Supplementary Materials for
A multimodal study of a first episode psychosis cohort:
potential markers of antipsychotic treatment resistance

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SUPPLEMENTARY METHODS

Longitudinal analysis of brain volume

Three significant brain regions were identified by comparisons between TR and non-TR (including or excluding those with short follow-ups) patients: left gyrus rectus, right hippocampus, and left superior frontal gyrus. We further analyzed the longitudinal changes in volume to see if they could be trait markers. Among the 136 first episode psychosis (FEP) patients recruited in this study, 88 patients came back for annual 3 tesla (T) magnetic resonance imaging (MRI) scans during a 4-year follow-up period. We compared the baseline volumes of these 4 brain regions between the entire cohort (n=136) and the longitudinal cohort (n=88), and didn’t find significant differences. This suggests that there is no return bias in the studied cohort that could affect the longitudinal analysis results. Next, we used the analytic pipeline developed by our previous study to analyze the longitudinal changes in brain volume [1]. Specifically, to quantitatively analyze longitudinal changes, we calculated the annual percentage change (APC) by using the following equation:

\[
APC = \frac{1}{n-1} \sum_{i=1}^{n-1} \frac{V_{i+1} - V_i}{(D_{i+1} - D_i)/365}
\]

\(V\) is the level of metabolite, \(D\) is the date of the visit, \(i\) is the ith visit, \(D_{i+1} - D_i\) is the number of days between two visits, and \(n\) is the total number of visits. We performed one sample t-test and Bayesian test to evaluate whether the APC was significantly different from zero in FEP patients. The Benjamini-Hochberg (BH) procedure was used for multiple comparison correction. P values corrected with the BH procedure are presented as q values. The analyte was considered significant if its q value was smaller than 0.05. We found a significant decline in the left gyrus rectus, while the APC of the right hippocampus and left superior frontal gyrus were close to 0 (Table S9).

References

1. Wang M, Barker PB, Cascella N, Coughlin JM, Nestadt G, Nucifora FC, et al. Longitudinal changes in brain metabolites in healthy subjects and patients with first episode psychosis (FEP): a 7-Tesla MRS study. BioRxiv. 2020:2020.08.25.267419.
TABLE S1. Brain regions analyzed in the present study.
Volumes of the left and right hemisphere of the following regions were used in the present study

| Symbol | Full Name                      |
|--------|--------------------------------|
| SFG    | Superior frontal gyrus         |
| MFG    | Middle frontal gyrus           |
| IFG    | Inferior frontal gyrus         |
| OG     | Supra orbital gyrus            |
| GR     | Gyrus rectus                   |
| PrCG   | Precentral gyrus               |
| PoCG   | Postcentral gyrus              |
| SPG    | Superior parietal gyrus        |
| SMG    | Supramarginal gyrus            |
| AG     | Angular gyrus                  |
| PrCu   | Pre-cuneus                     |
| Cu     | Cuneus                         |
| LG     | Lingual gyrus                  |
| SOG    | Superior occipital gyrus       |
| IOG    | Inferior occipital gyrus       |
| FuG    | Fusiform gyrus                 |
| MOG    | Middle occipital gyrus         |
| STG    | Superior temporal gyrus        |
| MTG    | Middle temporal gyrus          |
| ITG    | Inferior temporal gyrus        |
| Insula | Insula                         |
| Hippo  | Hippocampus                    |
| CGH    | Hippocampus cingulum           |
| Amyg   | Amygdala                       |
| CGC    | Cingulate cortex               |
| Cingulate | Cingulate gyrus     |
| Caud   | Caudate nucleus                |
| Caudate tail | Caudate tail     |
| GP     | Globus pallidus                |
| Put    | Putamen                        |
| Thalamus | Thalamus                   |

(continued on next page)
| White matter          | Deep white matter                              |
|-----------------------|------------------------------------------------|
| ALIC                  | Anterior limb of internal capsule              |
| PLIC                  | Posterior limb of internal capsule             |
| BCC                   | Body of corpus callosum                       |
| SCC                   | Splenium of corpus callosum                   |
| GCC                   | Genu of corpus callosum                       |
| Fx                    | Fornix                                         |
| Fx.ST                 | Stria terminalis of fornix                    |
| ant_DPWM              | Anterior deep white matter (part of corona radiata) |
| inf_DPWM              | Inferior deep white matter (part of corona radiata) |
| post_DPWM             | Posterior deep white matter (part of corona radiata) |
| PVA_anterior          | Anterior periventricular white matter          |
| PVA_posterior         | Posterior periventricular white matter         |
| Peripheral            | Cingulate white matter                         |
| PeripheralFrontalWM   | Frontal white matter                           |
| PeripheralOccipitalWM | Occipital white matter                         |
| PeripheralParietalWM  | Parietal white matter                          |
| PeripheralTemporalWM  | Temporal white matter                          |
| Mesencephalon         | Basal Forebrain                                |
|                       | Basal forebrain                                |
| Midsbrain             | Midbrain                                       |
| Metencephalon         | Pons                                           |
|                       | Pons                                           |
|                       | CerebellumWM                                   |
|                       | Cerebellum white matter                        |
|                       | Cerebellum                                     |
| Ventricles            | III ventricle                                  |
|                       | Third ventricle                                |
|                       | AnteriorLateralVentricle                       |
|                       | Anterior (frontal) horn of lateral ventricle   |
|                       | InferiorLateralVentricle                       |
|                       | Inferior (temporal) horn of the lateral ventricle |
|                       | PosteriorLateralVentricle                      |
|                       | Posterior (occipital) horn of lateral ventricle |
|                       | IV ventricle                                   |
|                       | Fourth ventricle                               |
| CSF spaces            | CentralSul                                     |
|                       | Central sulcus                                 |
|                       | CinguSul                                       |
|                       | Cingulate sulcus                               |
|                       | FrontSul                                       |
|                       | Frontal sulcus                                 |
|                       | OcciptSul                                      |
|                       | Occipital sulcus                               |
|                       | ParietSul                                      |
|                       | Parietal sulcus                                |
|                       | TempSul                                       |
|                       | Temporal sulcus                                |
|                       | SylFrontSul                                    |
|                       | Frontal pars of sylvian sulcus                 |
|                       | SylParieSul                                    |
|                       | Parietal pars of sylvian sulcus                |
|                       | SylTempSul                                     |
|                       | Temporal pars of sylvian sulcus                |
**TABLE S2. Demographic summary of patients.**

Significant results (p-value < 0.05) are highlighted in bold with a gray shadow. Abbreviations: sd, standard deviation; FEP, first episode psychosis; and TR, treatment resistant.

**A) TR and non-TR patients (excluding those with short follow-ups)**

| Characteristics                           | TR (32)    | non-TR (69) | p-value    |
|-------------------------------------------|------------|-------------|------------|
| Age (mean years ± sd)                     | 20.53 ± 2.97 | 22.78 ± 4.81 | **4.96E-03** |
| Gender (male/female)                      | 25/7       | 48/21       | 0.48       |
| Race (black/white)                        | 16/16      | 35/34       | 1.00       |
| Psychiatric family history (positive/negative/unknown) | 21/8/3     | 45/20/4     | 0.81       |
| Smoking status (yes/no)                   | 10/22      | 18/51       | 0.64       |
| Years of education (mean ± sd)            | 12.13 ± 2.20 | 13.26 ± 2.70 | **0.03**   |
| Employment (yes/no/unknown)               | 9/22/1     | 34/30/5     | **0.03**   |

**B) TR and all non-TR patients (including those with short follow-ups)**

| Characteristics                           | TR (32)    | non-TR (104) | p-value    |
|-------------------------------------------|------------|--------------|------------|
| Age (mean years ± sd)                     | 20.53 ± 2.97 | 22.89 ± 4.76 | **1.17E-03** |
| Gender (male/female)                      | 25/7       | 76/28        | 0.65       |
| Race (black/white)                        | 16/16      | 54/50        | 1.00       |
| Psychiatric family history (positive/negative/unknown) | 21/8/3     | 71/27/6     | 1.00       |
| Smoking status (yes/no)                   | 10/22      | 30/74        | 0.83       |
| Years of education (mean ± sd)            | 12.13 ± 2.20 | 13.12 ± 2.43 | **0.03**   |
| Employment (yes/no/unknown)               | 9/22/1     | 47/45/12     | **0.04**   |
TABLE S3. Comparison of clinical data between treatment resistant (TR) and all non-TR patients (including those with short follow-ups).

Clinical data were compared between TR (n=32) and all non-TR (n=104) patients. Significant results (q-value < 0.05) are highlighted in bold with a gray shadow. Abbreviations: CPZ, chlorpromazine; SANS, the scale for the assessment of negative symptoms; SAPS, the scale for the assessment of positive symptoms; and PFTD, positive formal thought disorder.

A) Clinical variables

| Characteristics           | mean (TR) | mean (non-TR) | p-value | q-value |
|---------------------------|-----------|---------------|---------|---------|
| CPZ dose (mg)             | 385.88    | 269.07        | 0.03    | 0.04    |
| Age of onset (years)      | 19.28     | 21.99         | 3.78E-03| 7.55E-03|
| # Hospitalizations        | 2.69      | 1.59          | 1.50E-03| 5.98E-03|
| Duration of illness (months) | 15.82    | 13.72         | 0.28    | 0.28    |

B) SANS/SAPS

| Characteristics | mean (TR) | mean (non-TR) | p-value | q-value |
|-----------------|-----------|---------------|---------|---------|
| SAPS Total score| 4.31      | 3.49          | 0.67    | 0.82    |
| Hallucination   | 1.83      | 1.25          | 0.62    | 0.82    |
| Delusion        | 1.66      | 1.45          | 0.59    | 0.82    |
| Bizarre behavior| 0.45      | 0.34          | 0.82    | 0.82    |
| PFTD            | 0.38      | 0.46          | 0.68    | 0.82    |

| SANS Total score | 10.34 | 7.22 | 0.01 | 0.04 |
|------------------|-------|------|------|------|
| Affective flattening | 1.97 | 1.38 | 0.09 | 0.14 |
| Alogia            | 1.83  | 1.12 | 0.15 | 0.15 |
| Avolition         | 2.38  | 1.53 | 5.21E-03 | 0.03 |
| Anhedonia         | 2.45  | 1.78 | 0.04 | 0.08 |
| Attention         | 1.79  | 1.40 | 0.14 | 0.15 |

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### C) Neuropsychological test

| Characteristics                  | mean (TR) | mean (non-TR) | p-value | q-value |
|----------------------------------|-----------|---------------|---------|---------|
| Composite score                  | 95.77     | 95.05         | 0.31    | 0.89    |
| Processing speed                 | 85.97     | 85.82         | 0.55    | 0.89    |
| Attention memory                 | 87.11     | 84.81         | 0.11    | 0.75    |
| Verbal learning and memory       | 86.67     | 85.27         | 0.52    | 0.89    |
| Visual learning and memory       | 84.93     | 87.13         | 0.88    | 0.89    |
| Ideational fluency               | 95.36     | 94.55         | 0.89    | 0.89    |
| Executive functioning            | 88.70     | 89.00         | 0.89    | 0.89    |

### D) Smell test

| Characteristics                  | mean (TR) | mean (non-TR) | p-value | q-value |
|----------------------------------|-----------|---------------|---------|---------|
| Odor discrimination              | 9.59      | 9.68          | 0.61    | 0.81    |
| Odor identification              | 11.18     | 11.39         | 0.81    | 0.81    |
| Detection sensitivity: Citralva  | -4.44     | -4.58         | 0.18    | 0.72    |
| Detection sensitivity: Lyral     | -4.35     | -4.27         | 0.80    | 0.81    |
TABLE S4. Analysis results of brain volume between treatment resistant (TR) and all non-TR patients (including those with short follow-ups).

Brain volumes were compared between TR (n=32) and all non-TR (n=104) patients. The top 10 brain regions are listed. Brain regions with differences between TR patients and non-TR patients (group comparison p-value < 0.05 and permutation test p-value < 0.05) are highlighted in bold with a gray shadow.

| Brain region                          | Hemisphere | Mean (TR) | Mean (non-TR) | p-value | p-value (permutation test) | q-value |
|---------------------------------------|------------|-----------|---------------|---------|---------------------------|---------|
| Hippocampus                           | right      | 3608.11   | 3895.38       | 0.01    | 0.01                      | 0.89    |
| Superior frontal gyrus                | left       | 24406.95  | 25600.59      | 0.02    | 0.02                      | 0.89    |
| Gyrus rectus                          | left       | 5390.74   | 5721.62       | 0.04    | 0.03                      | 0.89    |
| Middle occipital gyrus                | left       | 15138.05  | 16055.51      | 0.04    | 0.02                      | 0.89    |
| Parietal parts of syllabus sulcus     | right      | 5639.63   | 5931.11       | 0.05    | 0.04                      | 0.89    |
| Cuneus                                | left       | 206.63    | 259.73        | 0.07    | 0.15                      | 0.89    |
| Middle frontal gyrus                  | right      | 22359.63  | 23080.92      | 0.07    | 0.06                      | 0.89    |
| Cuneus                                | left       | 6235.74   | 6562.05       | 0.08    | 0.06                      | 0.89    |
| Middle frontal gyrus                  | left       | 23062.74  | 23876.25      | 0.09    | 0.10                      | 0.89    |
| Parietal sulcus                       | right      | 7136.21   | 7792.43       | 0.09    | 0.12                      | 0.89    |
TABLE S5. Analysis of the 7T MRS data.

7T MRS data (normalized by water or total creatine (tCr)) were compared between TR (n=32) and non-TR (n=69) patients (excluding those with short follow-ups), as well as, between TR (n=32) and all non-TR (n=104) patients (including those with short follow-ups). Results with a p value smaller than 0.05 are highlighted in bold with a gray shadow. Abbreviations: TR, treatment resistant; GABA, γ-aminobutyric acid; Glu, glutamate; GSH, glutathione; NAA, N-acetylaspartate; ACC indicates anterior cingulate cortex; Thal, thalamus; DLPFC, dorsolateral prefrontal cortex; CSO, centrum semiovale; and OFR, orbital frontal region.

A) TR and non-TR patients (excluding those with short follow-ups); metabolite levels are normalized by water.

| region | metabolite | mean (TR) | mean (non-TR) | p-value | q-value |
|--------|------------|-----------|---------------|---------|---------|
|        | GSH        | 1.40      | 1.51          | 1.68E-03| 0.03    |
| ACC    | NAA        | 7.06      | 7.18          | 0.47    | 0.82    |
|        | GABA       | 1.71      | 1.68          | 0.70    | 0.82    |
|        | Glu        | 8.06      | 8.05          | 0.93    | 0.96    |
| CSO    | GSH        | 1.29      | 1.35          | 0.40    | 0.82    |
|        | NAA        | 8.32      | 8.24          | 0.13    | 0.57    |
|        | GABA       | 1.68      | 1.82          | 0.02    | 0.18    |
|        | Glu        | 5.99      | 6.13          | 0.10    | 0.57    |
| DLPFC  | GSH        | 1.45      | 1.54          | 0.57    | 0.82    |
|        | NAA        | 7.98      | 8.34          | 0.28    | 0.82    |
|        | GABA       | 1.59      | 1.55          | 0.68    | 0.82    |
|        | Glu        | 6.83      | 7.33          | 0.14    | 0.57    |
| OFR    | GSH        | 1.48      | 1.52          | 0.65    | 0.82    |
|        | NAA        | 7.87      | 7.71          | 0.47    | 0.82    |
|        | GABA       | 1.67      | 1.68          | 0.96    | 0.96    |
|        | Glu        | 6.53      | 6.68          | 0.44    | 0.82    |
| Thal   | GSH        | 1.43      | 1.43          | 0.67    | 0.82    |
|        | NAA        | 7.43      | 7.58          | 0.54    | 0.82    |
|        | GABA       | 2.39      | 2.30          | 0.53    | 0.82    |
|        | Glu        | 6.50      | 6.61          | 0.83    | 0.92    |
B) TR and non-TR patients (excluding those with short follow-ups); metabolite levels are normalized by tCr.

| region | metabolite | mean (TR) | mean (non-TR) | p-value  | q-value  |
|--------|------------|-----------|---------------|----------|----------|
| ACC    | GSH        | 0.24      | 0.26          | 7.41E-03 | 0.15     |
|        | NAA        | 1.22      | 1.23          | 0.53     | 0.89     |
|        | GABA       | 0.29      | 0.29          | 0.84     | 0.95     |
|        | Glu        | 1.40      | 1.38          | 0.74     | 0.95     |
| CSO    | GSH        | 0.23      | 0.23          | 0.50     | 0.89     |
|        | NAA        | 1.42      | 1.39          | 0.20     | 0.75     |
|        | GABA       | 0.29      | 0.31          | 0.11     | 0.75     |
|        | Glu        | 1.03      | 1.04          | 0.58     | 0.89     |
| DLPFC  | GSH        | 0.27      | 0.26          | 0.85     | 0.95     |
|        | NAA        | 1.46      | 1.46          | 0.96     | 0.96     |
|        | GABA       | 0.29      | 0.27          | 0.20     | 0.75     |
|        | Glu        | 1.25      | 1.28          | 0.28     | 0.80     |
| OFR    | GSH        | 0.26      | 0.27          | 0.22     | 0.75     |
|        | NAA        | 1.39      | 1.39          | 0.57     | 0.89     |
|        | GABA       | 0.29      | 0.31          | 0.39     | 0.89     |
|        | Glu        | 1.15      | 1.20          | 0.12     | 0.75     |
| Thal   | GSH        | 0.25      | 0.24          | 0.40     | 0.89     |
|        | NAA        | 1.30      | 1.31          | 0.66     | 0.94     |
|        | GABA       | 0.43      | 0.41          | 0.80     | 0.95     |
|        | Glu        | 1.14      | 1.13          | 0.92     | 0.96     |
C) TR and all non-TR patients (including those with short follow-ups); metabolite levels are normalized by water.

| Brain region | Metabolite | mean (TR) | mean (non-TR) | p-value  | q-value |
|--------------|------------|-----------|---------------|----------|---------|
| ACC          | GSH        | 1.40      | 1.49          | 6.25E-03 | 0.12    |
|              | NAA        | 7.06      | 7.13          | 0.24     | 0.63    |
|              | GABA       | 1.71      | 1.67          | 0.90     | 0.95    |
|              | Glu        | 8.06      | 7.94          | 0.50     | 0.87    |
| CSO          | GSH        | 1.29      | 1.32          | 0.76     | 0.89    |
|              | NAA        | 8.32      | 8.20          | 0.23     | 0.63    |
|              | GABA       | 1.68      | 1.80          | 0.08     | 0.63    |
|              | Glu        | 5.99      | 6.11          | 0.25     | 0.63    |
| DLPFC        | GSH        | 1.45      | 1.53          | 0.61     | 0.87    |
|              | NAA        | 7.98      | 8.32          | 0.14     | 0.63    |
|              | GABA       | 1.59      | 1.52          | 0.67     | 0.87    |
|              | Glu        | 6.83      | 7.18          | 0.21     | 0.63    |
| OFR          | GSH        | 1.48      | 1.52          | 0.89     | 0.95    |
|              | NAA        | 7.87      | 7.60          | 0.45     | 0.87    |
|              | GABA       | 1.67      | 1.65          | 0.69     | 0.87    |
|              | Glu        | 6.53      | 6.57          | 0.69     | 0.87    |
| Thal         | GSH        | 1.43      | 1.43          | 0.97     | 0.97    |
|              | NAA        | 7.43      | 7.48          | 0.54     | 0.87    |
|              | GABA       | 2.39      | 2.24          | 0.16     | 0.63    |
|              | Glu        | 6.50      | 6.49          | 0.48     | 0.87    |
D) TR and all non-TR patients (including those with short follow-ups); metabolite levels are normalized by tCr.

| Brain region | Metabolite | mean (TR) | mean (non-TR) | p-value | q-value |
|--------------|------------|-----------|---------------|---------|---------|
| ACC          | GSH        | 0.24      | 0.26          | 2.50E-03| 0.05    |
|              | NAA        | 1.22      | 1.24          | 0.11    | 0.64    |
|              | GABA       | 0.29      | 0.29          | 0.73    | 0.86    |
|              | Glu        | 1.40      | 1.38          | 0.92    | 0.96    |
| CSO          | GSH        | 0.23      | 0.23          | 0.62    | 0.86    |
|              | NAA        | 1.42      | 1.40          | 0.57    | 0.86    |
|              | GABA       | 0.29      | 0.31          | 0.13    | 0.64    |
|              | Glu        | 1.03      | 1.05          | 0.43    | 0.86    |
| DLPFC        | GSH        | 0.27      | 0.27          | 0.68    | 0.86    |
|              | NAA        | 1.46      | 1.46          | 0.78    | 0.86    |
|              | GABA       | 0.29      | 0.26          | 0.18    | 0.64    |
|              | Glu        | 1.25      | 1.26          | 0.34    | 0.86    |
| OFR          | GSH        | 0.26      | 0.28          | 0.19    | 0.64    |
|              | NAA        | 1.39      | 1.37          | 0.58    | 0.86    |
|              | GABA       | 0.29      | 0.30          | 0.71    | 0.86    |
|              | Glu        | 1.15      | 1.19          | 0.17    | 0.64    |
| Thal         | GSH        | 0.25      | 0.24          | 0.48    | 0.86    |
|              | NAA        | 1.30      | 1.31          | 0.43    | 0.86    |
|              | GABA       | 0.43      | 0.40          | 0.65    | 0.86    |
|              | Glu        | 1.14      | 1.13          | 0.96    | 0.96    |
TABLE S6. Group comparison of negative symptoms between treatment resistant (TR) patients who took clozapine and TR patients who didn’t take clozapine at the first visit.

SANS total and global scores were compared between TR patients who took clozapine (n=9) and TR patients who didn’t take clozapine (n=23).

| Scores            | mean (clozapine TR) | mean (non-clozapine TR) | p-value | q-value |
|-------------------|---------------------|-------------------------|---------|---------|
| total score       | 12.25               | 9.62                    | 0.80    | 0.93    |
| affective flattening | 2.38               | 1.81                    | 0.80    | 0.80    |
| alogia            | 1.88                | 1.81                    | 0.80    | 0.93    |
| avolition         | 2.75                | 2.24                    | 0.93    | 0.93    |
| anhedonia         | 3.13                | 2.19                    | 0.78    | 0.93    |
| attention         | 2.13                | 1.65                    | 0.55    | 0.93    |
TABLE S7. Group comparison of 7T MRS data between treatment resistant (TR) patients who took clozapine and TR patients who didn’t take clozapine at the first visit.

7T MRS data [normalized by water or total creatine (tCr)] were compared between TR patients who took clozapine (n=9) and TR patients who didn’t take clozapine (n=23). Abbreviations: GABA, γ-aminobutyric acid; Glu, glutamate; GSH, glutathione; NAA, N-acetylaspartate; ACC indicates anterior cingulate cortex; Thal, thalamus; DLPFC, dorsolateral prefrontal cortex; CSO, centrum semiovale; and OFR, orbital frontal region.

A) metabolite levels are normalized by water.

| Brain region | Metabolite | mean (clozapine TR) | mean (non-clozapine TR) | p-value | q-value |
|--------------|------------|---------------------|-------------------------|---------|---------|
| ACC          | GSH        | 1.41                | 1.39                    | 0.93    | 0.93    |
|              | NAA        | 7.11                | 7.03                    | 0.37    | 0.82    |
|              | GABA       | 1.66                | 1.73                    | 0.54    | 0.93    |
|              | Glu        | 7.85                | 8.16                    | 0.92    | 0.93    |
| CSO          | GSH        | 1.25                | 1.31                    | 0.32    | 0.79    |
|              | NAA        | 8.37                | 8.30                    | 0.12    | 0.61    |
|              | GABA       | 1.74                | 1.65                    | 0.07    | 0.61    |
|              | Glu        | 5.93                | 6.02                    | 0.15    | 0.61    |
| DLPFC        | GSH        | 1.47                | 1.44                    | 0.87    | 0.93    |
|              | NAA        | 8.15                | 7.90                    | 0.15    | 0.61    |
|              | GABA       | 1.44                | 1.67                    | 0.67    | 0.93    |
|              | Glu        | 6.62                | 6.93                    | 0.79    | 0.93    |
| OFR          | GSH        | 1.50                | 1.48                    | 0.89    | 0.93    |
|              | NAA        | 7.83                | 7.89                    | 0.46    | 0.93    |
|              | GABA       | 1.44                | 1.83                    | 0.81    | 0.93    |
|              | Glu        | 6.26                | 6.70                    | 0.92    | 0.93    |
| Thal         | GSH        | 1.58                | 1.37                    | 0.24    | 0.79    |
|              | NAA        | 7.77                | 7.28                    | 0.11    | 0.61    |
|              | GABA       | 2.57                | 2.33                    | 0.59    | 0.93    |
|              | Glu        | 6.79                | 6.37                    | 0.32    | 0.79    |
B) metabolite levels are normalized by tCr.

| Brain region | Metabolite | mean (clozapine TR) | mean (non-clozapine TR) | p-value | q-value |
|--------------|------------|---------------------|-------------------------|---------|---------|
| ACC          | GSH        | 0.24                | 0.24                    | 0.36    | 0.86    |
|              | NAA        | 1.24                | 1.20                    | 0.61    | 0.87    |
|              | GABA       | 0.29                | 0.30                    | 0.41    | 0.86    |
|              | Glu        | 1.39                | 1.40                    | 0.83    | 0.91    |
| CSO          | GSH        | 0.23                | 0.23                    | 0.54    | 0.86    |
|              | NAA        | 1.44                | 1.41                    | 0.74    | 0.89    |
|              | GABA       | 0.29                | 0.29                    | 0.86    | 0.91    |
|              | Glu        | 1.03                | 1.03                    | 0.76    | 0.89    |
| DLPFC        | GSH        | 0.27                | 0.26                    | 0.40    | 0.86    |
|              | NAA        | 1.50                | 1.44                    | 0.93    | 0.93    |
|              | GABA       | 0.25                | 0.31                    | 0.40    | 0.86    |
|              | Glu        | 1.21                | 1.27                    | 0.41    | 0.86    |
| OFR          | GSH        | 0.27                | 0.26                    | 0.56    | 0.86    |
|              | NAA        | 1.40                | 1.38                    | 0.27    | 0.86    |
|              | GABA       | 0.26                | 0.31                    | 0.49    | 0.86    |
|              | Glu        | 1.12                | 1.18                    | 0.67    | 0.89    |
| Thal         | GSH        | 0.28                | 0.24                    | 0.24    | 0.86    |
|              | NAA        | 1.35                | 1.27                    | 0.41    | 0.86    |
|              | GABA       | 0.46                | 0.41                    | 0.48    | 0.86    |
|              | Glu        | 1.18                | 1.12                    | 0.53    | 0.86    |
**TABLE S8. Group comparison of brain volume between treatment resistant (TR) patients who took clozapine and TR patients who didn’t take clozapine at first visit.**

Brain volumes were compared between TR patients who took clozapine (n=9) and TR patients who didn’t take clozapine (n=23). The top 10 brain regions are listed.

| Brain region                        | Hemisphere | Mean (clozapine TR) | Mean (non-clozapine TR) | p-value | p-value (permutation test) | q-value |
|-------------------------------------|------------|---------------------|-------------------------|---------|----------------------------|---------|
| Parietal sulcus                     | right      | 7792.67             | 6833.23                 | 0.02    | 0.03                       | 0.97    |
| Parietal sulcus                     | left       | 7389.17             | 6522.77                 | 0.03    | 0.04                       | 0.97    |
| Postcentral gyrus                   | left       | 11988.83            | 11453.54                | 0.07    | 0.26                       | 0.97    |
| Cerebellum white matter             | right      | 13202.67            | 12270.38                | 0.08    | 0.07                       | 0.97    |
| Stria terminalis of fornix          | left       | 1454.33             | 1500.15                 | 0.09    | 0.10                       | 0.97    |
| Fourth ventricle                    | right      | 2887.83             | 2324.15                 | 0.11    | 0.19                       | 0.97    |
| Posterior deep white matter         | right      | 5539.50             | 4765.23                 | 0.12    | 0.11                       | 0.97    |
| Posterior periventricular white matter | left     | 832.00             | 732.69                  | 0.12    | 0.14                       | 0.97    |
| Occipital sulcus                    | left       | 1166.67             | 980.00                  | 0.14    | 0.22                       | 0.97    |
| Limbic                              | left       | 1920.33             | 1727.38                 | 0.14    | 0.12                       | 0.97    |
TABLE S9. Longitudinal analysis results for brain volume.

We performed one sample t-test and Bayesian test to evaluate whether the annual percentage change (APC) was significantly different from zero in first episode psychosis patients during longitudinal follow-ups. Significant results (q-value < 0.05) are in bold with a gray shadow. Abbreviations: APC, annual percentage change.

| Metabolite                  | Average APC (%) | Bayes factor | q-value (t-test) |
|-----------------------------|-----------------|--------------|-----------------|
| right hippocampus           | -0.08           | 0.17         | 0.77            |
| left superior frontal gyrus | 0.28            | 0.25         | 0.47            |
| left gyrus rectus           | -1.45           | **18.69**    | **0.01**        |
TABLE S10. The performance of classification models

We compared the performance of five classification models: 1) model of age of onset (denoted as Onset); 2) model of glutathione in anterior cingulate cortex (denoted as GSH); 3) model of right hippocampal volume (denoted as HP); 4) model of left superior frontal gyral volume (denoted as SFG); and 5) model of multimodal markers (denoted as Onset + GSH + HP + SFG). Abbreviations: AUC, area under the curve; CI, confidence interval; and AIC, Akaike information criterion.

A) TR and non-TR patients (excluding those with short follow-ups)

| Predictor                  | AUC  | CI       | AIC   |
|----------------------------|------|----------|-------|
| Onset                      | 0.64 | 0.48-0.80| 69.06 |
| GSH                        | 0.69 | 0.53-0.85| 67.49 |
| HP                         | 0.60 | 0.44-0.76| 71.26 |
| SFG                        | 0.55 | 0.39-0.71| 72.64 |
| Onset + GSH + HP + SFG     | 0.83 | 0.70-0.96| 51.92 |

B) TR and non-TR patients (including those with short follow-ups)

| Predictor                  | AUC  | CI       | AIC   |
|----------------------------|------|----------|-------|
| Onset                      | 0.64 | 0.49-0.79| 77.43 |
| GSH                        | 0.63 | 0.47-0.79| 79.17 |
| HP                         | 0.60 | 0.44-0.76| 79.26 |
| SFG                        | 0.57 | 0.41-0.73| 80.94 |
| Onset + GSH + HP + SFG     | 0.80 | 0.67-0.93| 63.45 |
SUPPLEMENTARY FIGURE LEGENDS

FIGURE S1. Classification models of treatment resistant (TR) and non-TR patients (including those with short follow-ups).

We compared the performance of five classification models: 1) model of age of onset (denoted as Onset), blue, AUC=0.64; 2) model of glutathione in anterior cingulate cortex (denoted as GSH), purple line, AUC=0.63; 3) model of right hippocampal volume (denoted as HP), green line, AUC=0.60; 4) model of left superior frontal gyral volume (denoted as SFG), orange line, AUC=0.57; and 5) model of multimodal markers (denoted as Onset + GSH + HP + SFG), red line, AUC=0.80.

FIGURE S2. Future perspective.

We have established a multimodal cohort of first episode psychosis patients and healthy controls with a collection of clinical and neuropsychological test scores, molecular measures from different types of biospecimens, and neuroimaging data. Multimodal cohorts like ours could provide a comprehensive understanding of diseases through hypothesis and/or data-driven approaches. We expect that such cohorts will become essential resources for tackling the diagnosis and treatment of brain disorders.
Figure S1.

The diagram shows the receiver operating characteristic (ROC) curves for different models. The x-axis represents 1 - Specificity, and the y-axis represents Sensitivity. The models compared include:

- Onset
- GSH
- HP
- SFG
- Onset + GSH + HP + SFG
Figure S2.

Recruitment

Criteria (all participants)
- From 13 to 35 years old
- No history of TBI, cancer, bleeding, etc.
- No drug or alcohol abuse in past three years
- No illicit drug use in past two months

Criteria (patients)
- Onset of positive symptoms within the last 24 months

Clinical symptoms

Neuronal Circuits

Cells  Blood  CSF

Genotype  Proteomics  Metabolomics

Hypothesis driven approach

Data driven approach