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Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed	
☐	☒	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒	A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒	A description of all covariates tested
☐	☒	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒	A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	All the traced neuronal images were taken using the EVOS FL Auto microscope (Life Technologies, Carlsbad, CA). Image J software (v. 1.51, NIH, Bethesda, MD) was used to count the cell number using the multi point function. ImageJ software (v. 1.51) with the NeuronJ plugin was used to obtain parameters of arborization. For synapse analysis, images were processed using Imaris software (v. 9.2, Bitplane, Switzerland). RNA-seq of Control and act.MG. samples were collected on Illumina NextSeq 550 or 500 system. Raw sequence reads were de-multiplexed and trimmed for adapters by using the Illumina bcl2fastq conversion software (v. 2.19).
Data analysis	Statistical analyses were performed using GraphPad Prism7 (GraphPad Software, La Jolla, CA) and SAS statistical software (9.4, SAS Institute, Cary, NC). FASTQ files were aligned to the human hg19 reference genome with GENCODE v19 transcriptome annotation using STAR (v.2.4.0) and gene expression levels were quantified as RPKM values using featureCount (v.2.0.0), taking into account the strandness of the reads and all transcript variants of each gene in the GENCODE annotation; or pseudo-aligned to the human hg38 reference transcriptome and the gene transcript abundance was quantified by using Kallisto (v.0.46.1). The Kallisto-Sleuth and Kallisto-DESeq2 workflows are based upon a previous publication (Bray et al., 2016, Nat. Biotechnol. 34, 525–527). Differential expression of genes and transcripts were achieved by using the Sleuth and/or DESeq2 (v.1.26.0) in R Studio packages (v.1.2.1335 with R v.3.6.1).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

The RNA-seq data were deposited at the GEO < https://www.ncbi.nlm.nih.gov/geo/> and the accession numbers are GSE118313, GSE132689 and GSE152438. For human cDNA ensemble database, we used human cDNA fasta file GRCh38 release 87 available at http://www.ensembl.org/info/data/ftp/index.html. The data that support the findings of this study are available from the corresponding authors upon request.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical method was used to pre-determine the sample sizes. However, the sample sizes we used in this study are similar to the largest one among previous publications (Jensen et al. Translational Psychiatry (2019) 9:96). This sample size was adequate to observe cIN intrinsic transcriptome abnormalities in metabolic gene expression under inflammatory conditions.
Data exclusions	No data were excluded.
Replication	All attempts in replication were successful. The major result of the paper is replicated with independent replication cohort as in Fig.1H, 5H, Extended data 3 , and Extended data 4, Full methodological protocols are reported in detail to allow replication by other groups as well.
Randomization	Experimental cohorts were chosen based on our selection criteria (Caucasian male patients treated with Clozapine vs. age- and gender matched Caucasian male healthy controls) without randomization to reduce variation caused by age, ethnicity and gender.
Blinding	When possible, data analysis was performed by an investigator blind to the testing condition, including for cell counting, arborization analysis and synapse analysis. Experiments involving cell culture-based samples were not performed blinded to experimenter due to the fact that individual cell lines had to be separately maintained and carefully documented by the experimenters, so blinding was not possible during experimental setup.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used	GAD1 (Millipore, AB1511, 1:1,000), SOX6 (Millipore, AB5805, 1:1,000), VGAT (Synaptic System, 131003, 1:1,000), Gephyrin (Synaptic System, 147011, 1:1,000), VGlut1 (UC Davis/NIH NeuroMab, 73-066, 1:1,000), GABA (IMMUNOSTAR, 20094, 1:1,000), Glutamate (Sigma-Aldrich, G6642, 1:1,000), b-Tubulin III (Covance, 802001, 1:2,000), Iba1 (FUJIFILM Wako, 019-19741, 1:1,000), OLIG2 (Millipore, AB9610, 1:1,000), GFAP (UC Davis/NIH NeuroMab, N206A/8, 1:1,000), CHAT (Chemicon, AB114P, 1:1,000), TH (Pel-Freez, P40101-150, 1:1,000), 5-HT (IMMUNOSTAR, 20080, 1:1,000) and VIP (IMMUNOSTAR, 20077, 1:1,000)

Validation	The antibodies were validated in previous publicatoins or by the manufacturers as below: anti-GAD1 (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019)) anti-SOX6 (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019)) anti-VGAT (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019)) anti-Gephyrin (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019)) anti-Vglut1 (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019)) anti-GABA (Eban-Rothschild, A. et al. ENEURO 10.1523/ENEURO.0356-19.2020) anti-Glutamate (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019)) anti-b-Tubulin III (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019)) anti-Iba1 (Yan, S., et al. Cell 173, 4, 989 (2018)) anti-OLIG2 (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019)) anti-GFAP (https://www.antibodiesinc.com/products/gfap-n206a-8) anti-CHAT (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019)) anti-TH (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019)) anti-5-HT (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019)) anti-VIP (Shao, Z. et al. Nat Neurosci 22, 229-242, doi:10.1038/s41593-018-0313-z (2019))

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Human fibroblasts were obtained from the laboratories of Dr. Bruce Cohen (McLean Hospital, cell line: 272, 190, 367, 226, PYAUM, 317, and 292 for HC/67, 128, 212, 162, 58, 282, and 285 for SCZ), Dr. Daniel Weinberger (Lieber Institute for Brain Development, cell line: L9, L7, and L5 for HC/L10 and L8 for SCZ), and Dr. Judith Rapoport (National Institute of Mental Health, cell line: 689 for SCZ). These study protocols were approved by the McLean Hospital/Partners Healthcare Institutional Review Board and New York Medical College Institutional Review Board. All procedures were performed in accordance with the Institutional Review Board's guidelines and all human samples were obtained with informed consents. Human fibroblasts were reprogrammed using modified RNA methods by Cellular Reprogramming, Inc. (San Diego, CA). Established iPSC cultures on rLaminin-521 (BioLamina, Sweden) in Nutristem XF media (Biological Industries, Israel) and expanded in the same culture system.
Authentication	iPSC lines were validated by immunocytochemistry in our previous publications (Shao et al., 2019 and Ni et al., 2019).
Mycoplasma contamination	All cell lines are routinely tested for mycoplasma contamination. Cell lines used in this study were verified to be mycoplasma free before undertaking any experiment with them.
Commonly misidentified lines (See ICLAC register)	No commonly misidentified cell line was used.

Human research participants

Policy information about studies involving human research participants

Population characteristics	SCZ patients were Caucasian males treated with Clozapine with age from 21 - 51 years old. Age and gender-matched healthy controls were also selected.
Recruitment	Tissue samples were obtained with proper consents from the participants under approved IRB protocols of each institute as described in "Cell Line Sources" section. The selection criteria for SCZ patients were Caucasian males treated with Clozapine. Age and gender-matched healthy controls were also selected. These selection criteria were to narrow down the samples to more severe cases of diseases for stronger phenotype. Thus, it is likely that our results may be more biased for the case of more severe form of disease.
Ethics oversight	These study protocols were approved by the McLean Hospital/Partners Healthcare Institutional Review Board and New York Medical College Institutional Review Board. All procedures were performed in accordance with the Institutional Review Board's guidelines and all human samples were obtained with informed consents. We have complied with all relevant ethical regulations.

Note that full information on the approval of the study protocol must also be provided in the manuscript.