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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. 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
☐	☒	An indication of 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 statistics 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
☐	☒	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Flow cytometry data analysis and sorting were performed on BD Influx using the BD FACS™ software (BD Biosciences). Confocal images were acquired with Zeiss LSM880 confocal microscope using Zen2012 software and with Leica TCS SP8X confocal microscope, using LAS AF software. Microscope images were acquired with Leica CTR6000 bright-field microscope, using LAS AF 3 software. Nanodrop measurements were done using NanoDrop 2000/2000c Operating Software, version 1.6.
Data analysis	Image analysis, processing, assembly and counting were performed with Zen2012 software, Image J/Fiji software (version 1.47v for Mac, Java 1.6.0_65), Imaris 7.6 (Bitplane), Adobe Photoshop CS6 and Illustrator CS6 for Mac. GraphPad Prism 7 software was used for all statistical analysis. MATLAB R2016 was used for mathematical modeling. Modeling equations are given in the supplementary data and references are described of previously established models.

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 upon request. 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 data supporting the findings in this study are available within the paper and its supplementary information.

Field-specific reporting

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

☒ Life sciences ☐ Behavioural & social sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences

Study design

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

Sample size	No statistical methods were used to predetermine sample size. Sample size sufficiency was based on previous experiments from our laboratory and previous publications using the 14C carbon dating strategy. In brief, by analysis of tissue samples from subjects of different ages using our strategy of birth dating cell nuclei by the content of nuclear bomb-test derived 14C in genomic DNA, we are able to get different information regarding cell generation and thus cellular generation dynamics. The sensitivity of determining the cell age is different for each subject depending on when the subjects was born in relation to the nuclear bomb test. A subject born before 1955 will have higher sensitivity for detecting cell generation late in life, whereas a subject born after the the nuclear bomb test will have higher sensitivity of detecting cell generation early in life. Hence, analyzing several subjects of different ages and of different birth dates in relation to the nuclear bomb test rather than analyzing several subjects of the same age will provides the highest total sensitivity of cell turnover detection and the information of when a cell population is generated in time. Moreover, 14C acts as a cumulative label. The number of subjects were sufficient when adding another subject did not change the information of the cell population's generation dynamics.
Data exclusions	Internal controls and individual controls (cortical neurons) were used to control for the AMS 14C measurements. If the controls were contaminated the MS sample was excluded. This exclusion criteria was pre-established. Estimated MS patient annual turnover rate of mature oligodendrocyte in normal appearing white matter were excluded due to poor fit based on residuals. Patient with residual over 1 or unrealistic turnover rate were excluded as stated in Supplementary Table 4. It was pre-established to exclude data points based on poor fit. The exclusion of unrealistic values were not pre-established.
Replication	Due to tissue limitation, replication of the experiment from the same tissue block of the subject was not possible for carbon dating experiment as the whole tissue sample were used per measurement. However, an internal control from the same subject was used to replicate the strategy (AMS measurement). Moreover, 40 samples were used verifying the reproducibility of the flow cytometry and carbon dating experiments.
Randomization	Randomization was not applicable in this study as the objective was to study a specific pathology process and not an intervention. The MS samples included were selected according to tissue and lesion type by independent neuropathologist using standard criteria (see method section) and all samples in the study were treated equally. Sex-specific differences were minimized by including similar number of male and female patient when possible.
Blinding	Tissue samples were not blinded in nuclei and flow cytometry experiments. Experiments by AMS of the following samples were blinded to sample identity. Patient pathology history was blinded during whole data collection.

Materials & experimental systems

Policy information about availability of materials

n/a	Involved in the study
☐	☒ Unique materials
☐	☒ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Research animals
☐	☒ Human research participants

Unique materials

Obtaining unique materials	Brain Postmortem tissue sample from multiple sclerosis patients (shadow plaques and normal appearing white matter) were

Obtaining unique materials | obtained from international biobanks and collaborators and only available for distribution from a third party: The Netherlands Brain Bank (NBB, Netherlands Institutet for Neuroscience, Amsterdam, open access: www.brainbank.nl), the Multiple Sclerosis Society Tissue Bank and the Cleveland Clinic (Lerner Research Institute, Cleveland, Ohio, US) as further described in the method section, "Tissue collection". Collection and use of tissue material were under institutional ethical guidelines and permission. All tissue obtained was used in the experiments and therefore not available.

Antibodies

Antibodies used | Following primary antibodies were used:
anti-SOX10 (goat, R&D Systems, AF2864, 1:250), anti-APC/CC1 (mouse, Millipore/Calbiochem, OP80, clone CC-1, 1:250), anti-Nogo-A (rabbit, Millipore, AB5888, 1:500, mAb 11C7, a generous gift from M.E. Schwab, Brain Research Institute, ETH and University of Zürich, 1:10 000), anti-PLP (rat, generous gift from B.D. Trapp, Lerner Research Institute, Cleveland Clinic, clone AA3, 1:250), anti-Ki67 (mouse, DAKO, GA626, clone MIB-1, 1:300), anti-Iba1 (rabbit, WAKO, #019-19741, 1:1000, goat, abcam, ab5076, 1:500), anti-CD68 (mouse, Abcam, ab955, clone KP1, 1:400) and anti-TMEM-119 (rabbit, Abcam, ab185333, 1:250). Following secondary antibodies were used: anti-goat, mouse, rat, rabbit, conjugated to AlexaFluor488, 555 and 647 (Molecular Probes, Invitrogen)- and to Cy3, and Cy5 (Jackson ImmunoResearch).

Validation | All antibodies used in this study have been extensively used in the literature. For most antibodies used they have been validated by the company (indicated from antibody product sheet), and further validated for our specific strategy in a previously published paper (Yeung et al., 2014, Cell). When not provided, control experiments were performed, including no primary antibody (negative) controls, positive control tissue with known expression of the marker used and comparison to mouse staining expression.
anti-SOX10, validated on manufacturer website, for ICC, IHC, WB, further validated for FACS in Yeung et al. Dynamics of oligodendrocyte generation and myelination in the human brain. Cell. 2014,159,766-774.
anti-APC/CC1, validated on manufacturer website, for IHC, IF, and further validated for FACS in Yeung et al. Dynamics of oligodendrocyte generation and myelination in the human brain. Cell. 2014,159,766-774.
anti-Nogo-A , validated on manufacturer website, and Wahl et al.,Neuronal repair. Asynchronous therapy restores motor control by rewiring of the rat corticospinal tract after stroke. Science. 2014,344,1250-1255.
anti-PLP, Chang et al. Cortical remyelination: a new target for repair therapies in multiple sclerosis. Ann Neurol. 2012, 72,918-926.
anti-Ki67, validated on manufacturer website, for IHC, WB.
anti-Iba1, validated on manufacturer website, for ICC, IHC, WB.
anti-CD68, validated on manufacturer website, for ICC, IHC.
anti-TMEM-119, validated on manufacturer website, for IHC.

Human research participants

Policy information about studies involving human research participants

Population characteristics | For healthy controls, tissue had no pathological conditions and diagnosis. For all multiple sclerosis cases, all tissue was obtained from international tissue banks and collaborators. All tissue sample characterization and identification were done by independent neuropathologist following standard criteria and further validated in experiments in our study as described in the methods section. The study included tissue samples of normal appearing white matter and shadow plaques from totally 40 multiple sclerosis patients and all relevant patient information from every individual such as age, multiple sclerosis disease type, duration, etc is further provided in Supplementary Table 1.

Method-specific reporting

n/a	Involved in the study
☒	☐ ChIP-seq
☐	☒ Flow cytometry
☒	☐ Magnetic resonance imaging

Flow Cytometry

Plots

Confirm that:

☒ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).

☒ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).

☒ All plots are contour plots with outliers or pseudocolor plots.

☒ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation | This is described in Methods under "Nuclear isolation and flow cytometry" section.

Instrument | BD Influx

Software	BD FACS software
Cell population abundance	The purity of the sorted nuclei fractions are provided in Supplemental Table 1. In brief, the mature oligodendrocyte nuclei sorted fraction in MS NAWM was 94.8 ± 2.1%, n=29. In shadow plaques, the mature oligodendrocyte sorted fraction was 96.5 ± 0.8%, n=11. The purity of the isolated nuclei fraction were defined as, gated nuclei population of interest in the sorted fraction/ by the total number of nuclei in the sorted fraction
Gating strategy	We have previously established a strategy to isolate mature oligodendrocyte cell nuclei to high purity by flow cytometry from human postmortem brain tissue (Yeung et al 2014., Cell). In brief, first, to exclude cell debris from cell nuclei, physical parameters FSC and SSC were used. Secondly, single nuclei were separated and exclusion of doublets and higher order aggregates was done by the FSC-H and the FSC-W parameters. Finally, to isolate mature oligodendrocyte nuclei, primary antibodies against SOX10 and CC1 followed by fluorescent-conjugated secondary antibodies were used. The mature oligodendocyte nuclei and the oligodendrocyte progenitor cell nuclei populations were defined by the fluorescence intensity of SOX10 and CC1 labeled antibodies. The exact boundaries of the gates were set using the pseudo color contour plot compared to the unstained nuclei control sample. The non-oligodendrocyte lineage cell nuclei population gate was defined by the control nuclei sample. See Fig. 1a-b.

☒ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.