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Corresponding author(s): Kristen Brennand and Gabriel Hoffman

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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 Authors & Referees 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	None
Data analysis	Whole transcriptome RNAseq data was processed using R. Code available at https://github.com/nadschro/synergy-analysis. R packages used: R version 3.5.0 (2018-04-23) R packages: limma_3.38.3 edgeR_3.24.3 pheatmap_1.0.12 RColorBrewer_1.1-2 ggplot2_3.1.1 ggpubr_0.2 qvalue_2.18.0 plyr_1.8.4 wesanderson_0.3.6 GSEABase_1.44.0 grid_3.6.2 scales_1.0.0 WebGestaltR_0.4.0 stringr_1.4.0

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/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

To facilitate improved sharing between stem cell laboratories, all hiPSCs have already been deposited at the Rutgers University Cell and DNA Repository (study 160; http://www.nimhstemcells.org/) and RNA-seq data is available at www.synapse.org/#!Synapse:syn20502314.

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	Sample size for RNA-seq was > 30, which allows an adequate observation to take the benefits of the Central limit Theorem, i.e. normally distributed data.
Data exclusions	No data were excluded.
Replication	hiPSCs, hiPSC-NPCs and hiPSC-neurons underwent multiple differentiations and multiple wells for each phenotypic assay and RT-qPCR. Whole-transcriptome RNA-seq was performed on 2 replicates per donor and cell type.
Randomization	All donor samples were allocated into both, control and experimental groups and analyzed in parallel and blinded to control for covariates.
Blinding	RNA sequencing was conducted by scientists at NYGC blinded to sample condition.

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
☒	☐ Animals and other organisms
☒	☐ Human research participants
☒	☐ Clinical data

Methods

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

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Validated control hiPSCs for CRISPR-editing and CRISPRa/i were selected from a previously reported case/control hiPSC cohort of childhood onset SZ (COS) (Hoffman et al, Nat Comm 2017). The following controls were used for CRISPRa/i (hiPSC NPCs NSB553- S1-1 (male), NSB2607-1-4 (male), NSB690-2-1 (male)). Commercial cell lines: HEK293T cells for virus generation: Verma Lab (https://jvi.asm.org/content/73/1/576) MEFs for hiPSC feeder culture: Millipore #PMEF-CF
Authentication	Source fibroblasts were re-genotyped using PsychChip and exome sequencing. hiPSCs were reprogrammed via sendai viral reprogramming (Life Technologies) and validated by karyotyping, gene expression and protein immunocytochemistry. All other cell lines were purchased and not re-validated.

Mycoplasma contamination	Cells were tested for mycoplasma monthly with all test being negative.
Commonly misidentified lines (See ICLAC register)	none.