Appendix 1

Definitions of each group

Tokyo cohort

All participants were aged 20 years or older and treated within the regular clinical practice at Komagino Hospital. Patients met inclusion criteria if they had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder. Symptom severity was assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, and Opler 1987) and Clinical Global Impression Severity Scale (CGI-S) (Guy 1976). Chlorpromazine (CPZ) equivalent daily dose was measured by the psychotropic dose equivalence in Japan (Inagaki and Inada 2006).

Antipsychotic treatment resistance was defined by the modified Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus criteria (Howes et al. 2017).

Optimal antipsychotic treatment was defined as treatment with ≥400 mg of CPZ equivalent daily dose for ≥6 consecutive weeks. Treatment response was defined by: (a) a CGI-S of ≤3, (b) scores of ≤3 on all positive symptom items of the PANSS, and (c) no symptomatic relapse in the previous 3 months. Antipsychotic treatment failure was defined by: (a) a CGI-S score of ≥4 (moderate) and (b) a score of ≥4 (moderate) on 2 PANSS positive symptom items after optimal antipsychotic treatment. To establish failure to previous antipsychotic treatments, CGI-S scores were retrospectively collected based on available information provided by patients, their
psychiatrists, chart, or other sources. The CGI-S scores were independently determined by two investigators (R.T. and S.N.). If there were discrepancies between them, we further discussed them with another investigator (Y·N.) to reach a consensus on group classification. TRS criteria included: (a) a history of treatment failure to optimal treatment with at least 2 previous non-CLZ antipsychotics and (b) current severity defined as a score of ≥5 (moderate-severe) on 2 PANSS positive symptom items or 4 (moderate) on 3 positive symptom items. FL-Resp criteria included: (a) current intake of a non-CLZ antipsychotic and (b) treatment response to this antipsychotic. HCs were assessed by the Mini-International Neuropsychiatric Interview to confirm if they met inclusion criteria that they had no psychiatric illness (Sheehan et al. 1998).

Exclusion criteria for all groups consisted of: (a) substance abuse or dependence within the past 6 months, (b) history of head trauma resulting in loss of consciousness for > 30 min, and (c) an unstable physical illness or neurological disorder. The patient groups and HCs were age- and sex-matched as closely as possible.

**Toronto cohort**

All the participants have been treated within the regular clinical practice at the Centre for Addiction and Mental Health. Patients met inclusion criteria if they had a DSM-IV/Structured Clinical Interview for DSM (Association and Others 1994) diagnosis of schizophrenia spectrum disorders. Chlorpromazine (CPZ) equivalent daily dose was measured...
by the method developed by Gardner and colleagues (Gardner et al. 2010). The definition of antipsychotic treatment resistance, optimal antipsychotic treatment, treatment response, and antipsychotic treatment failure was same as that in the Tokyo cohort. The CGI-S scores were independently determined by two investigators (Y.I. and S.N.) and were further discussed with another investigator (A.G.-G.) when there were discrepancies between them. More specifically, URS criteria included 1) current intake of CLZ, 2) a history of treatment failure to optimal treatment with at least two previous non-CLZ antipsychotics, and 3) subsequent treatment failure with CLZ after patients had taken CLZ for \( \geq \)6 weeks at a minimum dose of 300 mg/day. CLZ-Resp criteria included 1) current intake of CLZ, 2) a history of treatment failure to standard treatment with at least two previous non-CLZ antipsychotics, and 3) subsequent treatment response to CLZ. Criteria of FL-Resp and HC were same as those in the Tokyo cohort. Exclusion criteria for all groups consisted of 1) substance abuse or dependence during the past 6 months, 2) positive urine drug screen at inclusion or prior to MRI scanning, 3) history of head trauma resulting in loss of consciousness .30 minutes, 4) unstable physical illness or neurological disorder, and 5) current administration of lamotrigine, topiramate, or memantine. The patient groups and HCs were matched as closely as possible for age and sex.

**Extracting structural indices in the anterior cingulate cortex**
Cortical surface extraction was performed using the CIVET processing pipeline (version 2.1.0; Montreal Neurological Institute). Preprocessed T1-weighted images were non-linearly registered to the ICBM 152 average template through a twelve-parameter transformation (Collins et al. 1994). Next, images were segmented into grey matter, white matter, and cerebrospinal fluid (Zijdenbos, Forghani, and Evans 2002). Deformable models were then used to create gray matter and white matter surfaces for each hemisphere separately, resulting in four surfaces, each defined by 40,962 vertices (Kim et al. 2005). CT was estimated in native space using the Laplacian distance between the gray and white surfaces. CT was then blurred using a 30 mm FWHM surface-based diffusion kernel and non-linearly aligned to a template. Surface area (SA) was calculated at the mid-cortical surface and smoothed with a 20 mm FWHM surface-based diffusion kernel. FA and MD maps were sampled to CIVET mid-cortical surfaces of each participant and smoothed with a 20 mm FWHM surface-based diffusion kernel. A binary ACC mask was delineated using the combination of caudal and rostral anterior cingulate cortex defined by the Desikan Killany-Tourville atlas (Klein and Tourville 2012), resulting in 1694 vertices (847 vertices for each hemisphere). CT, SA, MD, and FA values of each vertex within the mask were extracted and utilized as inputs of NMF analysis.

Non-negative matrix factorization
In this study, we utilized an orthogonal variant of NMF, orthogonal projective NMF (OPNMF) (Sotiras, Resnick, and Davatzikos 2015; Yang and Oja 2010). This approach allows obtaining spatially non-overlapping components and a weight matrix describing how each participant loads into each component. OPNMF decomposes a given input matrix of dimensions m x n into a component matrix (m x k), and a weight matrix (k x n), in which k is the number of components. These matrices are generated so that their multiplication reconstructs the input matrix as best as possible by minimizing the reconstruction error between the original and reconstructed inputs. Clustering of vertices is obtained via a winner take all strategy of assigning each vertex to the cluster with corresponding largest component score. OPNMF was performed with non-negative double singular value decomposition initialization, max iterations = 100000 and tolerance = 0.00001. Codes we used for OPNMF are publicly available (https://github.com/asotiras/brainparts).

To characterize demographical relationships with the parcellated structure, linear models were used relate age and sex to the parcellated structure ignoring group categories. We found that age was related to reduced CT and increased MD in all regions of 4-component solution in both cohorts (p < 0.05, FDR corrected). Also, only in the Toronto cohort, age was related to reduced FA in components 3 and 4 (p < 0.05, FDR corrected). Furthermore, males
had larger surface area in all regions of 4-component solution than females in both cohorts (p < 0.05, FDR corrected).

Table S1 - Participant demographics in the Tokyo cohort

|                        | TRS (n=23) | FL-Resp (n=24) | HCs (n=26) | Difference |
|------------------------|------------|----------------|------------|------------|
|                        |            |                |            | p value    |
| Age, year (mean ± SD)  | 43.8 ± 11.4| 44.4 ± 12.8    | 43.5 ± 12.0| 0.79       |
| Sex (male/female)      | 12/11      | 10/14          | 11/15      | 0.72       |
| RBANS total score (mean ± SD) | 75.3 ± 14.6 | 82.5 ± 13.9 | 102.8 ± 13.9 | < 0.001   |
| Diagnosis (schizophrenia / schizoaffective) | 23/0 | 23/1 | 1 |
| Age of onset, year (mean ± SD) | 26.3 ± 6.9 | 26.9 ± 10.6 | 0.82 |
| Duration of illness, year (mean ± SD) | 18.6 ± 10.7 | 16.6 ± 13.4 | 0.57 |
| PANSS total score (mean ± SD) | 109.4 ± 20.2 | 49.5 ± 13.0 | < 0.001 |
| positive syndrome subscale (mean ± SD) | 26.5 ± 4.6 | 9.4 ± 2.7 | < 0.001 |
| Subscale                        | Mean ± SD Participants | Mean ± SD Controls | p-value |
|--------------------------------|-------------------------|--------------------|---------|
| Negative Syndrome Subscale     | 30.6 ± 6.1              | 14.7 ± 5.8         | < 0.001 |
| General Psychopathology Subscale | 52.3 ± 11.6            | 24.9 ± 5.8         | < 0.001 |
| CGI-S                          | 5.09 ± 0.4              | 2.3 ± 0.8          | < 0.001 |
| CPZ Equivalent Daily Dose, mg  | 961.2 ± 497.7           | 416.0 ± 251.2      | < 0.001 |

| Antipsychotic Medications (n) |
|-------------------------------|
| Risperidone (10), Olanzapine (10), Olanzapine (3), Aripiprazole (8), Aripiprazole (9), Blonanserin (4), Blonanserin (2), Quetiapine (2), Paliperidone (4), Quetiapine (3), Paliperidone (1), Haloperidol (2), Haloperidol (1), Perospirone (1), Risperidone (3), Perospirone (1) |

**Abbreviations:**
TRS; treatment-resistant schizophrenia, FL-Resp; First-Line Responder, HCs; Healthy Controls, RBANS; Repeatable Battery for the Assessment of Neuropsychological Status; PANSS; Positive and Negative Syndrome Scale; CGI-S; Clinical Global Impression Severity Scale, CPZ; chlorpromazine

**Table S2 - Participant demographics in the Toronto cohort**
|                      | URS (n=21) | CLZ-Resp (n=15) | FL-Resp (n=17) | HCs (n=26) | Difference p value |
|----------------------|------------|-----------------|----------------|------------|-------------------|
| Age, year (mean ± SD)| 44.3 ± 12.4| 40.7 ± 10.7     | 46.9 ± 13.7    | 40.8 ± 13.2| 0.79              |
| Sex (male/female)    | 17/4       | 11/4            | 13/4           | 19/7       | 0.92              |
| RBANS total score (mean ± SD)| 64.8 ± 12.7| 75.8 ± 11.0     | 76.0 ± 9.7     | 96.2 ± 13.0| < 0.001           |
| Diagnosis            | 17/4       | 10/5            | 12/5           |            | 0.596             |
| (schizophrenia/schizoaffective) |         |                 |                |            |                   |
| Age of onset, year (mean ± SD)| 21.2 ± 5.1 | 24.5 ± 8.2     | 25.3 ± 7.9     |            | 0.18              |
| Duration of illness, year (mean ± SD)| 23.0 ± 13.1 | 16.2 ± 9.7     | 22.1 ± 12.5    |            | 0.223             |
| PANSS total score (mean ± SD)| 83.2 ± 12.4| 52.6 ± 10.0    | 57.3 ± 9.4     |            | < 0.001           |
| positive syndrome subscale (mean ± SD)| 22.8 ± 4.1 | 11.2 ± 2.2     | 11.0 ± 2.4     |            | < 0.001           |
| negative syndrome subscale (mean ± SD)| 20.9 ± 4.5 | 14.3 ± 3.1     | 16.1 ± 3.5     |            | < 0.001           |
| general psychopathology subscale (mean ± SD)| 39.6 ± 7.4 | 27.1 ± 5.6     | 30.2 ± 4.4     |            | < 0.001           |
| CGI-S (mean ± SD)    | 4.7 ± 0.7  | 2.8 ± 0.4       | 2.6 ± 0.5      |            | < 0.001           |
|                        | TRS         | FL-Resp     | HCs         | F-value | P-value |
|------------------------|-------------|-------------|-------------|---------|---------|
| **CPZ equivalent daily dose, mg** | 658.9 ± 194.3 | 483.7 ± 203.5 | 447.6 ± 187.5 | < 0.05  |         |
| (mean ± SD)            |             |             |             |         |         |
| **CLZ equivalent daily dose, mg** | 439.3 ± 129.6 | 322.5 ± 135.6 | < 0.05     |         |         |
| (mean ± SD)            |             |             |             |         |         |
| **Antipsychotic medications (n)** | Clozapine (21) | Clozapine (15) | Olanzapine (8), Flupenthixol (3), Risperidone (3), Paliperidone (1), Loxapine (1), Fluphenazine (1) |         |         |

**Abbreviations:** URS; Ultra treatment-Resistant Schizophrenia, CLZ-Resp; Clozapine Responder, FL-Resp; First-Line Responder, HCs; Healthy Controls, RBANS; Repeatable Battery for the Assessment of Neuropsychological Status; PANSS; Positive and Negative Syndrome Scale; CGI-S; Clinical Global Impression Severity Scale, CPZ; chlorpromazine

**Table S3 – Group comparisons of ACC structural indices in the Tokyo cohort**

| Component1 | TRS (0.15) | FL-Resp (0.15) | HCs (0.11) | F_{rest} = 12.11 | 2.53e^-4 |
|------------|------------|----------------|------------|-----------------|---------|
| CT         |            |                |            |                 |         |
| Component | Mean ± SD | Mean ± SD | Mean ± SD | Degrees of Freedom | F-statistic | p-value |
|-----------|-----------|-----------|-----------|--------------------|-------------|---------|
| Component2 | 2.53 (0.14) | 2.56 (0.14) | 2.72 (0.10) | F<sub>2,68</sub> = 15.86 | 3.55e⁻⁵ |
| Component3 | 2.02 (0.13) | 2.01 (0.12) | 2.12 (0.09) | F<sub>2,68</sub> = 8.38 | 2.52e⁻³ |
| Component4 | 2.23 (0.18) | 2.25 (0.14) | 2.40 (0.18) | F<sub>2,68</sub> = 8.04 | 2.52e⁻³ |
| SA | | | | | |
| Component1 | 2.08 (0.23) | 2.03 (0.27) | 2.18 (0.17) | F<sub>2,68</sub> = 3.35 | 0.06 |
| Component2 | 1.64 (0.20) | 1.59 (0.22) | 1.71 (0.13) | F<sub>2,68</sub> = 3.06 | 0.07 |
| Component3 | 1.79 (0.19) | 1.75 (0.22) | 1.87 (0.17) | F<sub>2,68</sub> = 3.40 | 0.06 |
| Component4 | 1.70 (0.15) | 1.57 (0.24) | 1.61 (0.22) | F<sub>2,68</sub> = 3.36 | 0.06 |
| MD | | | | | |
| Component1 | 9.7e⁻⁵ (4.2e⁻⁵) | 9.6e⁻⁵ (5.5e⁻⁵) | 9.2e⁻⁵ (4.2e⁻⁵) | F<sub>2,68</sub> = 7.61 | 0.003 |
| Component2 | 9.2e⁻⁵ (3.9e⁻⁵) | 9.1e⁻⁵ (4.9e⁻⁵) | 8.9e⁻⁵ (3.6e⁻⁵) | F<sub>2,68</sub> = 4.97 | 0.02 |
| Component3 | 1.2e⁻⁵ (7.9e⁻⁵) | 1.2e⁻⁵ (9.5e⁻⁵) | 1.2e⁻⁵ (8.1e⁻⁵) | F<sub>2,68</sub> = 7.95 | 0.003 |
| Component4 | 9.9e⁻⁵ (5.6e⁻⁵) | 9.9e⁻⁵ (5.9e⁻⁵) | 9.5e⁻⁵ (4.7e⁻⁵) | F<sub>2,68</sub> = 6.70 | 0.005 |
| FA | | | | | |
| Component1 | 0.23 (0.02) | 0.23 (0.02) | 0.23 (0.02) | F<sub>2,68</sub> = 0.52 | 0.64 |
| Component2 | 0.20 (0.02) | 0.20 (0.02) | 0.21 (0.02) | F<sub>2,68</sub> = 0.30 | 0.74 |
| Component3 | 0.27 (0.02) | 0.27 (0.02) | 0.28 (0.02) | F<sub>2,68</sub> = 2.55 | 0.11 |
| Component4 | 0.27 (0.03) | 0.27 (0.03) | 0.28 (0.03) | F<sub>2,68</sub> = 1.43 | 0.28 |
Values are mean (SD). Group comparisons were conducted using analysis of covariance controlling for age and sex. P-values were corrected for multiple comparisons using a false discovery rate.

**Abbreviations:** TRS; treatment-resistant schizophrenia, FL-Resp; First-Line Responder, HCs; Healthy Controls, CT; Cortical Thickness, SA; Surface Area, MD; Mean Diffusivity, FA; Fractional Anisotropy

### Table S4 – Group comparisons of ACC structural indices in the Toronto cohort

|         | URS  | CLZ-Resp | FL-Resp | HCs | F-value | P-value |
|---------|------|----------|---------|-----|---------|---------|
| **CT**  |      |          |         |     |         |         |
| Component1 | 2.58 (0.15) | 2.59 (0.11) | 2.64 (0.15) | 2.73 (0.13) | $F_{3,73} = 6.79$ | **0.003** |
| Component2 | 2.73 (0.15) | 2.74 (0.10) | 2.80 (0.16) | 2.90 (0.13) | $F_{3,73} = 8.91$ | $6.66 \times 10^{-4}$ |
| Component3 | 2.06 (0.14) | 2.07 (0.11) | 2.12 (0.11) | 2.13 (0.10) | $F_{3,73} = 2.67$ | 0.113 |
| Component4 | 2.43 (0.20) | 2.39 (0.14) | 2.43 (0.22) | 2.53 (0.15) | $F_{3,73} = 2.91$ | 0.107 |
| **SA**  |      |          |         |     |         |         |
| Component1 | 2.13 (0.26) | 2.16 (0.33) | 2.33 (0.27) | 2.24 (0.20) | $F_{3,73} = 2.57$ | 0.11 |
| Component2 | 1.64 (0.19) | 1.69 (0.28) | 1.83 (0.22) | 1.74 (0.16) | $F_{3,73} = 3.25$ | 0.08 |

Appendix 1 to Ochi R, Plitman P, Patel R, et al. Investigating structural subdivisions of the anterior cingulate cortex in schizophrenia, with implications for treatment resistance and glutamatergic levels. J Psychiatry Neurosci 2022. doi: 10.1503/jpn.210113
| Component | Mean (SD) | Mean (SD) | Mean (SD) | Mean (SD) | F(3,73) | p-value |
|-----------|----------|----------|----------|----------|---------|---------|
| Component3 | 1.84 (0.21) | 1.86 (0.24) | 2.00 (0.22) | 1.92 (0.16) | 2.41 | 0.11 |
| Component4 | 1.69 (0.21) | 1.72 (0.27) | 1.86 (0.23) | 1.77 (0.18) | 2.35 | 0.11 |
| MD | | | | | | |
| Component1 | 1.0e^{-3} (6.2e^{-5}) | 9.8e^{-4} (3.2e^{-5}) | 9.9e^{-4} (6.5e^{-5}) | 9.7e^{-4} (4.4e^{-5}) | 3.99 | 0.044 |
| Component2 | 9.9e^{-4} (5.5e^{-5}) | 9.5e^{-4} (3.4e^{-5}) | 9.7e^{-4} (5.9e^{-5}) | 9.5e^{-4} (4.0e^{-5}) | 4.30 | 0.040 |
| Component3 | 1.3e^{-3} (1.3e^{-5}) | 1.2e^{-3} (7.4e^{-5}) | 1.2e^{-3} (1.2e^{-5}) | 1.2e^{-3} (8.0e^{-5}) | 1.65 | 0.213 |
| Component4 | 1.1e^{-3} (8.1e^{-5}) | 1.0e^{-3} (3.9e^{-5}) | 1.0e^{-3} (9.2e^{-5}) | 1.0e^{-3} (4.7e^{-5}) | 2.23 | 0.113 |
| FA | | | | | | |
| Component1 | 0.22 (0.02) | 0.22 (0.02) | 0.23 (0.02) | 0.23 (0.02) | 0.88 | 0.455 |
| Component2 | 0.20 (0.02) | 0.20 (0.02) | 0.21 (0.02) | 0.21 (0.02) | 1.30 | 0.302 |
| Component3 | 0.26 (0.02) | 0.27 (0.02) | 0.27 (0.02) | 0.28 (0.02) | 2.28 | 0.113 |
| Component4 | 0.28 (0.03) | 0.29 (0.04) | 0.30 (0.03) | 0.30 (0.04) | 2.25 | 0.113 |

Values are mean (SD). Group comparisons were conducted using analysis of covariance controlling for age and sex. P-values were corrected for multiple comparisons using a false discovery rate.
Abbreviations: URS; Ultra treatment-Resistant Schizophrenia, CLZ-Resp; Clozapine Responder, FL-Resp; First-Line Responder, HCs; Healthy Controls, CT; Cortical Thickness, SA; Surface Area, MD; Mean Diffusivity, FA; Fractional Anisotropy

Figure S1. Left panel: Voxel locations of the $^1$H-MRS. The dorsal anterior cingulate cortex voxel (voxel size: 9.0 mL [3.0 × 2.0 × 1.5 cm$^3$]) was positioned on an oblique axial image acquired parallel to the AC–PC line and oblique sagittal image acquired to parallel to head midline. The tip of the voxel was placed on top of the most anterior part of genu with paralleling to the cingulate cortex. Right panel: H-MRS spectra of the dorsal anterior cingulate cortex of FL-Resp patient in the Tokyo cohort.


**Figure S2.** Stability index and gradient of the reconstruction error for number of components from 2 to 10 in the Tokyo cohort (left) and in the Toronto cohort (right).

from 2 to 10 in the Tokyo cohort (left) and in the Toronto cohort (right).
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