Supplemental Methods

Participants

All patients received physical examination and laboratory screening to rule out medical causes for their psychotic symptoms. Patients in the first-episode schizophrenia group received double-blind treatment with either risperidone (dose range: 1-6 mg) or aripiprazole (5-30 mg) for twelve weeks. Simultaneous treatment with mood stabilizers or antidepressants was not allowed, though patients were treated with diphenhydramine or benztropine as needed for extrapyramidal symptoms, and lorazepam for akathisia, agitation, and anxiety. Patient diagnoses were based on the Structured Clinical Interview for Axis I Diagnostic and Statistical Manual-IV Disorders (SCID). Careful assessments were made to rule out a diagnosis of a substance-induced psychotic disorder. Patients were required to have a one-month period in which psychotic symptoms existed without the influence of substance intoxication or withdrawal. In our first-episode schizophrenia cohort, patients met criteria for a lifetime history of following substance use disorders: 9 for nicotine use, 2 alcohol abuse, 4 for alcohol dependence, 6 for cannabis abuse, 12 for cannabis dependence, 1 for cocaine abuse, 2 for cocaine dependence.

Exclusion criteria for the healthy control group included present use of any psychotropic medications, and the presence of any lifetime history of a major mood or psychotic disorder as determined by clinical interview using the SCID, Non-Patient edition.

Exclusion criteria for all study participants included magnetic resonance imaging contraindications (e.g., pacemaker), neurologic conditions (Gilles de la Tourette's, Huntington's Disease, Parkinson's Disease, encephalitis, strokes, aneurysms, tumors, central nervous system

infections or degenerative brain diseases), and any serious medical disorder that could affect brain functioning or the participant's capacity to provide informed consent.

Clinical raters were blind to medication status and trained according to our standardized NIMH protocol (P50MH080173). Medication adherence was assessed by pill counts and medication logs.

Eighteen patients with first episode schizophrenia were treated with aripiprazole and 22 patients were treated with risperidone. No significant differences were found in the distribution of these medications between responders and non-responders in the first-episode schizophrenia cohort.

Our generalizability cohort consisted of patients with the following diagnoses: schizophrenia (n=10), schizophreniform disorder (n=3), schizoaffective disorder (n=11), bipolar disorder I with psychosis (n=11), and psychotic disorder not otherwise specified (n=5). Four patients in out generalizability cohort were treated with first-generation antipsychotic agents alone (haloperidol, perphenazine), four were treated with clozapine, three were treated with clozapine and a first-generation agent, 28 were treated with second-generation antipsychotics other than clozapine, and one patient was treated with a non-clozapine second-generation and a first-generation agent. Due to limited numbers of subjects treated with individual medications, drug by connectivity index analyses could not be performed. Additional medications were used to treat these patients, including lithium (N=6), non-lithium mood stabilizers (n=17), benzodiazepines (n=18), anticholinergic agents (n=13), and antidepressant agents (n=7). In this cohort, 6 patients met criteria for a lifetime history of cannabis abuse, 3 for cannabis dependence, 1 for opioid dependence, and one for alcohol dependence.

Resting state scanning and preprocessing

All scans were acquired on a 3T GE Signa HDx scanner. In each scan session, an anatomical scan was acquired in the coronal plane using an inversion-recovery prepared 3D fast spoiled gradient (IR-FSPGR) sequence (TR = 7.5 ms, TE = 3 ms, TI = 650 ms matrix = 256x256, FOV = 240 mm) that produced 216 contiguous images (slice thickness = 1mm), comprising a total of 150 echo-planner imaging (EPI) volumes with the following parameters: TR = 2000 ms, TE = 30 ms, matrix = 64*64, FOV = 240 mm, slice thickness = 3 mm, 40 continuous axial oblique slices (one voxel = 3.75x3.75x3 mm). All participants were spoken to between scan sequences to ensure they were not asleep, and remembered to keep eyes closed. No behavioral differences were observed between groups during scanning.

For preprocessing of resting-state scans, FSL (http://www.fmrib.ox.ac.uk) and AFNI (http://afni.nimh.nih.gov/afni) based scripts were used. The first four EPI volumes were discarded. Each participant's structural image was normalized by a 12-parameter affine transformation to MNI152 space. This transformation was then applied to each individual's functional dataset. Rigid body motion correction was performed with FLIRT and skull stripping was performed with BET. Images were spatial smoothed with a 6-mm FWHM Gaussian kernel. The resulting time series was then high-, and low-pass filtered at 0.05 Hz and 0.1 Hz, respectively. For removal of nuisance variables, each individual's 4D time series data were regressed with eight predictors in a general linear model: white matter (WM), cerebrospinal fluid (CSF), and six motion parameters. To avoid interference with our connectivity measures, the global mean was not included in this calculation. In our generalizability cohort 4 5-minute resting state scans were obtained. Following pre-processing, the mean signal across these scans was used in subsequent analyses.

Motion correction

Both relative and absolute motion displacement were examined for each resting state scan. Head motion was calculated as a scalar quantity by the empirical formula detailed in Power et al. (1), and similarly for the other rigid body parameters. Rotational displacement was calculated by displacement on the surface of a sphere of radius 50 mm, which is approximately the mean distance from the cerebral cortex to the center of the head. Using an independent Welch t-test, we compared the distribution of frame-wise displacement. Additionally we performed a group-wise comparison of the derivative of the root mean squared variance (DVARS), which indexes the rate of change of BOLD signal across the entire brain at each frame of data (2). We used Thomas Nichols' script to calculate standardized DVARS. We observed no differences between groups in these measures ($F=1.216$, $p= 0.308$).

Functional connectivity

Our ROIs were spherical regions with a radius of 3.5mm around a seed voxel (supplemental table 1). AFNI (3dfim+) was used to create our functional maps. All relevant statistical calculations, including calculation of our prognostic score were performed in the R statistical environment (http://www.r-project.org).

Results

In our first episode schizophrenia group, no differences in our striatal connectivity index were observed between patients treated with aripiprazole versus risperidone. We observed no significant interaction between out striatal connectivity index and age, sex, level of education in both of our patient cohorts. In addition we observed no interaction between our connectivity index and duration of untreated psychosis, or exposure to antipsychotic in our first-episode schizophrenia cohort. In our first-episode cohort, 8 out of 17 non-responders (47%), and 15 out

of 24 (63%) responders were naïve to antipsychotic drug prior to scanning. No difference was found in numbers of med-naïve patients between groups (P = 0.79). No patients were naïve to antipsychotic drug at time of scanning in our generalizability cohort.

References

1 Power JD, Barnes KA, Snyder AZ, Schlaggar BL, Petersen SE. Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage* 2012; 59: 2142–54.

2 Power JD, Cohen AL, Nelson SM, *et al.* Functional Network Organization of the Human Brain. *Neuron* 2011; 72: 665–78.

TABLE S1. Location of our ROIs

Seed	MNI coordinates
Dorsal caudate	x = ±13, y = 15, z = 9
Ventral caudate	x = ±10, y = 15, z = 0
Nucleus accumbens	x = ±9, y = 9, z = -8
Dorsal rostral putamen	x = ±25, y = 8, z = 6
Dorsal caudal putamen	x = ±28, y = 1, z = 3
Ventral rostral putamen	x = ±20, y = 12, z = -3

TABLE S2. Significant predictors of response from right hemispheric seeds

Seed region	Direction of result (-/+)	k	Z score (max)	Brodmann Area	Montreal Neurological Institute Coordinates (x, y, z)	Functional connection
Ventral rostral putamen	-	217	4.34	13	-38, -2, -2	Left insular cortex
	-	62	3.51	11, 25	12, 36, -18	Orbital frontal cortex, subcallosal cortex, medial frontal cortex
	-	62	3.42	32	4, 48, 8	Anterior Cingulate cortex
	-	25	3.45	32, 10	14, 44, 2	anterior cingulate cortex
	-	19	3.13	13	38, 0, 0	Right insular cortex
	-	48	3.45	11, 25	-8, 34, -22	Orbitofrontal cortex, subcallosal cortex, medial frontal cortex
	-	25	3.16	40	56, -20,26	Right supramarginal gyrus
	-	15	3.07	22	52, -26, 0	Superior temporal gyrus
	-	13	3.24	1	-66, -14, 20	Postcentral gyrus
	-	12	3.46	13	-26, 14, -20	Orbital frontal cortex
	+	33	3.98	9	-42, 32, 28	Middle frontal gyrus, dorsolateral prefrontal cortex
	+	10	3.08	7	-6, -54, 50	Precuneus cortex
Nucleus accumbens	-	76	3.78	39	-44, -60, 10	Middle temporal gyrus
	-	89	3.77	44, 45	-54, 20, 6	Inferior frontal gyrus
	-	31	3.37	9	-8, 54, 30	Superior frontal gyrus, paracingulate

						gyrus
	-	32	3.29	22	50, -24, -2	Superior temporal gyrus
	-	74	3.57	21	-62, -40, -4	Middle temporal gyrus
	-	9	2.95	9	-44, 8, 42	Middle frontal gyrus
	-	12	3.2	6	-8, 4, 64	Supplemental motor area
	-	9	3.02		-36, -20, -12	Hippocampus/parahippocampal gyrus
	-	25	3.35	9	6, 56, 14	Frontal pole
	+	293	4.06	7	10, -68, 48	Precuneus cortex
	+	27	3.29	7	-8, -68, 50	Precuneus cortex
Dorsal caudate	-	171	4.15	6	54, 6, 36	Precentral gyrus
	-	41	3.26	13, 44	54, 8, 2	Insula, operculum cortex
	-	10	3.3	45	-58, 28, 8	Inferior frontal gyrus
	-	48	3.24	6	-54, 8, 14	Precentral gyrus
	-	36	3.26	45	-40, 28, 4	Frontal opercular cortex
	+	86	3.84	30	8, -40, 18	Posterior Cingulate
	+	13	3.14	19	-38, -58, 14	Angular Gyrus
Dorsal caudal putamen	-	774	4.37	13, 22, 6	-42, -4, 6	Insula, central opercular cortex, precentral gyrus
	-	291	4.33	13, 22	48, 12, -2	Insula, central opercular cortex
	-	24	3.31	NA	-6, -14, 0	thalamus
	-	11	3.16	10	-48, 50, 4	Frontal pole
	-	16	3.01	43	62, -10, 12	Central Opercular cortex
	+	57	3.19	21	-60, -46, -4	Middle temporal gyrus
	+	15	3.31	9	-44, 30, 34	Dorsolateral prefrontal cortex
Dorsal rostral putamen	-	669	4.06	13, 22, 6	-42, -4, 6	Insula, central opercular cortex, precentral gyrus
	-	211	3.63	13, 22	46, 12, 0	Insula, central opercular cortex

	-	17	3.47	8	58, 12, 38	Precentral gyrus
	-	12	3.19	47	28, 20, -16	Orbitofrontal cortex
Ventral caudate	-	165	3.61	31	12, -74, 18	Posterior cingulate cortex
	-	124	4.79	31	-22, -60, 16	Precuneus cortex
	-	116	3.79	22	52, -38, 14	Supramarginal gyrus
	-	84	3.65	22	-54, -44, 16	Supramarginal gyrus
	-	59	3.5	41	-34, -32, 14	Planum temporale
	-	53	3.32	30	18, -50, 12	Precuneus cortex
	-	43	3.27	46	44, 50, 2	Frontal pole
	-	29	2.94	40	54, -36, 34	Supramarginal gyrus
	-	20	3.39		16, -26, 12	Thalamus
	-	16	3.23		-14, -24, 8	Thalamus
	-	11	3.17	32	10, 22, 30	Anterior cingulate

TABLE S3. Significant predictors of response from left hemispheric seeds

Seed region	Direction of result (-/+)	k	Z score (max)	Brodmann Area	Montreal Neurological Institute Coordinates (x, y, z)	Functional connection
Ventral rostral putamen	-	15	3.21	25, 11	12, 36, -18	Orbital frontal cortex
	-	15	3.04	13	-40, -2, -2	Insula
	-	10	2.97	25	6, 20, -18	Subcollosal cortex
	+	74	4.25	NA	24, -26, 8	Thalamus
	+	29	3.07	NA	-16, -26, 10	Thalamus
	+	11	3.41	46	-42, 32, 26	Dorsolateral prefrontal cortex
Nucleus Accumbens	-	29	3.78	39	-44, -58, 10	Middle temporal gyrus
	-	24	3.26	44	-54, 20, 4	Inferior frontal gyrus
	+	56	3.48	7	-14, -68, 46	Superior parietal lobule
	+	52	3.44	NA	-12, -14, 8	Thalamus
	+	12	2.89	40	54, -38, 48	Supramarginal gyrus
	+	10	3.08	7	16, -74, 44	Lateral occipital cortex/Precuneus
Dorsal Caudate	-	18	3.13	37	-54, -64, -8	Inferior temporal gyrus
	-	22	3.2	11	24, 36, -16	Frontal pole, orbital frontal cotex
	-	10	3.2	NA	-22, 16, 2	Putamen
	-	32	3.49	NA	6,18,2	Accumbens, caudate
	+	100	3.98	41	-36, -32, 14	Planum temporale
	+	25	3	18	10, -76, 18	occipital cortex
	+	21	3.26	41	46, -36, 14	Planum temporale
	+	20	3.25	6	-16, 22, 58	Superior frontal gyrus
Dorsal caudal putamen	-	63	3.41	4,43, 13	-58,-2,14	Insula, opercular cortex, precentral gyrus

	-	114	3.62	4,43, 13	48,8,0	Insula, opercular cortex, precentral gyrus
	-	119	3.3	13	-42, -8, 4	Insula
	-	16	3.21	43	60, -6, 12	planum polare
	+	43	3.7	9	-40, 30, 28	Dorsolateral prefrontal cortex
Dorsal rostral putamen	-	49	3.65	13	50,12,0	Frontal operculum cortex, interior frontal gyrus
	-	54	3.09	13	-42,-8, 4	Insula, heschl's gyrus
	-	11	3.78	11	16, 34, -14	Orbital frontal cortex, medial frontal cortex
	-	15	3.22	32,9	12, 58, 12	Anterior cingulate cortex, paracingulate gyrus
	+	22	3.39	21	-62, -48, 2	Middle temporal gyrus
	+	12	3.13	9	-42, 30, 28	Middle frontal gyrus
Ventral caudate	-	60	3.3	NA	-18, 18, -10	Accumbens, putamen, caudate
	-	13	3.13	NA	4,16,0	Acumbens, caudate
	-	12	3.32	6	-34, 4, 34	Middle frontal gyrus
	+	70	3.77	NA	16, -26, 12	Thalamus
	+	50	3.2	13	-36, -22, 20	Insula
	+	45	3.27	NA	-10, -18, 12	Thalamus
	+	40	3.32	18	16, -76, 18	Occipital cortex
	+	18	3.41	22	44, -38, 14	Supramarginal gyrus

FIGURE S1. Seed regions displayed