenia.
- **Supplementary Fig. 3** – Consistent patterns in extra-striatal FC across 12 subregions within the striatum.
- **Supplementary Fig. 4** – Distribution of FSA scores in schizophrenia and healthy comparison groups, stratified according to data acquisition site.
- **Supplementary Fig. 5** – FSA characterizes treatment response in a five-factor PANSS model.
- **Supplementary Fig. 6** – Regional specificity of FSA by whole-brain FC.
- **Supplementary Fig. 7** – FSA based on different striatal candidates characterize antipsychotic response
- **Supplementary Fig. 8** – Spatial association between fALFF / ReHo t-statistic map and risk gene expression across control regions brain.
- **Supplementary Figs. 9-13** – Enrichment analysis of top 206 genes identified by fALFF and ReHo.
- **Supplementary Fig. 14** – Diagram for study participants.
  
- **Supplementary Table 1** – Demographic and clinical characteristics of participants, stratified according to site.
- **Supplementary Table 2** – Comparison of standard deviation (SD) for schizophrenia patients (SZ) and healthy controls (NC), in terms of FSA scores and scores derived from classification from whole-brain functional connectivity.
- **Supplementary Table 3** – Characteristics of antipsychotic-naïve patients, acute antipsychotic-exposure patients, and chronic patients with a long medication history.
- **Supplementary Table 4** – Study sample characteristics of diverse first-episode schizophrenia patients, chronic patients, and patients with missing medication information
- **Supplementary Table 5** – Study sample characteristics of medicated and unmedicated schizophrenia groups at the time of scanning.
- **Supplementary Table 6** – Medication and clinical information for the longitudinal patients assessed in the study.
- **Supplementary Table 7** – Demographic information for validation samples (in Datasets 1-5).
- **Supplementary Table 8** – Description of Threat Risk Assessment Scale.
- **Supplementary Table 9** – Technical details of the MRI, software and head coils of the seven scanners used.
- **Supplementary Table 10** – Performance of the classification model using whole-brain functional connectivity based on AAL atlas (striatum excluded).
- **Supplementary Table 11** – Performance of the classification model using whole-brain functional connectivity based on Power's coordinates (striatum excluded).
  
- **REFERENCES**
  
- **STARD checklist**

## Supplementary Figure 1



**Supplementary Figure 1. Alterations in fALFF and ReHo across the brain in schizophrenia.** The *t*-statistic values are visualized for significantly different voxels (FDR adjusted,  $P < .05$ ; unpaired two-sided *t*-test).  $n = 560$  subjects with schizophrenia and  $n = 540$  controls. Both the fALFF and ReHo showed that the striatum was the most distinguishing region for schizophrenia. For each map, the first row shows sagittal sections at Montreal Neurological Institute (MNI)  $x$  coordinates from -60 mm to 60 mm; the second row shows coronal sections at Montreal Neurological Institute (MNI)  $y$  coordinates from -60 mm to 60 mm; the last row shows transverse sections at Montreal Neurological Institute (MNI)  $y$  coordinates from -60 mm to 60 mm.

## Supplementary Figure 2



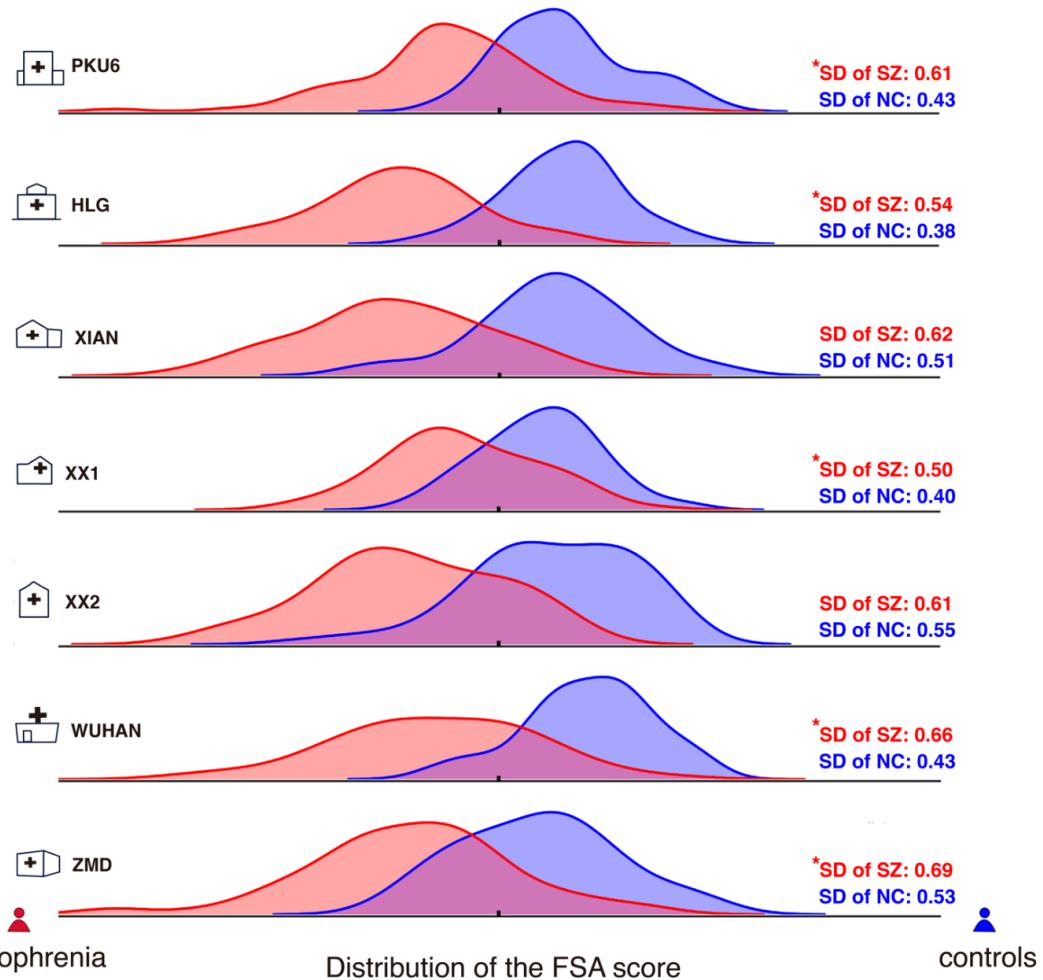
**Supplementary Figure 2. Alterations in extra-striatal FC across the brain in schizophrenia.** The *t*-statistic values are visualized for significantly different voxels (FDR adjusted,  $P < .05$ ; unpaired two-sided *t*-test).  $n = 560$  subjects with schizophrenia and  $n = 540$  controls. The first row shows sagittal sections at the Montreal Neurological Institute (MNI) *x* coordinates from -60 mm to 60 mm; the second row shows coronal sections at the Montreal Neurological Institute (MNI) *y* coordinates from -60 mm to 60 mm; the last row shows transverse sections at Montreal Neurological Institute (MNI) *y* coordinates from -60 mm to 60 mm.

### Supplementary Figure 3



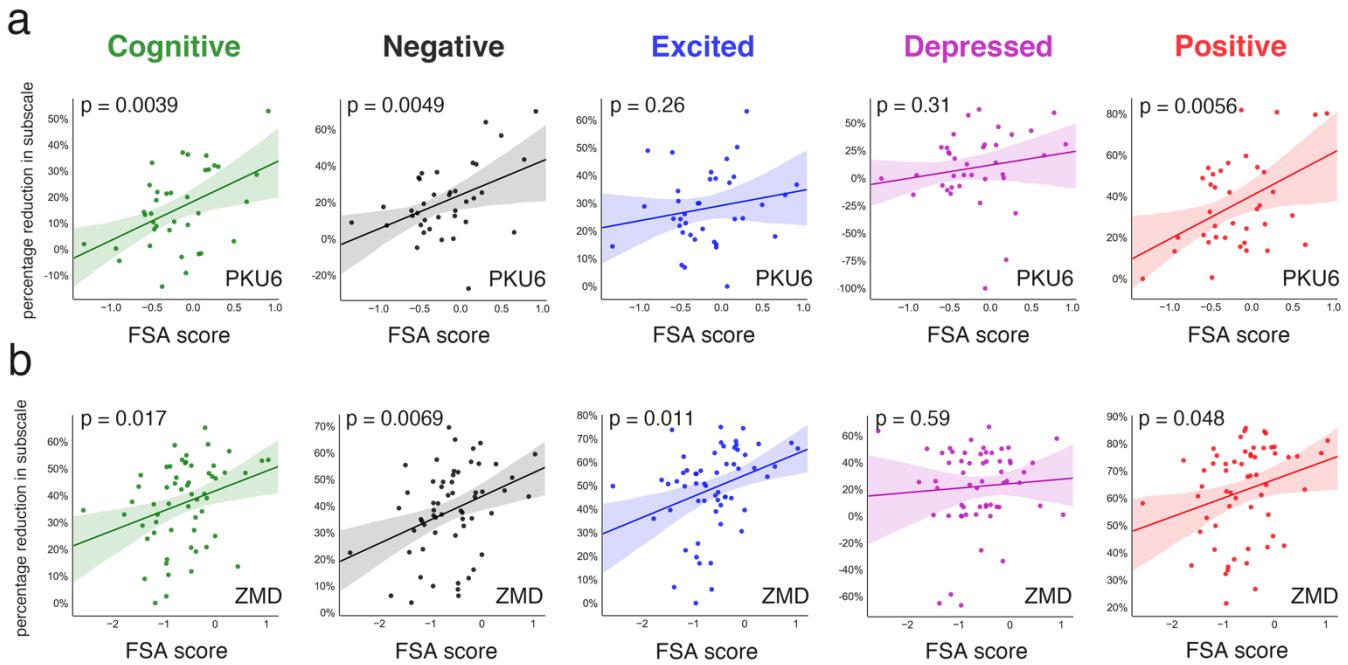
**Supplementary Figure 3. Consistent patterns in extra-striatal FC across 12 subregions within the striatum.**  
 The  $t$ -statistic values are visualized for significantly different voxels (FDR adjusted,  $P < .05$ ; unpaired two-sided  $t$ -test).  
 $n = 560$  subjects with schizophrenia and  $n = 540$  controls. For each map, the first row shows sagittal sections at the Montreal Neurological Institute (MNI)  $x$  coordinates from -60 mm to 60 mm; the second row shows coronal sections at the Montreal Neurological Institute (MNI)  $y$  coordinates from -60 mm to 60 mm; the last row shows transverse sections at the Montreal Neurological Institute (MNI)  $y$  coordinates from -60 mm to 60 mm.

## Supplementary Figure 4



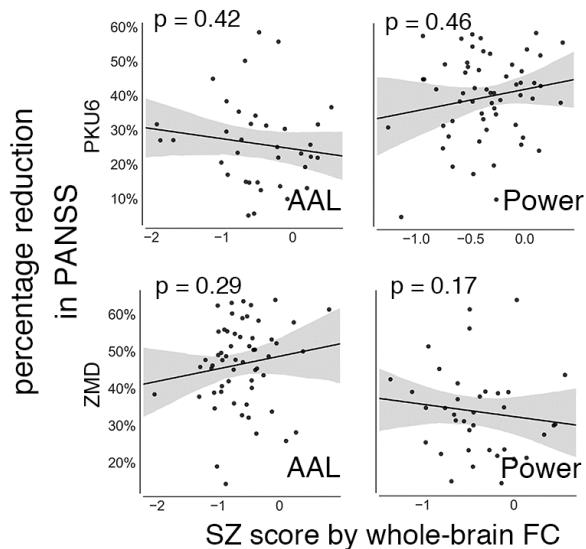
**Supplementary Figure 4. Distribution of FSA scores in schizophrenia and healthy comparison groups, stratified according to data acquisition site.** The FSA score is z-scored and aligned for better visualization. The asterisk indicates  $P < .05$  in a two-sided F-test comparing the variances between the two groups. Standard deviation (SD) is represented for each group and scanner from top to bottom: 1) Peking University Sixth Hospital (FSA SD in schizophrenia = 0.61, n = 92; FSA SD in control = 0.43, n = 98; F-test  $P = .00089$ ). 2) Beijing Huilongguan Hospital (FSA SD in schizophrenia = 0.54, n = 83; FSA SD in control = 0.38, n = 90; F-test  $P = .011$ ). 3) Xijing Hospital (FSA SD in schizophrenia = 0.62, n = 90; FSA SD in control = 0.51, n = 54; F-test  $P = .16$ ). 4) Henan Mental Hospital with SIEMENS scanner (FSA SD in schizophrenia = 0.50, n = 81; FSA SD in control = 0.40, n = 102; F-test  $P = .024$ ) 5) Henan Mental Hospital with GE scanner (FSA SD in schizophrenia = 0.61 n = 49; FSA SD in control = 0.55, n = 69; F-test  $P = .41$ ) 6) Renmin Hospital of Wuhan University (FSA SD in schizophrenia = 0.66, n = 82; FSA SD in control = 0.43, n = 89; F-test  $P = .00012$ ). 7) Zhumadian Psychiatric Hospital (FSA SD in schizophrenia = 0.69, n = 83; FSA SD in control = 0.53, n = 69; F-test  $P = .029$ ).

## Supplementary Figure 5



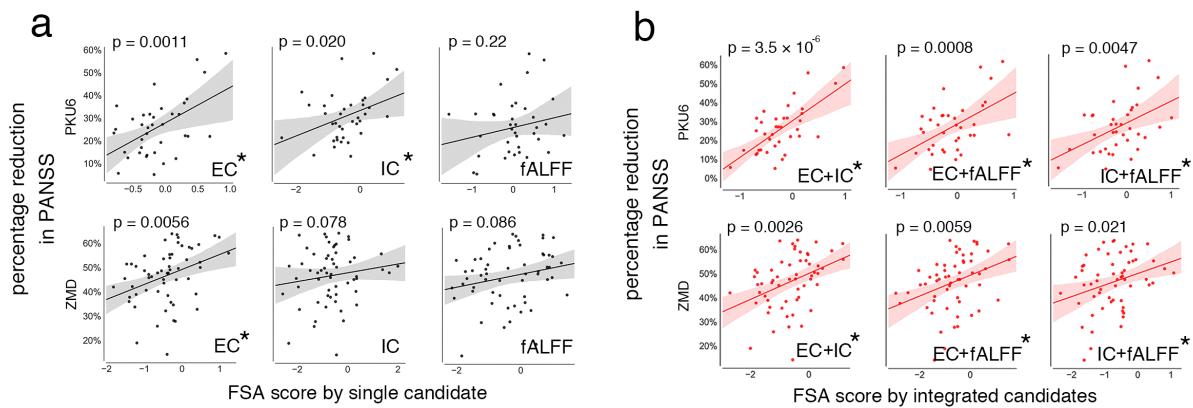
**Supplementary Figure 5. FSA characterizes treatment response in a five-factor PANSS model.** The subscales in a five-factor model were used to index treatment response: positive (total scores of P1, P5, P6, G9), negative (total score of N1, N2, N3, N4, N6, G16), excitement (total score of P4, P7, G4, G14), depression/anxiety (total score of G1, G2, G3, G6, G15), and cognitive (total score of P2, N5, G5, G10, G11), according to the factor analysis from a previous study<sup>1</sup>. P: positive psychopathology scale, N: negative psychopathology scale, G: general psychopathology scale. Association between interindividual variation in FSA scores and percentage change in each of the five factors comprising PANSS in a) Longitudinal samples at PKU6 hospital, n = 37. b) Longitudinal samples at ZMD hospital, n = 58. P value of Pearson correlation test is represented.

## Supplementary Figure 6



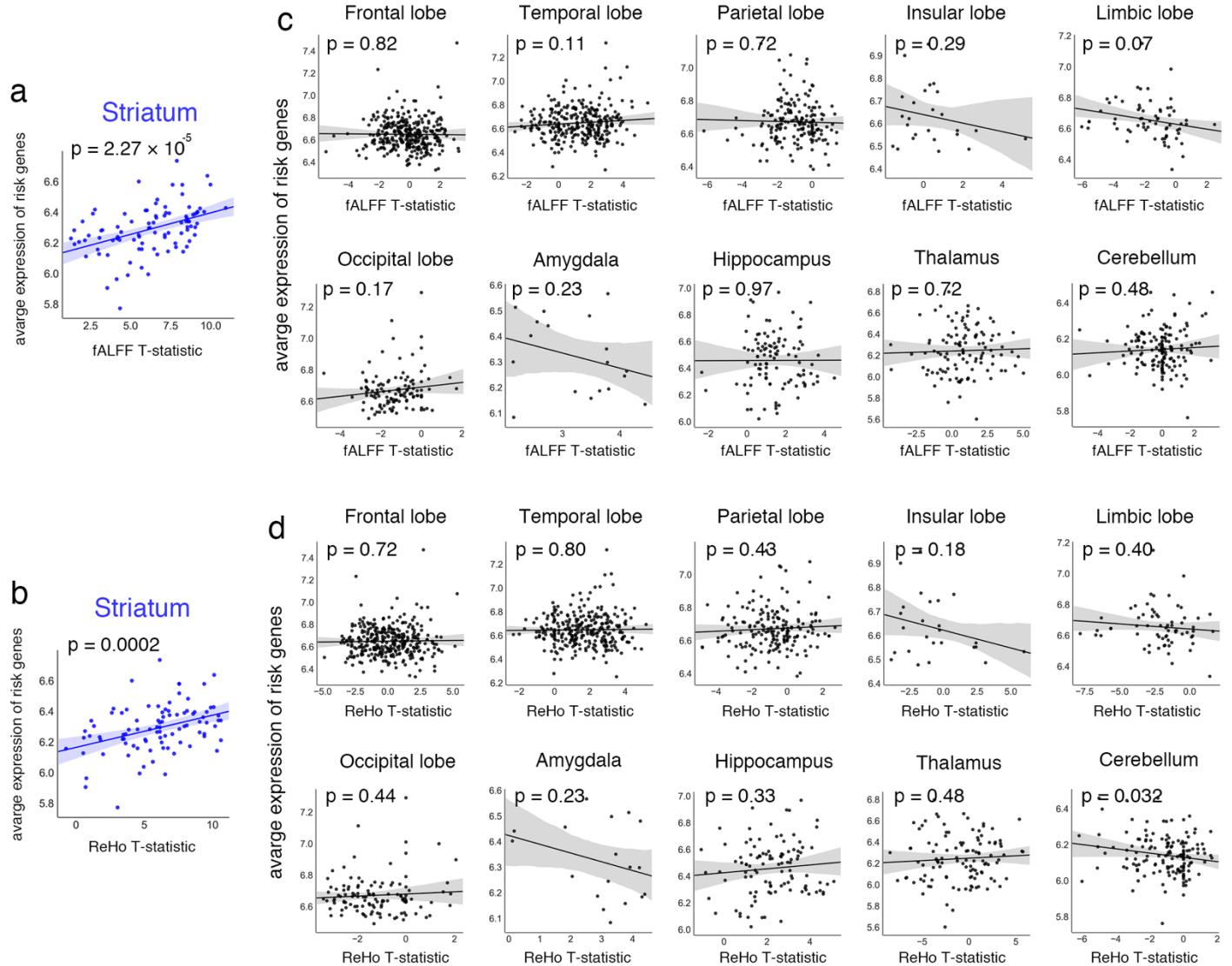
**Supplementary Figure 6. Regional specificity of FSA by whole-brain FC.** Association between percentage symptom reduction in PANSS and schizophrenia score by whole-brain FC (defined by the AAL atlas and Power parcellation). Top: PKU6 hospital, n = 37. Bottom: ZMD hospital n = 58. P value of Pearson correlation test is represented.

## Supplementary Figure 7



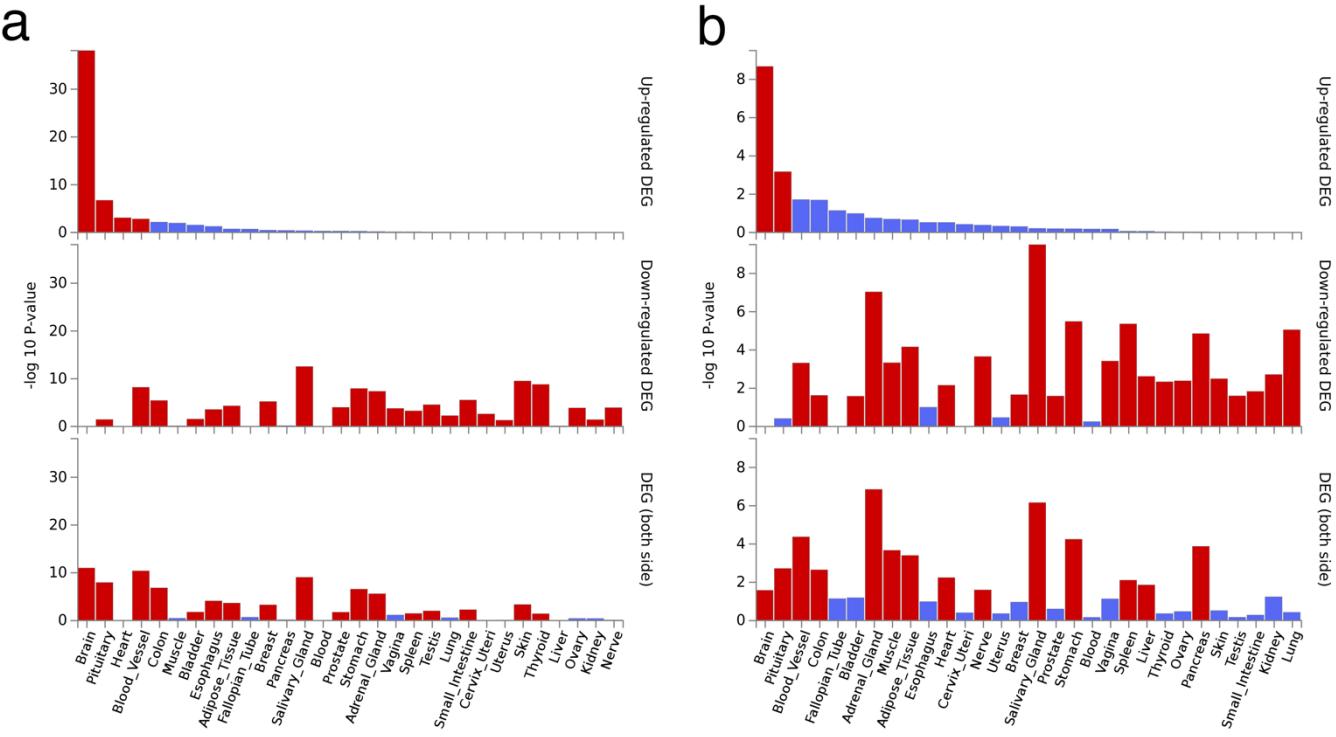
**Supplementary Figure 7. FSA based on different striatal candidates characterize antipsychotic response.** IC=intra-striatal FC, EC=extra-striatal FC, asterisk indicates  $P < .05$ . Using the same cross-validation strategy, the prediction accuracy deteriorated when any one or two of these features was omitted (average accuracy of fALFF: 71%, intra-striatal FC: 73.8%, extra-striatal FC: 72.5%; fALFF and intra-striatal FC: 74.8%, fALFF and extra-striatal FC: 76.5%, intra- and extra-striatal FC: 77.4%). Top: PKU6 hospital, n = 37. Bottom: ZMD hospital n = 58. Associations are represented between the percentage symptom reduction in PANSS and the FSA score by different candidates of striatal features from a) a single striatal feature. b) two integrated striatal features.  $P$  value of Pearson correlation test was represented.

## Supplementary Figure 8



**Supplementary Figure 8. Spatial association between fALFF / ReHo t-statistic map and risk gene expression across control regions brain.** a) Spatial association between the fALFF t-statistic map and the average schizophrenia risk gene expression for samples within the striatum ( $n = 92$ ). b) Spatial association between the ReHo t-statistic map and the average expression levels of schizophrenia risk genes for samples within the striatum ( $n = 92$ ). c) Spatial associations between the fALFF t-statistic map and the average schizophrenia risk gene expression for samples across ten control regions. d) Spatial associations between the ReHo t-statistic map and the average schizophrenia risk gene expression for samples across ten control regions. P value of Pearson correlation test was represented. Sample size in control brain regions:  $n = 326$  in frontal lobe,  $n = 288$  in temporal lobe,  $n = 181$  in parietal lobe,  $n = 25$  in insular lobe,  $n = 66$  in limbic lobe,  $n = 118$  in occipital lobe,  $n = 18$  in amygdala,  $n = 105$  in hippocampus,  $n = 111$  in thalamus,  $n = 160$  in cerebellum.

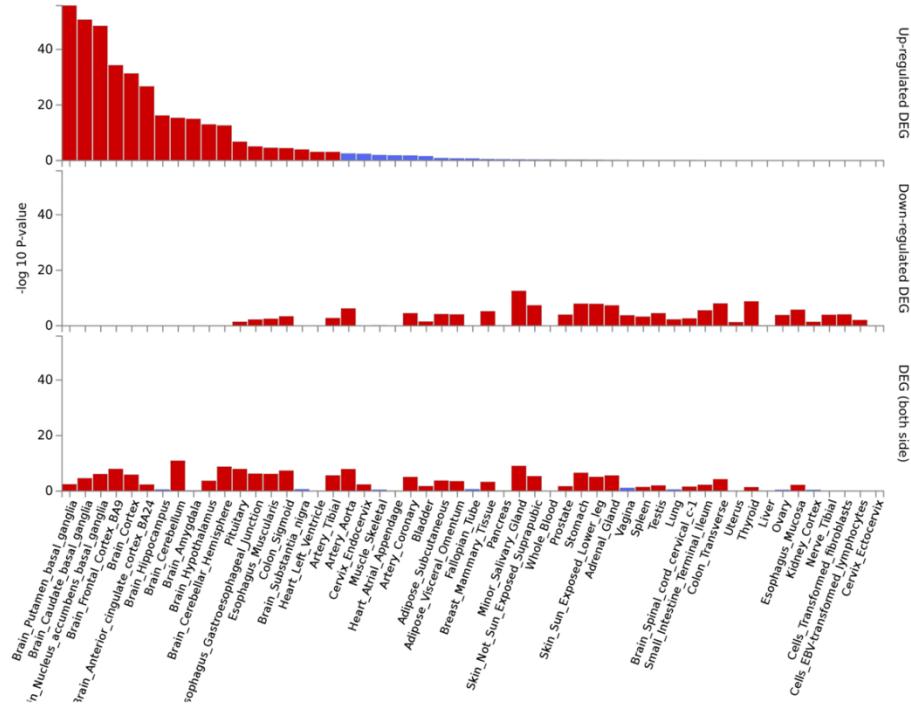
## Supplementary Figure 9



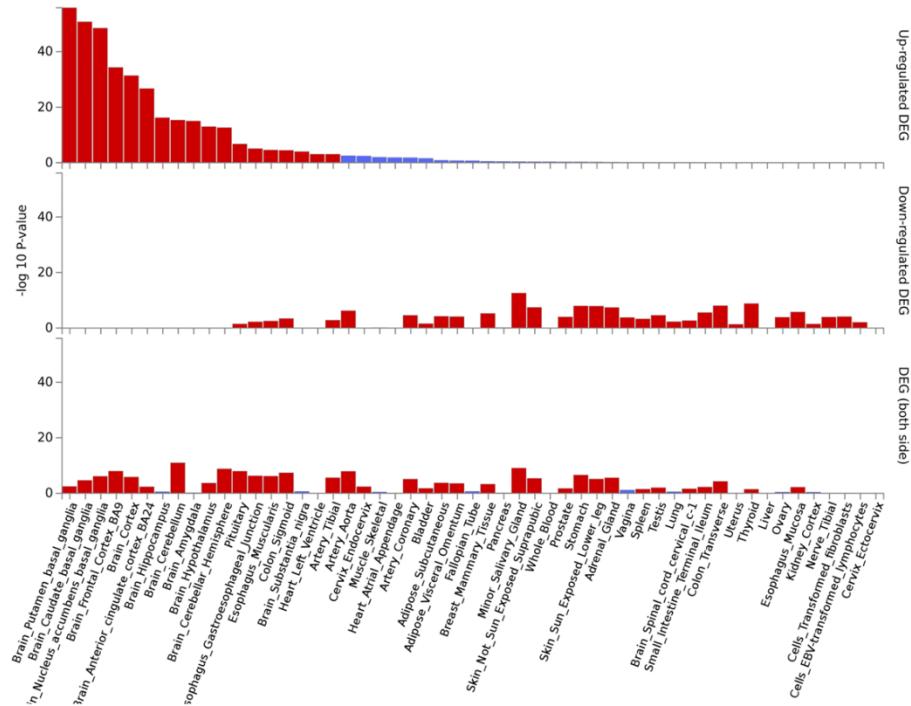
**Supplementary Figure 9. Tissue expression profile analysis for top 206 genes.** Gene-set enrichment analysis was performed to identify tissues enriched with respect to the top 206 genes (with 20737 genes as background) whose spatial expression pattern positively correlated with (a) the t-statistic values of fALFF, (b) the t-statistic values of ReHo, from Genotype-Tissue Expression (GTEx) consortium V6<sup>2</sup> (30 general tissue types). Significantly enriched differentially expressed genes (DEF) sets (Bonferroni correction,  $P < 0.05$ ) are highlighted in red (otherwise blue). Pathway analysis was conducted using MAGMA<sup>3</sup> gene-set analysis in FUMA<sup>4</sup>.

## Supplementary Figure 10

a



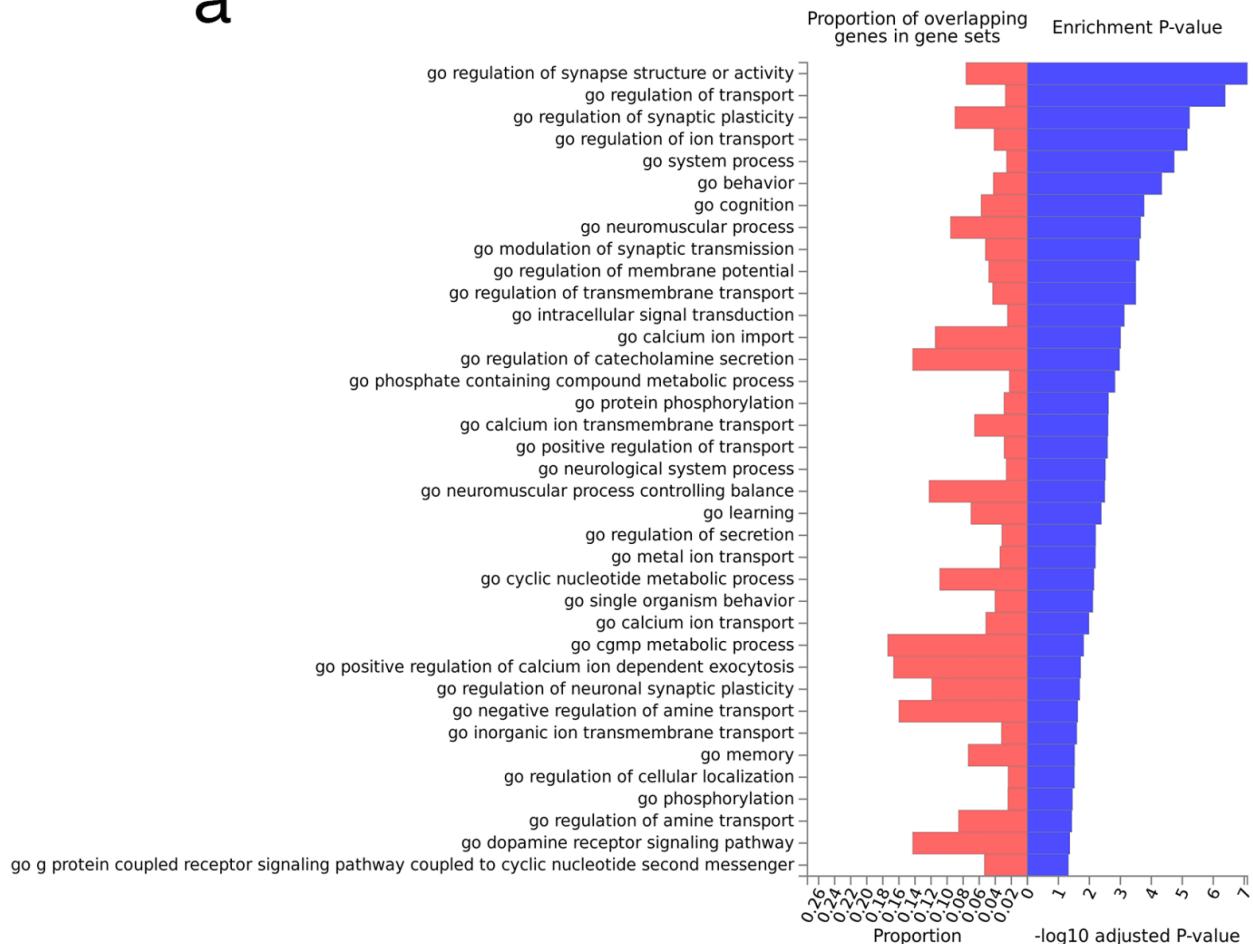
b



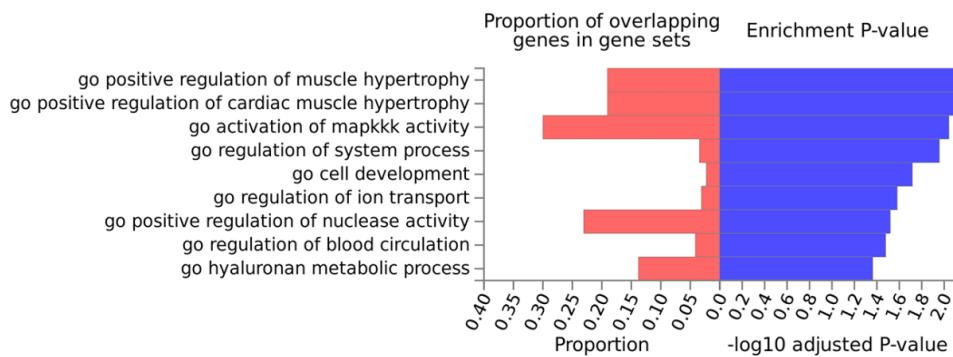
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## Supplementary Figure 11

a



b

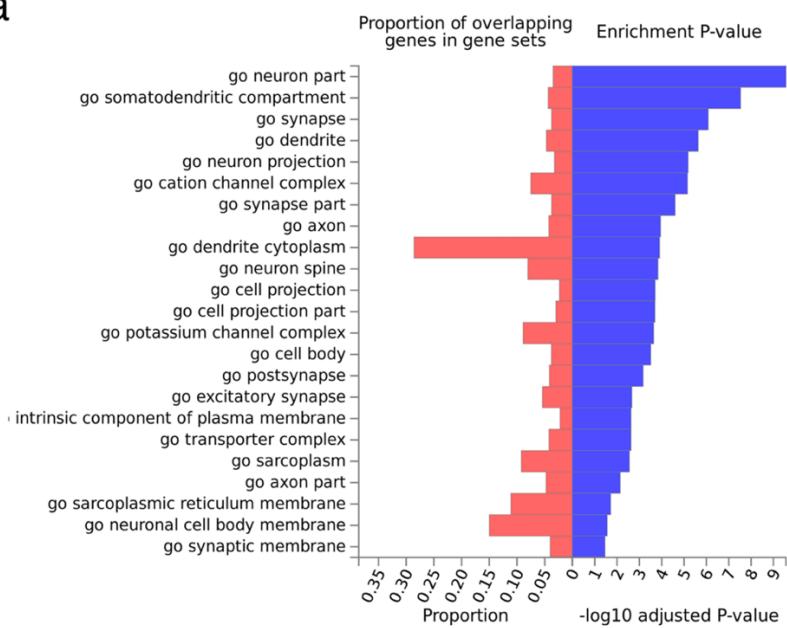


**Supplementary Figure 11. Gene Ontology (GO) biological processes pathway analysis for top 206 genes.**

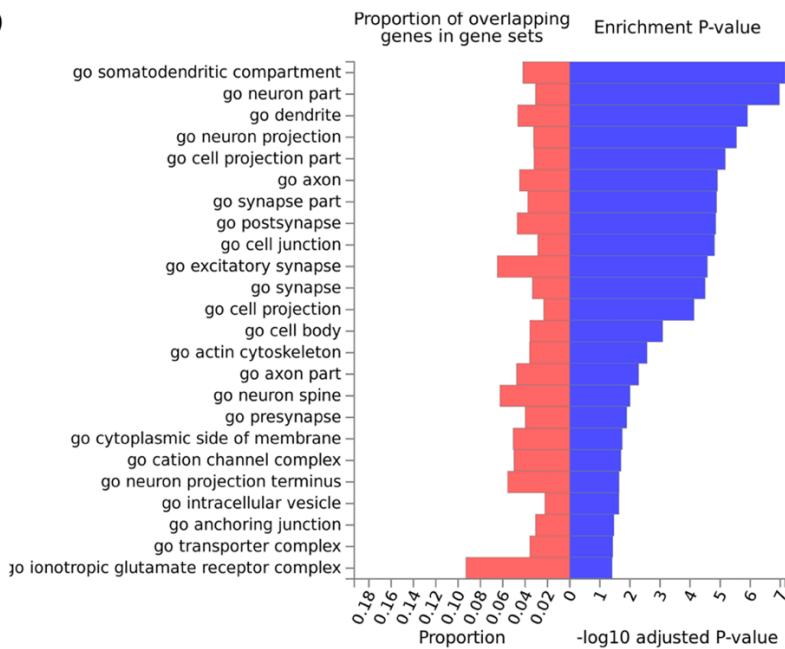
Gene-set enrichment analysis was performed to identify biological pathways enriched with respect to the top 206 genes (with 20737 genes as background) whose spatial expression pattern positively correlated with (a) the t-statistic values of fALFF, (b) the t-statistic values of ReHo, from GO biological processes, MsigDB C5<sup>6</sup>. Only significantly enriched gene sets (FDR adjusted,  $P < 0.05$ ) are represented. Pathway analysis was conducted using MAGMA<sup>3</sup> gene-set analysis in FUMA<sup>4</sup>.

## Supplementary Figure 12

a



b

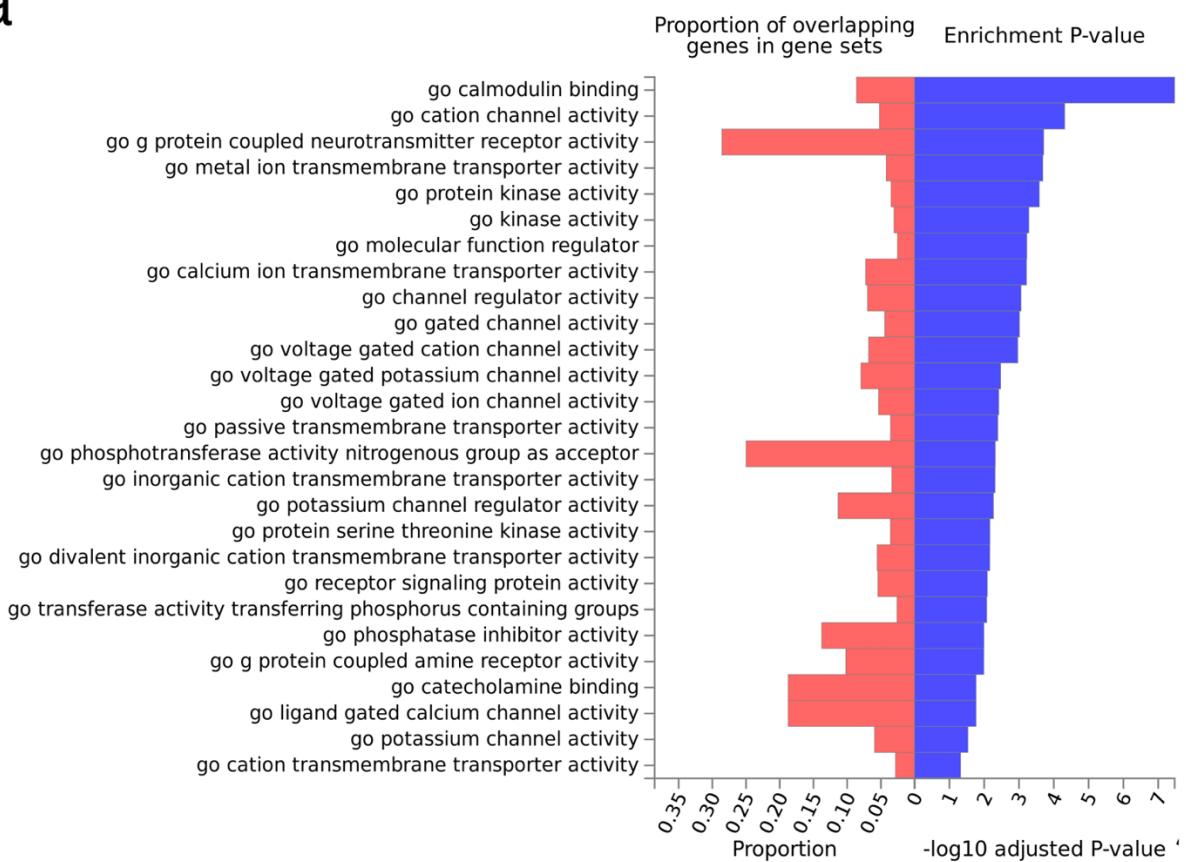


**Supplementary Figure 12. Gene Ontology (GO) cellular components pathway analysis for top 206 genes.**

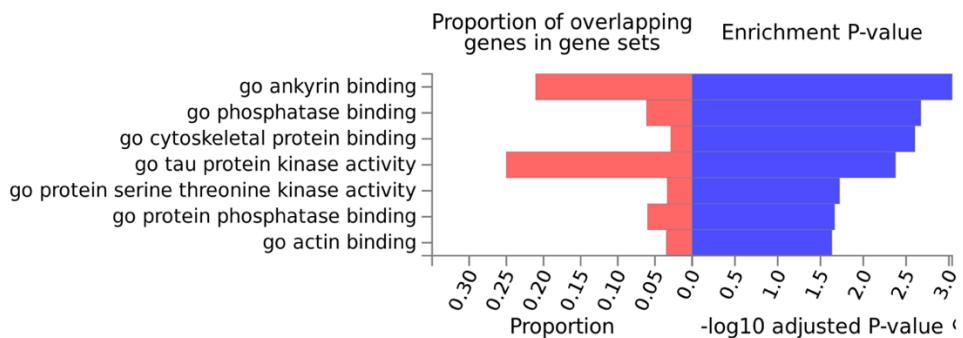
Gene-set enrichment analysis was performed to identify biological pathways enriched with respect to the top 206 genes (with 20737 genes as background) whose spatial expression pattern positively correlated with (a) the t-statistic values of fALFF, (b) the t-statistic values of ReHo, from GO cellular components, MsigDB C5<sup>6</sup>. Only significantly enriched gene sets (FDR adjusted,  $P < 0.05$ ) are represented. Pathway analysis was conducted using MAGMA<sup>3</sup> gene-set analysis in FUMA<sup>4</sup>.

## Supplementary Figure 13

a



b



**Supplementary Figure 13. Gene Ontology (GO) molecular function pathway analysis for top 206 genes.** Gene-set enrichment analysis was performed to identify biological pathways enriched with respect to the top 206 genes (with 20737 genes as background) whose spatial expression pattern positively correlated with (a) the t-statistic values of fALFF, (b) the t-statistic values of ReHo, from GO molecular function, MsigDB C5<sup>6</sup>. Only significantly enriched gene sets (FDR adjusted,  $P < 0.05$ ) are represented. Pathway analysis was conducted using MAGMA<sup>3</sup> gene-set analysis in FUMA<sup>4</sup>.

## Supplementary Figure 14

### Cross-sectional Samples

560 individuals with schizophrenia (SZ) and 540 normal controls (NC) from seven independent sites

SZ: n = 92 NC: n = 98 PKU6 site	SZ: n = 83 NC: n = 59 HLG site	SZ: n = 90 NC: n = 54 XIAN site	SZ: n = 81 NC: n = 102 XX_1 site	SZ: n = 49 NC: n = 69 XX_2 site	SZ: n = 82 NC: n = 89 WUHAN site	SZ: n = 83 NC: n = 69 ZMD site
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### Longitudinal Samples

95 individuals with schizophrenia (SZ) from two independent sites managed with 6-week antipsychotic treatment

SZ: n = 37 PKU6 site	SZ: n = 58 ZMD site
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### Validation Samples

280 individuals with schizophrenia (SZ), 50 individuals with obsessive-compulsive disorder (OCD), 39 individuals with attention deficit hyperactivity disorder (ADHD), 141 individuals with bipolar disorder (BP), and 431 normal controls (NC) from five independent sites

SZ: n = 30 NC: n = 29 BP: n = 25 OCD: n = 30 DEP: n = 27 PKU6_2 site	SZ: n = 30 NC: n = 29 BP: n = 30 KM site	SZ: n = 81 NC: n = 102 BP: n = 41 XX_1 site	SZ: n = 47 NC: n = 115 BP: n = 45 DEP: n = 92 ADHD: n = 39 UCLA site	SZ: n = 92 NC: n = 98 OCD: n = 20 PKU6 site
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**Supplementary Figure 14. Diagram for study participants.** From top to bottom: cross-sectional samples, longitudinal samples and validation samples. PKU6: Peking University Sixth Hospital. HLG: Beijing Huilongguan Hospital. XIAN: Xijing Hospital. XX\_1: Henan Mental Hospital with SIEMENS scanner. XX\_2: Henan Mental Hospital with GE scanner. WUHAN: Renmin Hospital of Wuhan University. ZMD: Zhumadian Psychiatric Hospital. PKU6\_2: Peking University Sixth Hospital with a different MR scanner. KM: First People's Hospital of Kunming. UCLA: UCLA Consortium for Neuropsychiatric Phenomics dataset<sup>7</sup>.

**Supplementary Table 1. Demographic and clinical characteristics of participants, stratified according to site.**

Sites	Number	Age (y)	Duration (y)	Sex (M/F)	PANSS positive	PANSS negative	PANSS general	MR scanner	TSNR	Mean FD (mm)
<b>PKU6</b>	Control 98	25.8 (5.3)		53 / 45						0.11 (0.04)
	Patient 92	27.4 (6.7)	4.7 (4.6)	57 / 35	23.6 (4.3)	18.3(5.8)	35.7 (5.3)	Siemens Trio 3T	79.2 (18.9)	0.14 (0.07)
<b>HLG</b>	Control 59	25.3 (5.4)		31 / 28						0.15 (0.08)
	Patient 83	29.6 (8.7)	5.9 (5.5)	33 / 50	25.8 (4.2)	16.2 (3.7)	35.4 (5.5)	Siemens Trio 3T	76.0 (13.4)	0.16 (0.11)
<b>XIAN</b>	Control 54	31.0 (6.9)		31 / 23						0.13 (0.07)
	Patient 90	25.7 (6.4)	1.8 (2.4)	51 / 39	22.6 (5.0)	22.3 (6.8)	44.7 (8.4)	Siemens Trio 3T	75.7 (14.3)	0.13 (0.06)
<b>XX_1</b>	Control 102	29.2 (7.2)		53 / 49						0.12 (0.06)
	Patient 81	26.0 (5.3)	3.2 (3.2)	43 / 38	22.5 (2.9)	19.6 (5.3)	39.0 (5.4)	Siemens Verio 3T	61.8 (9.5)	0.13 (0.08)
<b>XX_2</b>	Control 69	30.8 (7.2)		35 / 34						0.14 (0.07)
	Patient 49	29.5 (7.5)	3.9 (4.8)	28 / 21	24.4 (3.6)	23.4 (5.3)	40.1 (6.5)	GE Signa HDx 3T	81.3 (19.0)	0.14 (0.08)
<b>WUHAN</b>	Control 89	26.2 (6.3)		46 / 43						0.01 (0.05)
	Patient 82	24.7 (4.7)	4.0 (3.9)	30 / 52	23.5 (4.8)	20.8 (6.3)	42.7 (8.8)	GE Signa HDxt 3T	89.9 (21.9)	0.12 (0.10)
<b>ZMD</b>	Control 69	34.2 (7.5)		28 / 41						0.13 (0.09)
	Patient 83	29.8 (7.5)	4.7 (4.6)	48 / 35	24.5 (4.7)	20.6 (5.4)	39.7 (6.2)	GE Signa HDxt 3T	91.8 (20.5)	0.14 (0.09)

**Supplementary Table 2. Comparison of standard deviation (SD) for schizophrenia patients (SZ) and healthy controls (NC), in terms of FSA scores and scores derived from classification from whole-brain functional connectivity (AAL atlas and Power's parcellation, with striatum excluded).**

Site	FSA score in SZ / NC	P value	score by AAL in SZ / NC	P value	score by Power in SZ / NC	P value
<b>PKU6</b>	<b>SD = 0.61 / 0.43</b>	<i>P</i> = .00089	SD = 0.62 / 0.51	<i>P</i> = .07	<b>SD = 0.48 / 0.36</b>	<i>P</i> = .0053
<b>HLG</b>	<b>SD = 0.54 / 0.38</b>	<i>P</i> = .011	<b>SD = 0.65 / 0.47</b>	<i>P</i> = .01	SD = 0.45 / 0.44	<i>P</i> = .86
<b>XIAN</b>	SD = 0.62 / 0.51	<i>P</i> = .16	SD = 0.59 / 0.61	<i>P</i> = .78	SD = 0.46 / 0.41	<i>P</i> = .35
<b>XX_1</b>	<b>SD = 0.50 / 0.40</b>	<i>P</i> = .024	SD = 0.59 / 0.56	<i>P</i> = .58	SD = 0.30 / 0.32	<i>P</i> = .53
<b>XX_2</b>	SD = 0.61 / 0.55	<i>P</i> = .41	SD = 0.60 / 0.67	<i>P</i> = .40	SD = 0.43 / 0.52	<i>P</i> = .19
<b>WUHAN</b>	<b>SD = 0.66 / 0.43</b>	<i>P</i> = .00012	SD = 0.53 / 0.55	<i>P</i> = .75	SD = 0.35 / 0.38	<i>P</i> = .48
<b>ZMD</b>	<b>SD = 0.69 / 0.53</b>	<i>P</i> = .029	SD = 0.50 / 0.54	<i>P</i> = .46	SD = 0.35 / 0.36	<i>P</i> = .69

Significantly different variances between NC and SZ are represented in red (two-sided F-test, *P* < .05) From top to bottom: 1) Peking University Sixth Hospital (PKU6, n = 92 SZ, n = 98 NC). 2) Beijing Huilongguan Hospital (HLG, n = 83 SZ, n = 90 NC). 3) Xijing Hospital (XIAN, n = 90 SZ, n = 54). 4) Henan Mental Hospital with SIEMENS scanner (XX\_1, n = 81 SZ, n = 102 NC) 5) Henan Mental Hospital with GE scanner (XX\_2, n = 49 SZ, n = 69 NC) 6) Renmin Hospital of Wuhan University (WUHAN, n = 82 SZ, n = 89 NC). 7) Zhumadian Psychiatric Hospital (ZMD, n = 83 SZ, n = 69 NC).

**Supplementary Table 3. Characteristics of antipsychotic-naïve patients, acute antipsychotic-exposure patients, and chronic patients with a long medication history.**

	First-episode patients (minimal prior exposure to antipsychotics)	Chronic patients	P value
	Antipsychotic-naïve	Medication at baseline	
N	41	85	227
Age	26.6 (6.7)	25.2 (6.2)	30.0 (7.5) <i>P</i> = 0.50
Gender (M / F)	22 / 19	48 / 37	118 / 109 <i>P</i> = 0.69
PANSS positive	22.6 (5.8)	24.1 (4.1)	24.2 (4.5) <i>P</i> = 0.19
PANSS negative	19.9 (6.1)	18.9 (5.7)	19.6 (5.9) <i>P</i> = 0.09
PANSS general	41.1 (10.1)	39.8 (7.4)	39.0(7.4) <i>P</i> = 0.57
PANSS Total	83.5 (16.9)	82.8 (13.5)	82.9 (13.3) <i>P</i> = 0.88
Duration of illness	0.15y (0.36)	0.21y (0.41)	7.48y (4.46) <i>P</i> < .0001
CPZ-eq at scanning	N/A	394 (194)	452.8 (219) <i>P</i> = 0.02
Sensitivity	78.05%	78.82%	81.50%
<b>FSA score</b>	<b>-0.61 (0.87)</b>	<b>-0.45 (0.77)</b>	<b>-0.66 (0.83)</b> <i>P</i> = 0.36

The FSA score was controlled for MR scanners, and the z score residual is shown. The *P* values were obtained by a one-way ANOVA.

The definition of first-episode schizophrenia patients with minimal prior exposure to antipsychotics was referenced from the standard of the European First Episode Schizophrenia Trial<sup>8</sup> (EUFEST): Patients with a DSM-IV diagnosis of schizophrenia, whose duration of illness were less than six months were further confirmed as schizophrenic by at least a 6-month follow-up; patients were excluded if they were not in the first episode; patients were excluded if more than 2 years had passed since the onset of positive symptoms ; patients were excluded if any antipsychotic drug had been used for more than 2 weeks in the previous years, or for 6 weeks at any time. The definition of chronic patients was referenced from the standard of the Clinical Antipsychotic Trials of Intervention Effectiveness<sup>9</sup> (CATIE) Project: Patients with a DSM-IV diagnosis of schizophrenia; patients in their first episode of schizophrenia were excluded; patients were excluded if they first began antipsychotic drug-treatment for psychosis within the previous 12 months and have had psychotic symptoms for less than 3 years (in our case, we used a more conservative definition to check for long-term medication effects).

**Supplementary Table 4. Study sample characteristics of diverse first-episode schizophrenia patients, chronic patients, and patients with missing medication information**

	First-episode schizophrenia patients			Chronic schizophrenia patients		Missing information
N	Antipsychotic-naïve	Medication at baseline	Other FE patients	< 2 years medication	≥ 2 years medication	
	41	85	94	71	227	42
Age	26.6 (6.7)	25.2 (6.2)	25.3 (6.9)	27.5 (6.1)	30.0 (7.5)	26.4 (6.4)
Gender (M / F)	22 / 19	48 / 37	47 / 47	39 / 32	118 / 109	16 / 26
PANSS positive	22.6 (5.8)	24.1 (4.1)	23.3 (4.0)	23.9 (4.4)	24.2 (4.5)	23.3 (4.1)
PANSS negative	19.9 (6.1)	18.9 (5.7)	20.9 (5.9)	20.5 (6.6)	19.6 (5.9)	21.1 (6.2)
PANSS general	41.1 (10.1)	39.8 (7.4)	39.7(6.2)	39.2 (7.4)	39 (7.4)	41 (7.8)
PANSS Total	83.5 (16.9)	82.8 (13.5)	83.8 (10.5)	83.6 (13.4)	82.9 (13.3)	85.4 (12.2)
Duration of illness	0.15y (0.36)	0.21y (0.41)	0.53y (0.50)	3.28 (2.22)	7.48 (4.46)	
CPZ-eq at scanning	N/A	394 (194)	415 (214)	349 (207)	453 (219)	467 (228)
FSA score	-0.61 (0.87)	-0.45 (0.77)	-0.63 (0.97)	-0.62 (0.96)	-0.66 (0.83)	-0.76 (0.85)

The FSA score was controlled for MR scanners, and the z score residual is shown.

The definitions of ‘antipsychotic-naïve patients’, ‘medication at baseline’ and ‘Chronic schizophrenia patients (≥ 2 years medication)’ were consistent with the description in Supplementary Table 3. Other FE patients: individuals with schizophrenia who had had psychotic symptoms for less than 2 years and were not classified in Supplementary Table 3; chronic schizophrenia patients (< 2 years medication): patients who had had psychotic symptoms for over 2 years and first began antipsychotic drug-treatment for psychosis within two years. The grouping strategy ensures that the duration of all first-episode patients were less than 2 years. Missing information: patients for whom illness duration or medication information was lacking.

**Supplementary Table 5. Study sample characteristics of medicated and unmedicated schizophrenia groups at the time of scanning**

	Medicated at scanning	Not medicated at scanning	P value
N	377	111	
Age	27.4 (6.9)	27.2 (6.6)	P = 0.77
Gender (M / F)	195 / 182	58 / 53	P = 0.92
PANSS positive	24.0 (4.3)	22.3 (4.9)	P = 0.0005
PANSS negative	20.4 (5.8)	20.5 (6.7)	P = 0.85
PANSS general	39.8 (6.9)	40.9 (9.2)	P = 0.17
PANSS Total	84.2 (12.2)	83.8 (15.7)	P = 0.76
CPZ-eq at scanning	422.6 (214.6)		
Antipsychotic drugs	risperidone (36.1%), olanzapine (23.1%), clozapine (9.5%), aripiprazole (8.2%), quetiapine (5.8%), ziprasidone (4.2%), amisulpride (4.0%), paliperidone (3.2%), blonanserin (2.4%), haloperidol (2.1%), sulpiride (0.8%), iloperidone (0.3%), promethazine (0.3%)		
Sensitivity	79.05%	79.28%	
FSA score	-0.62 (0.87)	-0.65 (0.85)	P = 0.74

The FSA score was controlled for MR scanners, and the z-score residual is shown. The P values were obtained by unpaired two-sided t-test. From 560 individuals with schizophrenia, we ascertained whether 488 of the schizophrenia individuals were or were not taking antipsychotic medication at the time of scanning.

**Supplementary Table 6. Medication and clinical information for the longitudinal patients assessed in the study (Part I)**

ID	hospital	age	gender	duration of illness (m)	baseline FSA score	baseline PANSS positive	baseline PANSS negative	baseline PANSS general	baseline PANSS score
SZ_01	PKU6	18	Female	9	0.067752952	22	13	35	70
SZ_02	PKU6	18	Male	15	-0.230773383	23	21	36	80
SZ_03	PKU6	21	Female	12	-0.47336054	30	24	30	84
SZ_04	PKU6	42	Female	31	-0.12706805	31	19	32	82
SZ_05	PKU6	39	Female	6	-0.51270061	32	21	44	97
SZ_06	PKU6	38	Male	12	0.917287545	23	22	37	82
SZ_07	PKU6	31	Female	96	-0.58755228	29	21	52	102
SZ_08	PKU6	36	Female	120	-0.50158165	20	25	31	76
SZ_09	PKU6	25	Female	36	-0.43630533	24	24	40	88
SZ_10	PKU6	21	Male	6	-0.06412662	27	29	33	89
SZ_11	PKU6	23	Male	65	-1.33243017	16	26	36	78
SZ_12	PKU6	24	Male	48	-0.13955545	17	21	34	72
SZ_13	PKU6	29	Male	2	0.776327791	25	11	37	73
SZ_14	PKU6	32	Male	5	-0.28964393	28	11	38	77
SZ_15	PKU6	20	Male	60	-0.45025637	23	19	30	72
SZ_16	PKU6	35	Female	11	-0.5309067	25	14	48	87
SZ_17	PKU6	38	Male	24	0.654035975	28	17	34	79
SZ_18	PKU6	25	Female	132	0.064537484	30	15	41	86
SZ_19	PKU6	23	Male	72	0.161081417	22	21	28	71
SZ_20	PKU6	42	Female	48	-0.48742732	23	13	46	82
SZ_21	PKU6	34	Male	180	-0.37934055	30	30	34	94
SZ_22	PKU6	24	Male	84	-0.27119551	24	18	39	81
SZ_23	PKU6	46	Female	228	-0.94282669	26	27	45	98
SZ_24	PKU6	39	Male	180	-0.52785225	22	19	33	74
SZ_25	PKU6	18	Male	36	-0.32533748	16	29	28	73
SZ_26	PKU6	29	Male	63	0.097171118	26	19	40	85
SZ_27	PKU6	24	Male	27	-0.4499272	26	7	28	61
SZ_28	PKU6	24	Female	13	-0.07204683	23	26	43	92

SZ_29	PKU6	27	Female	60	-0.60006449	22	14	36	72
SZ_30	PKU6	25	Female	1	0.258797237	26	13	32	71
SZ_31	PKU6	18	Male	13	0.148829966	20	14	36	70
SZ_32	PKU6	20	Male	36	0.306091032	26	18	35	79
SZ_33	PKU6	19	Male	8	-0.90053732	19	26	32	77
SZ_34	PKU6	24	Male	36	-0.06466794	19	19	35	73
SZ_35	PKU6	31	Female	48	-0.08809527	22	17	38	77
SZ_36	PKU6	31	Female	132	0.495066889	22	13	38	73
SZ_37	PKU6	28	Female	48	0.191426655	27	18	40	85
SZ_38	ZMD	41	Male	1	-0.13785127	22	32	47	101
SZ_39	ZMD	24	Female	25	-0.17125278	33	19	41	93
SZ_40	ZMD	42	Female	85	-0.21148693	28	15	40	83
SZ_41	ZMD	29	Female	60	-0.56162131	28	24	31	83
SZ_42	ZMD	21	Male	24	-0.94483843	25	25	35	85
SZ_43	ZMD	38	Male	15	-0.94041833	22	20	32	74
SZ_44	ZMD	20	Male	6	-1.37701889	21	23	30	74
SZ_45	ZMD	18	Male	9	-0.00142718	19	19	32	70
SZ_46	ZMD	33	Female	12	-0.88156184	23	16	35	74
SZ_47	ZMD	35	Female	74	-1.32631046	22	19	36	77
SZ_48	ZMD	39	Male	36	-0.95333091	25	18	41	84
SZ_49	ZMD	23	Male	1	-0.64335693	18	21	29	68
SZ_50	ZMD	38	Female	16	-0.5849454	36	15	46	97
SZ_51	ZMD	27	Female	132	0.274837667	27	29	50	106
SZ_52	ZMD	42	Female	240	-2.57394874	18	17	38	73
SZ_53	ZMD	30	Male	102	-1.62106269	23	24	41	88
SZ_54	ZMD	33	Female	14	-0.91127678	32	19	42	93
SZ_55	ZMD	22	Male	79	-0.1972116	26	14	41	81
SZ_56	ZMD	45	Female	96	-0.57341013	22	11	47	80
SZ_57	ZMD	25	Male	49	-1.49465324	29	29	39	97
SZ_58	ZMD	36	Female	24	-0.75894906	26	27	52	105
SZ_59	ZMD	41	Male	10	-0.78733918	27	15	37	79
SZ_60	ZMD	22	Male	13	-0.51681741	20	25	38	83

SZ_61	ZMD	29	Male	60	-0.16150379	25	22	42	89
SZ_62	ZMD	19	Male	6	-0.02746253	22	16	39	77
SZ_63	ZMD	20	Male	27	-1.45113145	22	20	37	79
SZ_64	ZMD	24	Male	48	-0.45896564	24	22	45	91
SZ_65	ZMD	22	Male	48	-1.41827145	22	22	43	87
SZ_66	ZMD	28	Female	156	-0.46614749	33	29	51	113
SZ_67	ZMD	40	Male	108	-0.52406079	21	17	28	66
SZ_68	ZMD	20	Male	6	-0.05959739	19	13	32	64
SZ_69	ZMD	19	Female	37	-0.37671754	28	20	43	91
SZ_70	ZMD	39	Male	120	0.010382924	25	35	53	113
SZ_71	ZMD	23	Male	2	-0.54506123	21	25	38	84
SZ_72	ZMD	23	Male	12	1.036701981	23	25	38	86
SZ_73	ZMD	41	Female	120	-0.90638575	24	18	46	88
SZ_74	ZMD	24	Male	40	0.912101069	20	21	40	81
SZ_75	ZMD	34	Male	120	-0.40865806	25	9	41	75
SZ_76	ZMD	24	Male	24	-1.17100321	20	15	33	68
SZ_77	ZMD	42	Female	240	-0.78359868	37	25	56	118
SZ_78	ZMD	30	Female	126	0.591283833	36	24	43	103
SZ_79	ZMD	22	Female	24	-0.94294164	32	16	40	88
SZ_80	ZMD	23	Female	108	-0.46575415	25	25	37	87
SZ_81	ZMD	38	Female	193	-0.25798841	22	22	38	82
SZ_82	ZMD	36	Female	21	-0.46892244	22	21	39	82
SZ_83	ZMD	37	Male	50	-0.38246777	22	19	31	72
SZ_84	ZMD	22	Male	25	-0.85632751	23	18	35	76
SZ_85	ZMD	36	Male	61	-0.12232073	27	29	52	108
SZ_86	ZMD	30	Male	157	-1.77462028	24	18	38	80
SZ_87	ZMD	26	Female	6	-1.15447337	23	22	37	82
SZ_88	ZMD	22	Female	6	-1.12457077	22	23	40	85
SZ_89	ZMD	37	Male	123	-1.19063817	23	23	38	84
SZ_90	ZMD	33	Male	1	-1.19871755	22	19	38	79
SZ_91	ZMD	33	Female	88	-0.35682725	22	23	47	92
SZ_92	ZMD	21	Male	61	-0.6621351	19	13	32	64

SZ_93	ZMD	34	Male	25	-0.95502507	20	14	36	70
SZ_94	ZMD	38	Male	74	0.441531917	22	21	38	81
SZ_95	ZMD	36	Male	13	0.186576187	22	15	37	74

**Supplementary Table 6. Medication and clinical information of the longitudinal patients assessed in the study (Part II)**

ID	hospital	follow-up PANSS positive	follow-up PANSS negative	follow-up PANSS general	follow-up PANSS score	Drugs	dosage (mg/day)	chlorpromazine equivalents (CPZ-eq, mg/day)
SZ_01	PKU6	10	15	24	49	Aripiprazole	0-12.5	0-250
SZ_02	PKU6	18	21	32	71	Olanzapine	12.5-15	350-400
SZ_03	PKU6	14	17	22	53	Risperidone	5.0-6.0	500-600
SZ_04	PKU6	7	9	24	40	Risperidone	3.0-6.0	300-600
SZ_05	PKU6	20	13	33	66	Olanzapine	10.0-15.0	300-400
SZ_06	PKU6	8	9	17	34	Olanzapine	20	600
SZ_07	PKU6	21	18	42	81	Amisulpride	900-1200	900-1200
SZ_08	PKU6	10	14	25	49	Risperidone	6	600
SZ_09	PKU6	18	19	28	65	Olanzapine	20	600
SZ_10	PKU6	15	23	32	70	Risperidone	0-6	0-600
SZ_11	PKU6	16	25	33	74	Olanzapine	20	600
SZ_12	PKU6	15	17	23	55	Amisulpride	900-1200	900-1200
SZ_13	PKU6	9	7	20	36	Risperidone	4	400
SZ_14	PKU6	19	10	25	54	Quetiapine	400	300
SZ_15	PKU6	16	20	26	62	Risperidone	4.0-6.0	400-600
SZ_16	PKU6	12	15	30	57	Aripiprazole	20	400
SZ_17	PKU6	25	17	26	68	Quetiapine	0-400	0-300
SZ_18	PKU6	15	16	25	56	Olanzapine	20	600
SZ_19	PKU6	14	17	22	53	Amisulpride	1200	1200
SZ_20	PKU6	22	11	39	72	Aripiprazole	25	500
SZ_21	PKU6	15	31	32	78	Olanzapine	5.0-20.0	150-600
SZ_22	PKU6	16	16	27	59	Blonanserin	16-24	400-600
SZ_23	PKU6	21	21	38	80	Risperidone	3.0-8.0	300-800
SZ_24	PKU6	19	15	31	65	Paliperidone	12	600

SZ_25	PKU6	13	22	24	59	Blonanserin	24	600
SZ_26	PKU6	16	27	30	73	Risperidone	3.0-8.0	300-800
SZ_27	PKU6	11	7	21	39	Olanzapine	20	600
SZ_28	PKU6	10	26	24	60	Risperidone	2.0-4.0	200-400
SZ_29	PKU6	9	12	23	44	Olanzapine	20	600
SZ_30	PKU6	14	8	22	44	Amisulpride	900	900
SZ_31	PKU6	12	10	20	42	Paliperidone	3.0-12.0	100-600
SZ_32	PKU6	7	11	17	35	Olanzapine	10-17.5	300-575
SZ_33	PKU6	15	26	24	65	Amisulpride	800-1300	800-1300
SZ_34	PKU6	16	18	31	65	Olanzapine	15.0-20	400-600
SZ_35	PKU6	16	17	32	65	Risperidone	5	500
SZ_36	PKU6	13	7	24	44	Paliperidone	6	300
SZ_37	PKU6	17	11	28	56	Olanzapine	5.0-10	150-300
SZ_38	ZMD	12	14	25	51	Clozapine	100-200	200-400
SZ_39	ZMD	7	10	20	37	Risperidone	4.0-6.0	400-600
SZ_40	ZMD	7	9	16	32	Clozapine	100-150	200-300
SZ_41	ZMD	7	10	18	35	Clozapine	50-300	100-600
SZ_42	ZMD	8	14	21	43	Risperidone	2.0-5.0	200-500
SZ_43	ZMD	10	12	26	48	Risperidone	4	400
SZ_44	ZMD	9	20	34	63	Risperidone	4	400
SZ_45	ZMD	7	15	23	45	Clozapine	200-300	400-600
SZ_46	ZMD	11	7	19	37	Risperidone	2.0-4.0	200-400
SZ_47	ZMD	9	12	25	46	Risperidone	4	400
SZ_48	ZMD	17	17	38	72	Risperidone	4	400
SZ_49	ZMD	7	7	18	32	Risperidone	4	400
SZ_50	ZMD	7	10	18	35	Clozapine	50-150	100-300
SZ_51	ZMD	8	11	23	42	Clozapine	100-150	200-300
SZ_52	ZMD	7	13	21	41	Clozapine	250-300	500-600
SZ_53	ZMD	16	11	26	53	Risperidone	6	600
SZ_54	ZMD	22	14	31	67	Quetiapine	600	400
SZ_55	ZMD	7	7	20	34	Clozapine	200-350	400-700
SZ_56	ZMD	7	7	19	33	Risperidone	4	400

SZ_57	ZMD	13	13	24	50	Risperidone	6	600
SZ_58	ZMD	11	13	26	50	Aripiprazole	20	400
SZ_59	ZMD	15	7	19	41	Clozapine	0-350	0-700
SZ_60	ZMD	10	18	25	53	Olanzapine	10.0-20.0	300-600
SZ_61	ZMD	9	19	23	51	Risperidone	3.0-4.0	300-400
SZ_62	ZMD	7	7	18	32	Risperidone	2.0-3.0	200-300
SZ_63	ZMD	12	12	23	47	Risperidone	1.0-5.0	100-500
SZ_64	ZMD	12	22	24	58	Risperidone	6	600
SZ_65	ZMD	9	17	25	51	Olanzapine	10.0-30.0	300-800
SZ_66	ZMD	8	14	22	44	Risperidone	2.0-5.0	200-500
SZ_67	ZMD	7	7	16	30	Risperidone	2.0-5.0	200-500
SZ_68	ZMD	7	7	18	32	Risperidone	2.0-4.0	200-400
SZ_69	ZMD	19	12	33	64	Aripiprazole	20	400
SZ_70	ZMD	8	16	27	51	Clozapine	100-350	200-700
SZ_71	ZMD	12	11	24	47	Clozapine	50-200	100-400
SZ_72	ZMD	7	11	18	36	Risperidone	2.0-5.0	200-500
SZ_73	ZMD	15	9	32	56	Olanzapine	15	400
SZ_74	ZMD	7	11	21	39	Olanzapine	20	600
SZ_75	ZMD	7	7	18	32	Risperidone	2.0-4.0	200-400
SZ_76	ZMD	11	9	26	46	Olanzapine	10.0-20.0	300-600
SZ_77	ZMD	12	16	29	57	Clozapine	150-200	300-400
SZ_78	ZMD	12	10	25	47	Risperidone	4	400
SZ_79	ZMD	16	9	27	52	Risperidone	2.0-4.0	200-400
SZ_80	ZMD	9	22	31	62	Risperidone	4	400
SZ_81	ZMD	8	18	26	52	Clozapine	100-300	200-600
SZ_82	ZMD	8	18	32	58	Clozapine	50-300	100-600
SZ_83	ZMD	7	12	20	39	Clozapine	150-300	300-600
SZ_84	ZMD	11	11	23	45	Risperidone	4	400
SZ_85	ZMD	11	16	28	55	Risperidone	1.0-6.0	100-600
SZ_86	ZMD	9	17	25	51	Amisulpride	800-1200	800-1200
SZ_87	ZMD	12	16	34	62	Risperidone	0-4	0-400
SZ_88	ZMD	7	15	25	47	Risperidone	4	400

SZ_89	ZMD	7	14	22	43	Clozapine	250-300	500-600
SZ_90	ZMD	8	16	25	49	Clozapine	100-200	200-400
SZ_91	ZMD	7	14	26	47	Risperidone	4	400
SZ_92	ZMD	9	7	19	35	Clozapine	100-300	200-600
SZ_93	ZMD	8	7	22	37	Risperidone	4	400
SZ_94	ZMD	7	12	22	41	Clozapine	50-250	100-500
SZ_95	ZMD	11	7	23	41	Olanzapine	0-20	0-600

**Supplementary Table 7 (part I). Demographic information for validation samples in Dataset 1.**

	Dataset 1				
Group	Healthy controls	Schizophrenia	Bipolar Disorder	Depression	OCD
N	29	30	25	27	30
Age	25.4 (4.2)	29.3 (6.6)	30.1 (8.4)	24.9 (5.2)	29.3 (6.4)
Gender (M / F)	15 / 14	15 / 15	13 / 12	13 / 14	15 / 15
Diagnostic type	N/A	Schizophrenia (30)	Bipolar I Disorder (25)	Depression (27)	Obsessive-Compulsive disorder (30)
Racial and ethnic categories	Asian (Han Chinese)				
FSA score	0.28 (0.57)	-0.61 (0.64)	-0.035 (0.58)	0.25 (0.69)	-0.045 (0.72)

**Supplementary Table 7 (part II). Demographic information for validation samples in Dataset 2.**

	Dataset 2		
Group	Healthy controls	Schizophrenia	Bipolar Disorder
N	29	30	30
Age	34.5 (9.8)	25.3 (8.3)	28.6 (8.5)
Gender (M / F)	7 / 22	14 / 16	12 / 18
Diagnostic type	N/A	Schizophrenia (30)	Bipolar Disorder (30)
Racial and ethnic categories	Asian (Han Chinese)		
FSA score	0.23 (0.66)	-0.31 (0.52)	-0.037 (0.60)

**Supplementary Table 7 (part III). Demographic information for validation samples in Datasets 3-5.**

	Dataset 3	Dataset 4 (UCLA Consortium for Neuropsychiatric Phenomics)				Dataset 5
Group	Bipolar Disorder	Healthy controls	Schizophrenia	Bipolar Disorder	ADHD	OCD
N	41	115	47	45	39	20
Age	33.0 (9.4)	31.3 (8.6)	36.5 (8.7)	35.0 (8.9)	31.6 (10.0)	27.6 (7.6)
Gender (M / F)	23 / 18	61 / 54	35 / 12	26 / 19	20 / 19	10 / 10
Diagnostic type	Bipolar I Disorder (41)	N/A	Schizophrenia (36) Schizoaffective Disorder (11)	Bipolar I Disorder (45)	Attention-Deficit/Hyperactivity Disorder (39)	Obsessive-Compulsive disorder (20)
Racial and ethnic categories	Asian (Han Chinese)	White; Hispanic or Latino				Asian (Han Chinese)
FSA score	- 0.19 (0.48)	0.304 (0.89)	-0.721 (1.00)	-0.175 (0.91)	0.173 (0.93)	0.35 (0.69)

**Supplementary Table 8. Description of Threat Risk Assessment Scale**

Threat Risk Assessment Scale	
Level 1	Verbal threats, shouting, but no beating and smashing behaviors.
Level 2	Having beating and smashing behaviors, but limited to at home, to property. Can be persuaded to stop.
Level 3	Having obvious beating and smashing behaviors, regardless of occasion, to property. Cannot be persuaded to stop.
Level 4	Continuous beating and smashing behaviors, regardless of the occasion, to property or person, cannot be persuaded to stop.
Level 5	Any violent act against a person with controlled dangerous weapons, or arson, explosion, etc. whether at home or in public.

**Supplementary Table 9. Technical details of the MRI, software and head coils for the seven scanners used.**

Site	MRI & Software	Head coil
<b>PKU6</b>	Siemens Trio 3T (syngo MR B17)	Head/Neck 20 coil (12 channels for head and 8 channels for neck)
<b>XX_2</b>	GE Signa HDx 3T (15\lx\mr Software release.15.0.M4A.0947.)	8-channel head and neck (HDNV) coil
<b>XX_1</b>	Siemens Verio 3T (syngo MR B17)	12-channel head coilin
<b>WUHAN</b>	GE Signa HDxt 3T (5\lx\mr Software release.15.0.M4A.0947.a)	8-channel head coil
<b>XIAN</b>	Siemens Trio 3T (syngo MR B15)	Head/Neck 20 coil (12 channels for head and 8 channels for neck)
<b>ZMD</b>	GE Signa HDxt 3T (24\lx\mr Software release.HD16.0.V02.1131.a)	8-channel head and neck (HDNV) coil

**Supplementary Table 10. Performance of the classification model using whole-brain functional connectivity based on the AAL atlas<sup>10</sup> (striatum excluded).**

	PKU6	HLG	XIAN	XX1	XX2	WUHAN	ZMD
<b>Sensitivity</b>	72.8%	78.3%	76.7%	88.9%	79.6%	90.2%	89.2%
<b>Specificity</b>	79.6%	89.8%	85.2%	65.7%	82.6%	73.0%	81.2%
<b>PPV (positive predictive value)</b>	77.0%	91.5%	89.6%	67.2%	76.5%	75.5%	85.1%
<b>NPV (negative predictive value)</b>	75.7%	74.6%	68.7%	88.2%	85.1%	89.0%	86.2%
<b>Accuracy</b>	76.3%	83.1%	79.9%	76.0%	81.4%	81.3%	85.5%

**Supplementary Table 11. Performance of the classification model using whole-brain functional connectivity based on the Power's parcellation<sup>11</sup> (striatum excluded).**

	PKU6	HLG	XIAN	XX1	XX2	WUHAN	ZMD
<b>Sensitivity</b>	79.3%	74.7%	76.7%	44.1%	77.6%	92.7%	84.3%
<b>Specificity</b>	84.7%	81.4%	87.0%	92.6%	85.5%	71.9%	75.4%
<b>PPV (positive predictive value)</b>	83.0%	84.9%	90.8%	88.2%	79.2%	75.2%	80.5%
<b>NPV (negative predictive value)</b>	81.4%	69.6%	69.1%	56.8%	84.3%	91.4%	80.0%
<b>Accuracy</b>	82.1%	77.5%	80.6%	65.6%	82.2%	81.9%	80.2%

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Section & Topic	No	Item	Reported on page #
<b>TITLE OR ABSTRACT</b>			
	<b>1</b>	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	3
<b>ABSTRACT</b>	<b>2</b>	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	3
<b>INTRODUCTION</b>			
	<b>3</b>	Scientific and clinical background, including the intended use and clinical role of the index test	4
	<b>4</b>	Study objectives and hypotheses	4
<b>METHODS</b>			
<i>Study design</i>	<b>5</b>	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	17
<i>Participants</i>	<b>6</b>	Eligibility criteria	17
	<b>7</b>	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	17
	<b>8</b>	Where and when potentially eligible participants were identified (setting, location and dates)	17
	<b>9</b>	Whether participants formed a consecutive, random or convenience series	17 , 18
<i>Test methods</i>	<b>10a</b>	Index test, in sufficient detail to allow replication	22
	<b>10b</b>	Reference standard, in sufficient detail to allow replication	22
	<b>11</b>	Rationale for choosing the reference standard (if alternatives exist)	22
	<b>12a</b>	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	15
	<b>12b</b>	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	15
	<b>13a</b>	Whether clinical information and reference standard results were available to the performers/readers of the index test	18
	<b>13b</b>	Whether clinical information and index test results were available to the assessors of the reference standard	18
<i>Analysis</i>	<b>14</b>	Methods for estimating or comparing measures of diagnostic accuracy	22
	<b>15</b>	How indeterminate index test or reference standard results were handled	Not Applicable
	<b>16</b>	How missing data on the index test and reference standard were handled	Not Applicable
	<b>17</b>	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	18
	<b>18</b>	Intended sample size and how it was determined	Not Applicable
<b>RESULTS</b>			
<i>Participants</i>	<b>19</b>	Flow of participants, using a diagram	18
	<b>20</b>	Baseline demographic and clinical characteristics of participants	17
	<b>21a</b>	Distribution of severity of disease in those with the target condition	17
	<b>21b</b>	Distribution of alternative diagnoses in those without the target condition	17
	<b>22</b>	Time interval and any clinical interventions between index test and reference standard	18
<i>Test results</i>	<b>23</b>	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	15
	<b>24</b>	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	15
	<b>25</b>	Any adverse events from performing the index test or the reference standard	Not Applicable
<b>DISCUSSION</b>			
	<b>26</b>	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	9 , 10
	<b>27</b>	Implications for practice, including the intended use and clinical role of the index test	10
<b>OTHER INFORMATION</b>			
	<b>28</b>	Registration number and name of registry	Not Applicable
	<b>29</b>	Where the full study protocol can be accessed	31
	<b>30</b>	Sources of funding and other support; role of funders	10 , 11



# STARD 2015

## AIM

STARD stands for “Standards for Reporting Diagnostic accuracy studies”. This list of items was developed to contribute to the completeness and transparency of reporting of diagnostic accuracy studies. Authors can use the list to write informative study reports. Editors and peer-reviewers can use it to evaluate whether the information has been included in manuscripts submitted for publication.

## Explanation

A **diagnostic accuracy study** evaluates the ability of one or more medical tests to correctly classify study participants as having a **target condition**. This can be a disease, a disease stage, response or benefit from therapy, or an event or condition in the future. A medical test can be an imaging procedure, a laboratory test, elements from history and physical examination, a combination of these, or any other method for collecting information about the current health status of a patient.

The test whose accuracy is evaluated is called **index test**. A study can evaluate the accuracy of one or more index tests. Evaluating the ability of a medical test to correctly classify patients is typically done by comparing the distribution of the index test results with those of the **reference standard**. The reference standard is the best available method for establishing the presence or absence of the target condition. An accuracy study can rely on one or more reference standards.

If test results are categorized as either positive or negative, the cross tabulation of the index test results against those of the reference standard can be used to estimate the **sensitivity** of the index test (the proportion of participants *with* the target condition who have a positive index test), and its **specificity** (the proportion *without* the target condition who have a negative index test). From this cross tabulation (sometimes referred to as the contingency or “2x2” table), several other accuracy statistics can be estimated, such as the positive and negative **predictive values** of the test. Confidence intervals around estimates of accuracy can then be calculated to quantify the statistical **precision** of the measurements.

If the index test results can take more than two values, categorization of test results as positive or negative requires a **test positivity cut-off**. When multiple such cut-offs can be defined, authors can report a receiver operating characteristic (ROC) curve which graphically represents the combination of sensitivity and specificity for each possible test positivity cut-off. The **area under the ROC curve** informs in a single numerical value about the overall diagnostic accuracy of the index test.

The **intended use** of a medical test can be diagnosis, screening, staging, monitoring, surveillance, prediction or prognosis. The **clinical role** of a test explains its position relative to existing tests in the clinical pathway. A replacement test, for example, replaces an existing test. A triage test is used before an existing test; an add-on test is used after an existing test.

Besides diagnostic accuracy, several other outcomes and statistics may be relevant in the evaluation of medical tests. Medical tests can also be used to classify patients for purposes other than diagnosis, such as staging or prognosis. The STARD list was not explicitly developed for these other outcomes, statistics, and study types, although most STARD items would still apply.

## DEVELOPMENT

This STARD list was released in 2015. The 30 items were identified by an international expert group of methodologists, researchers, and editors. The guiding principle in the development of STARD was to select items that, when reported, would help readers to judge the potential for bias in the study, to appraise the applicability of the study findings and the validity of conclusions and recommendations. The list represents an update of the first version, which was published in 2003.

More information can be found on <http://www.equator-network.org/reporting-guidelines/stard>.

