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Reporting Summary

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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	Asipro Vm (Concorde Microsystems, Knoxville, TN); AMIDE software v 0.9.0 (Crump Institute for Molecular Imaging, UCLA School of Medicine, Los Angeles, CA); StereoInvestigator v10.0 software (MicroBrightField, Williston, VA)
Data analysis	GraphPad Prism (version 8.0, GraphPad Software); R v3.5.3 (R Foundation for statistical Computing, Vienna, Austria); Origin 2017

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

All requests for raw and analyzed data and materials will be promptly reviewed by the corresponding author and the University of Wisconsin, Madison to verify whether the request is subject to any intellectual property or confidentiality obligations. Any data and materials that can be shared will be released via a Material Transfer Agreement.

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	The number of subjects per group was defined by previous studies assessing treatments in ICA MPTP-treated monkeys in which a minimum n = 4-5 detected statistically significant therapeutic effects in in vivo and post mortem outcome measures. References: 1, Emborg, M. E. et al. Response of aged parkinsonian monkeys to in vivo gene transfer of GDNF. Neurobiol Dis 36, 303-311, doi:10.1016/j.nbd.2009.07.022 (2009). 2, Swanson, C. R. et al. The PPAR-gamma agonist pioglitazone modulates inflammation and induces neuroprotection in parkinsonian monkeys. J Neuroinflammation 8, 91, doi:10.1186/1742-2094-8-91 (2011). 3, Ohshima-Hosoyama, S. et al. A monoclonal antibody-GDNF fusion protein is not neuroprotective and is associated with proliferative pancreatic lesions in parkinsonian monkeys. PLoS One 7, e39036, doi:10.1371/journal.pone.0039036 (2012).
Data exclusions	1 monkey data from each group was excluded because they died early post-transplantation.
Replication	As presented in figure legends, the results were reliably reproduced across subjects over time. Scorers underwent reliability training.
Randomization	The MPTP lesioned monkeys were matched according to disability and then blindly and randomly assigned into two groups, for allogenic or autologous transplantation.
Blinding	Data collection and analysis were performed by investigators blind to the treatment groups.

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	TH (Immunostar, 22941; Millipore, AB152), CD68 (DAKO, M0814), CD45 (DAKO, M0701), CD3 (DAKO, A0452), FOXA2 (R&D systems, AF2400), NANOG (Stemgent, 09-0020), OCT4 (Santa Cruz Biotechnology, sc-5279), SOX2 (R&D systems, AF2018), TRA-1-80 (Santa Cruz Biotechnology, sc-21706), EN1 (DSHB, 4G11-c), GFAP (DAKO, Z0334), GIRK2 (Alamone Labs, APC006), Calbindin (Sigma, HPA023099), COL1A1(R&D systems, AF6220), vGLUT1 (synaptic systems, 135303), 5-HT (Immunostar, 20080), GABA (Sigma, A2052) and GFP (Millipore, MAB3580).
Validation	TH (Immunostar, 22941; Millipore, AB152), CD68 (DAKO, M0814), CD45 (DAKO, M0701), CD3 (DAKO, A0452), FOXA2 (R&D systems, AF2400), NANOG (Stemgent, 09-0020), OCT4 (Santa Cruz Biotechnology, sc-5279), SOX2 (R&D systems, AF2018), TRA-1-80 (Santa Cruz Biotechnology, sc-21706), EN1 (DSHB, 4G11-c), GFAP (DAKO, Z0334), GIRK2 (Alamone Labs, APC006), Calbindin (Sigma, HPA023099),vGLUT1 (synaptic systems, 135303), 5-HT (Immunostar, 20080), GABA (Sigma, A2052) and GFP (Millipore, MAB3580) have been validated by the manufacturers and also used in our lab routinely. COL1A1(R&D systems, AF6220) were used in paper: Tiklova, K. et al. Single cell transcriptomics identifies stem cell-derived graft composition in a model of Parkinson's disease. Nat Commun 11, 2434, doi:10.1038/s41467-020-16225-5 (2020).

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	Rhesus monkey primary dermal fibroblasts; Five RhiPSC lines were generated from monkey fibroblasts; one RhiPSC was established in previous study.
Authentication	None of the cell lines were authenticated.
Mycoplasma contamination	All the cell lines tested negative for mycoplasma.
Commonly misidentified lines (See ICLAC register)	not applicable

Animals and other organisms

Policy information about studies involving animals; ARRIVE guidelines recommended for reporting animal research

Laboratory animals	Adult male rhesus macaques (Macaca mulatta; 10-14 years old; 8-19 kg) were used in this study.
Wild animals	no wild animals were used in this study.
Field-collected samples	no samples were collected from field.
Ethics oversight	The present study was performed in strict accordance with the recommendations in the National Research Council Guide for the Care and Use of Laboratory Animals (8th edition, 2011) in an AAALAC accredited facility (Wisconsin National Primate Research Center, WNPRC, University of Wisconsin-Madison). Experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Wisconsin-Madison.

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

Magnetic resonance imaging

Experimental design

Design type	Neither task nor resting state; neither event-related nor block design, because no fMRI was performed. Preoperative structural MRIs were used to plan the placement of surgical hardware on the skull, and intraoperative structural MRIs were viewed immediately after acquisition to guide the delivery of cells, as the aiming and injection procedures were performed inside the MRI scanner. All MRIs were acquired in a 3-Tesla GE Discovery MR750 scanner with a custom 3-inch diameter, receive-only surface coil (MR Instruments, Inc. Minneapolis, MN). During the scans the animals were deeply sedated and their vital signs (heart rate, blood oxygen, respiration and temperature) were monitored during the procedure using MRI-compatible instruments. The animals were wrapped to retain body heat and placed in a MRI-compatible stereotaxic frame. A baseline T1 neuronatomical MRI was performed in all monkeys for neurosurgical planning. The autologous cells were intracerebrally delivered using Real Time-Intraoperative Magnetic Resonance Imaging (RT-IMRI). The allogenic grafts were delivered using MRI-guided stereotaxic methods (based on a pre-surgery baseline MRI) in a surgical suite.
Design specifications	No blocks, trials, nor experimental units because no fMRI was performed. The RT-IMRI system utilized a pivot point-based MRI-compatible external trajectory guide (Medtronic Inc., Minnesota, MN) to guide a fused silica single endport cannula (Engineering Resources Group, Inc. Pembroke Pines, FL). A clear infusion line (FEP Fluoropolymer infusion line, IDEX Health & Science, Lake Forest, IL) was used to connect the cannula to a pressure transducer fixed to a 100 µL Hamilton syringe (Hamilton, Reno, NV). A MRI-compatible syringe pump (PHD 2000, Harvard Apparatus, Inc., Holliston, MA) was used to drive the syringe. The cannula attached to the loading lines was secured in place by an MRI-compatible uploader device (Engineering Resources Group, Inc.; Pembroke Pines, FL). A pressure-monitoring and infusion pump controller (Engineering Resources Group, Inc. Pembroke Pines, FL) was used to regulate the infusion and monitor pressure in the infusion line. The real time targeting utilized RTHawk scanner interface (HeartVista, Los Altos, CA), and the VURTIGO toolkit (Visual Understanding of Real-Time Image Guided Operations, Sunnybrook Health Sciences Centre; Toronto, Canada) to allows the operator to align the trajectory guide with real-time feedback in an interactive manner. Real-time scan control and visualization was conducted on a high-performance external workstation with two quad-core Intel Xeon E5620, 2.4 GHz CPUs, 12 GB of memory, an NVIDIA GF100 Quadro 4000 graphics card, and dual gigabit Ethernet controllers, running 64-bit Linux. Scanner interface was via an internal Ethernet switch. The operator tracked the position of the MR-visible fluid-filled alignment stem through a screen placed in the scanner room window.
Behavioral performance measures	Behavioral testing was not performed during MRI acquisition as subjects were under general anesthesia.

Acquisition

Imaging type(s): Structural

Field strength: 3

Sequence & imaging parameters:

Planning and monitoring volumes: 3D gradient echo inversion recovery Cartesian, 180 x 180 x 99 mm^3 field of view, 256 x 224 x 124 acquisition matrix, 0.8 mm slice thickness, coronal slab with 3.9 ms echo time, 9.1 ms repetition time, 450 ms inversion time, 12° flip angle, 6 minute acquisition time.

Real-time device tracking: 2D balanced steady-state free precession radial, 200 x 200 mm^2, 512 sample 18 projection, 3 mm slice thickness, plane perpendicular to planned trajectory with 1.5 ms echo time, 11 ms repetition time, 50° flip angle, 0.2 seconds acquisition time (yielding a real-time feed of 5 updates per second).

For RT-IMRI a high-resolution, volume scan was acquired and viewed by the operator to identify the anatomical target point in the brain, and the pivot point of the trajectory guide. The prospective stereotaxy software then calculated an "aim point" outside the skull that was along the planned trajectory (co-linear with the target and pivot points). A real-time MR acquisition was initiated in the plane containing the aim point and perpendicular to the planned trajectory, allowing the software to compute and display the point where the alignment stem intersected with the MR acquisition plane. The trajectory guide was manipulated into different orientations and the computed stem-plane intersection points were sampled so the software could calculate refined coordinates for the pivot point. Using the trajectory defined by the target and this improved pivot point, the prescribed location of the real-time plane was updated for the final aiming step. The operator manipulated the trajectory guide while viewing a rendering of both the aim point and the computed stem-plane intersection point until they overlapped, indicating alignment with the target.

Once the alignment stem was in position, the trajectory guide ball joint was locked, the alignment stem was removed and the cannula was inserted in its place. The cannula was partially inserted (to within 10 mm of the calculated depth) and the previously described 3D volume was reacquired to confirm that the cannula had not been deflected from the planned trajectory, and to measure the remaining distance from cannula tip to target. Once confirmed, the cannula was advanced to its final depth. When the pressure reading on the injection pump controller system stabilized, the injection began. To visualize the injection delivery region, 3D volumes were reacquired during and immediately after the injection using the previously described sequence. The free water in the buffer of the injection provided image contrast against the surrounding brain matter and validation that the injection was delivered to the intended region.

Area of acquisition: For 3D planning & monitoring scans: whole brain. For real-time device tracking: in a plane outside the head and perpendicular to the planned trajectory (location and orientation of plane computed by Vurtigo prospective stereotaxy software, and scan plane prescribed, acquired, and reconstructed by RTHawk real-time scanner control software).

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software: ITK-SNAP v3.6.0-rc1 was used to manually segment cell deposit volumes in post-infusion images for use as ROIs during analysis of the post-surgical PET data. MRI immediately after infusion during the surgical procedure was used to simply to confirm that the infusion of cells was delivered to then intended brain region.

Normalization: No normalization because no statistical analysis of MRI data was performed.

Normalization template: No normalization template used because no statistical analysis of MRI data was performed.

Noise and artifact removal: No noise or artifact removal because no statistical analysis of MRI data was performed.

Volume censoring: No volumes censored because no statistical analysis of MRI data was performed.

Statistical modeling & inference

Model type and settings: No model used because no statistical analysis of MRI data was performed. MRI immediately after infusion during the surgical procedure was used to simply to confirm that the infusion of cells was delivered to then intended brain region.

Effect(s) tested: No effect tested because no statistical analysis of MRI data was performed.

Specify type of analysis: ☐ Whole brain ☒ ROI-based ☐ Both

Anatomical location(s): Cell deposit regions in putamen and caudate were manually segmented based on the stronger negative contrast arising from the artificial CSF delivered along with the cells, which is rendered hypointense by the CSF-nulling inversion recovery MRI sequence.

Statistic type for inference (See Eklund et al. 2016): Neither voxel-wise nor cluster-wise because no statistical analysis of MRI data was performed.

Correction: No correction applied because no statistical analysis of MRI data was performed.

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis