

## **Supplementary information**

### **Peripheral Inflammation Mediates Cognitive Deficits in Drug-naive Schizophrenia through Hippocampal-thalamo-visual Circuitry Dysfunction**

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**Figure S1**

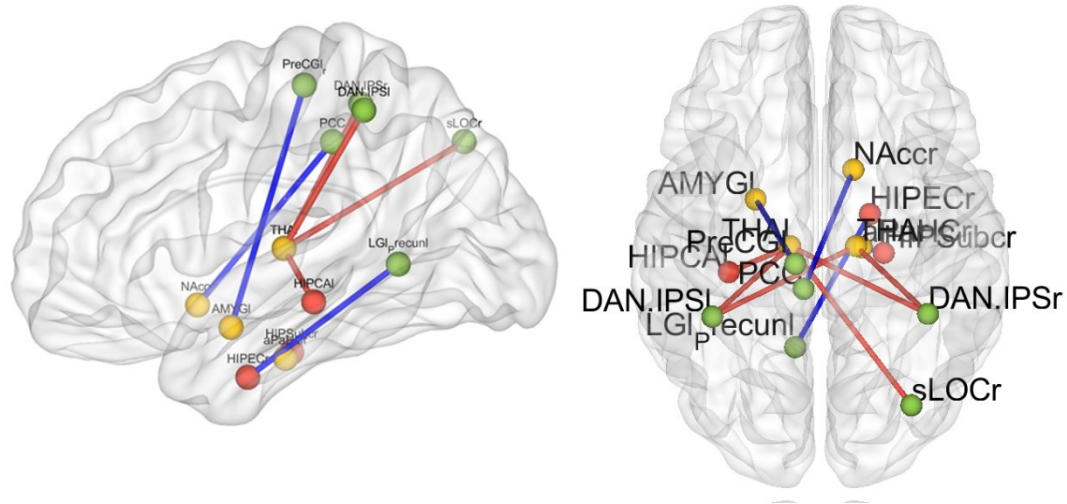


**Figure S1. Functional connectivity patterns exhibiting concurrent associations (uncorrected for multiple comparisons) with both inflammatory markers and cognitive domains.** HIPCA: the Cornu Ammonis of the Hippocampus; THA: thalamus; HIPEC: the Entorhinal cortex of the Hippocampus; LG/Precun: the Lingual Gyrus/left Precuneous Cortex; HIPSu: the Subiculum of the Hippocampus; aPaHC: Parahippocampal Gyrus, anterior division; sLOC: Lateral Occipital Cortex, superior division; DAN.IPS: intraparietal sulcus (Dorsal attention network); AMYG: Amygdala; PreCG: Precentral Gyrus; NAcc: Nucleus accumbens; PCC: Posterior cingulate cortex. l: left, r: right.

**Table S1 Pearson correlations between cognition domains and education**

|     | TMT    | BACS    | HVLT    | WMS     | NAB     | BVMT    | Fluency |
|-----|--------|---------|---------|---------|---------|---------|---------|
| Edu | -0.226 | 0.568** | 0.443** | 0.388** | 0.489** | 0.356** | 0.321** |

BACS: Brief Assessment of Cognition in SCZ; WMS-III: Wechsler Memory Scale-

Third Edition; Fluency: category fluency test: Animal naming; HVLT-R: Hopkins

Verbal Learning Test-Revised; BVMT-R: Brief Visuospatial Memory Test-Revised;

NAB: Neuropsychological Assessment Battery; TMT: Trail Making Test.

Edu: education. \*  $p < 0.05$  \*\*  $p < 0.01$

**Table S2 Pearson analyses between psychotic symptom severity and cognition domains in the SCZ group**

|                   | TMT    | BACS   | HVLT   | WMS    | NAB    | BVMT    | Fluency |
|-------------------|--------|--------|--------|--------|--------|---------|---------|
| PANSS total score | 0.253  | -0.284 | -0.163 | -0.253 | -0.217 | -0.100  | -0.381  |
| Positive score    | 0.305  | -0.228 | -0.032 | -0.231 | -0.242 | -0.418* | -0.015  |
| Negative score    | -0.068 | -0.172 | -0.354 | -0.182 | -0.060 | 0.170   | -0.401  |
| General score     | 0.145  | -0.186 | 0.001  | -0.126 | -0.143 | 0.022   | -0.374  |

BACS: Brief Assessment of Cognition in SCZ; WMS-III: Wechsler Memory Scale-Third Edition;

Fluency: category fluency test: Animal naming; HVLT-R: Hopkins Verbal Learning Test-Revised;

BVMT-R: Brief Visuospatial Memory Test-Revised; NAB: Neuropsychological Assessment Battery;

TMT: Trail Making Test.

SCZ: schizophrenia \*  $p < 0.05$  \*\*  $p < 0.01$

**Table S3 Pearson correlations between psychotic symptom severity and neuroimaging in the SCZ group**

| Brain functional metrics | PANSS total<br>score | Positive<br>score | Negative<br>score | General<br>score |
|--------------------------|----------------------|-------------------|-------------------|------------------|
| HIPSubcr_aPaHCr          | -0.009               | 0.018             | -0.024            | -0.012           |
| THAl_sLOCr               | 0.042                | 0.175             | -0.077            | 0.031            |
| HIPCAI_THAl              | -0.030               | -0.010            | 0.090             | -0.111           |
| HIPECr_LG/Precunl        | -0.035               | -0.062            | 0.033             | -0.054           |
| AMYGl_PreCGl/r           | -0.025               | -0.027            | -0.008            | -0.029           |
| NAccr_PCC                | -0.012               | 0.042             | -0.076            | 0.001            |
| THAr_AMYGr/HIPr          | -0.070               | 0.173             | -0.121            | -0.157           |
| THAr_DAN.LPSl            | -0.017               | 0.037             | 0.020             | -0.066           |
| THAl_DAN.LPSl            | 0.004                | 0.047             | -0.024            | -0.003           |
| THAr_DAN.LPSr            | -0.092               | 0.077             | -0.113            | -0.152           |
| THAl_DAN.LPSr            | -0.110               | 0.040             | -0.187            | -0.118           |
| THAr_HIPl                | -0.091               | -0.041            | -0.051            | -0.121           |
| THAr_AMYGl               | 0.171                | 0.268             | 0.055             | 0.147            |
| THAl_AMYGr               | 0.209                | 0.211             | 0.048             | 0.202            |

HIPCA: the Cornu Ammonis of the Hippocampus; THA: thalamus; HIPEC: the Entorhinal cortex of the Hippocampus; LG/Precun: the Lingual Gyrus/left Precuneous Cortex; HIPSubc: the Subiculum of the Hippocampus; aPaHC: Parahippocampal Gyrus, anterior division; sLOC: Lateral Occipital Cortex, superior division; AMYG: Amygdala; PreCG: Precentral Gyrus; NAcc: Nucleus accumbens; PCC: Posterior cingulate cortex. l: left, r: right.

SCZ: schizophrenia \*  $p < 0.05$  \*\*  $p < 0.01$

**Table S4 Spearman correlations between psychotic symptom severity and peripheral inflammation in the SCZ group**

| Serum cytokines       | PANSS total<br>score | Positive<br>score | Negative<br>score | General<br>score |
|-----------------------|----------------------|-------------------|-------------------|------------------|
| Log10(TNF- $\alpha$ ) | 0.032                | -0.032            | 0.113             | 0.007            |
| Log10(IL-6)           | 0.018                | 0.067             | 0.054             | -0.056           |
| Log10(IL-8)           | 0.136                | 0.164             | 0.173             | 0.084            |
| Log10(IL-10)          | -0.192               | -0.124            | -0.111            | -0.219           |
| Log10(CCL-2)          | -0.210               | -0.156            | -0.137            | -0.202           |
| Log10(IL-1 $\beta$ )  | -0.044               | 0.161             | -0.094            | -0.158           |
| Log10(IFN- $\gamma$ ) | 0.085                | -0.063            | -0.023            | 0.077            |
| Log10(IL-4)           | -0.233               | -0.052            | -0.255            | -0.201           |
| Log(IL-12P70)         | 0.051                | 0.124             | -0.009            | 0.001            |

\*  $p < 0.05$  \*\*  $p < 0.01$

**Table S5 Demographic and clinical characteristics of SCZ with and without MCCB data**

| Variables                | SCZ with MCCB<br>(N=26) | SCZ without MCCB<br>(N=36) | $\chi^2/T$ | <i>P</i> -value |
|--------------------------|-------------------------|----------------------------|------------|-----------------|
| Sex (males/females)      | 14/12                   | 19/17                      | 0.007      | 0.934           |
| Age (years)              | 23.92 (7.48)            | 28.36 (10.73)              | -1.813     | 0.075           |
| Education (years)        | 12.15 (3.31)            | 11.50 (3.62)               | 0.727      | 0.470           |
| BMI (kg/m <sup>2</sup> ) | 21.21 (3.04)            | 21.82 (2.87)               | -0.803     | 0.425           |
| Illness duration (years) | 1.61 (1.89)             | 1.37 (0.92)                | 1.276      | 0.202           |
| PANSS total score        | 87.35 (14.66)           | 79.25 (32.77)              | 1.167      | 0.248           |
| PANSS positive score     | 22.69 (6.46)            | 21.69 (8.60)               | 0.493      | 0.624           |
| PANSS negative score     | 21.00 (6.18)            | 19.53 (10.24)              | 0.642      | 0.524           |
| PANSS general score      | 43.65 (8.73)            | 38.03 (16.13)              | 1.596      | 0.116           |

SCZ: schizophrenia; BMI: Body Mass Index; PANSS: positive and negative syndrome scale;

MCCB: MATRICS Consensus Cognitive Suite Battery

**Figure S2**

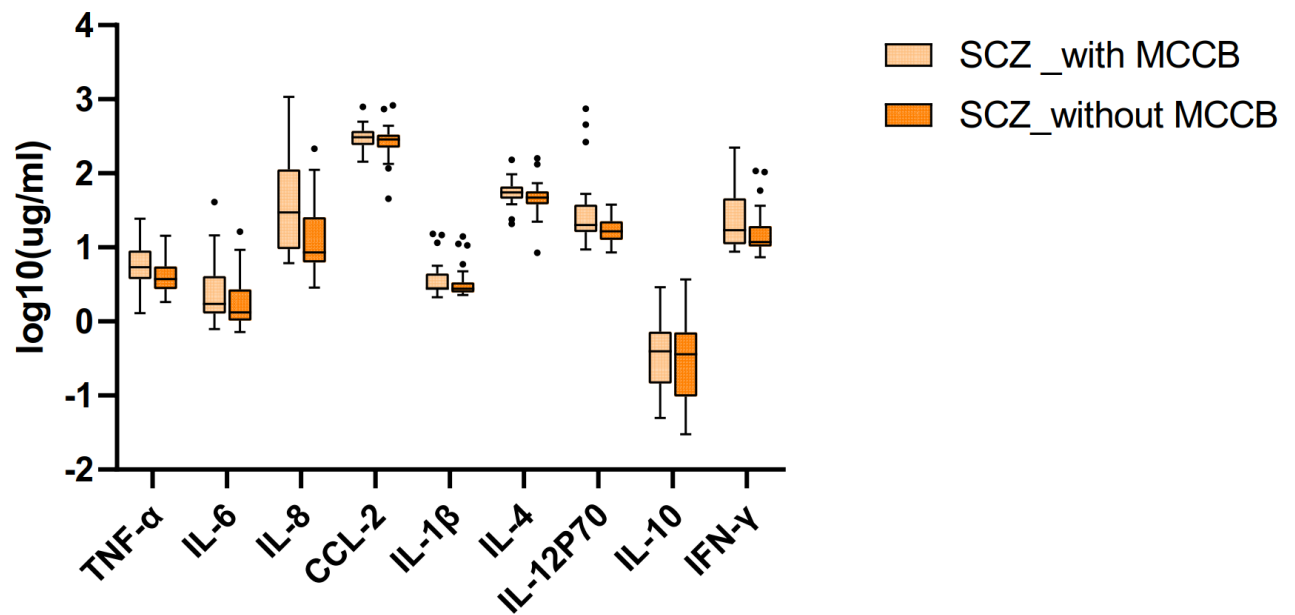


**Figure S2. Serum cytokine levels in schizophrenia patients with and without MCCB data.**

Group comparisons were performed using Two-T-tests followed by Bonferroni correction for multiple comparisons ( $p < 0.05$ ). SCZ: schizophrenia; MCCB: MATRICS Consensus Cognitive Suite Battery.

**Figure S3**

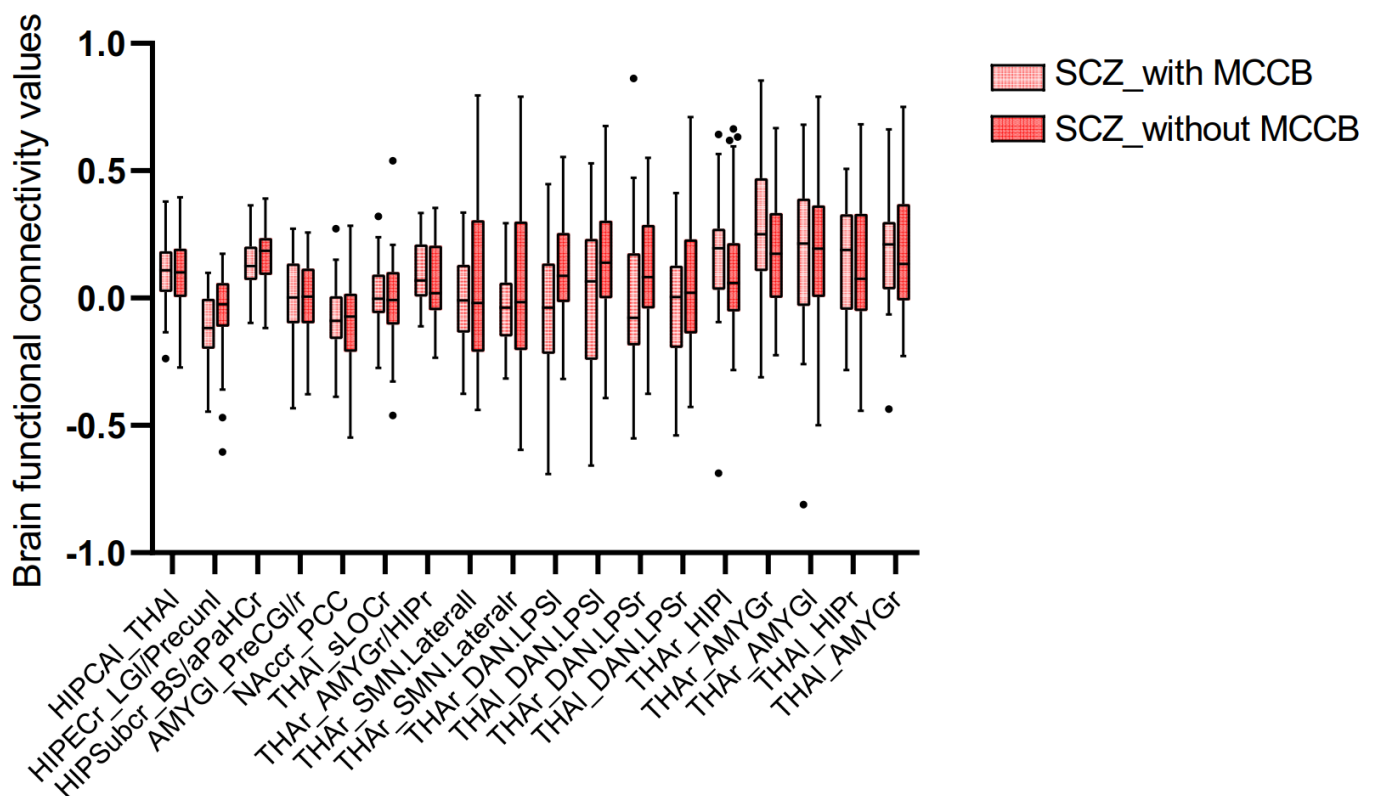


**Figure S3. Brain functional connectivity values in schizophrenia patients with and without**

**MCCB data.** Group comparisons were performed using Two-T-tests followed by Bonferroni

correction for multiple comparisons ( $p < 0.05$ ). SCZ: schizophrenia; MCCB: MATRICS

Consensus Cognitive Suite Battery. HIPCA: the Cornu Ammonis of the Hippocampus; HIPEC:

the Entorhinal cortex of the Hippocampus; HIPSubcr: the Subiculum of the Hippocampus; aPaHC:

Parahippocampal Gyrus, anterior division; THA: thalamus; LG/Precun: the Lingual Gyrus/left

Precuneous Cortex; sLOC: Lateral Occipital Cortex, superior division; AMYG: Amygdala;

PreCG: Precentral Gyrus; NAcc: Nucleus accumbens; PCC: Posterior cingulate cortex; IPS:

intraparietal sulcus; DAN: Dorsal attention network; SMN: Sensorimotor network. l: left, r: right.

## Abbreviations

|       |                                                   |
|-------|---------------------------------------------------|
| FC    | Functional connectivity                           |
| FCN   | Functional connectivity network                   |
| ROI   | Regions of interest                               |
| HIP   | Hippocampus                                       |
| CA1   | Cornu Ammonis 1                                   |
| EC    | Entorhinal cortex                                 |
| Subc  | Subiculum                                         |
| THA   | Thalamus                                          |
| sLOC  | Superior division of the lateral occipital cortex |
| aPaHC | Anterior parahippocampal gyrus                    |
| NAcc  | Nucleus accumbens                                 |
| AMYG  | Amygdala                                          |
| PCC   | Posterior cingulate cortex                        |
| IPS   | Intraparietal sulcus                              |
| SMN   | Sensorimotor network                              |
| DAN   | Dorsal attention network                          |
| WMS   | Wechsler Memory Scale                             |
| FDR   | false discovery rates                             |