Supplementary Table 1 ^{14}C data and related data of included patients

Case ID	Age	Date of birth	Date of death	Sex	$\Delta^{14}C$ (‰) purity corrected	$\Delta^{14}C$ (‰)	$\Delta^{14}C$ Error (2SD)	$F^{14}C$	$F^{14}C$ Error (2SD)	FACS Purity (%)	Immuno labeling	tissue	isolated nuclei (10^6)	carbon mass according to measured DNA (µg)	carbon mass measured in graphitization reactor (µg)	Disease type	Date of disease onset	Disease duration	Region
MS1	38.0	1974.4	2012.4	F	ND	318.39	27.6	1.329	0.028	96.8	Sox10+/APC+	NAWM	11.8	21.9	10.7	SPMS	1990.4	22.0	Prefrontal
MS2	39.0	1972.3	2011.3	F	380.88	390.79	39.8	1.384	0.040	95.3	Sox10+/APC+	NAWM	8.4	15.2	9.9	PPMS	1998.3	13.0	Frontal cortex
MS3	39.4	1974.3	2013.7	F	216.76	237.19	18.0	1.232	0.018	93.5	Sox10+/APC+	NAWM	37.6	38.9	34.9	SPMS	1999.7	14.0	Prefrontal
MS4	42.0	1971.0	2013.0	M	262.21	268.85	26.8	1.266	0.027	94.1	Sox10+/APC+	NAWM	9.0	13.3	12.7	SPMS	1992.0	21.0	Prefrontal
MS5	42.0	1972.7	2014.7	F	ND	183.53	28.3	1.193	0.028	95.4	Sox10+/APC+	NAWM	5.4	4.2	3.6	SPMS	2002.9	11.8	Frontal
MS6	42.0	1966.6	2008.6	M	584.09	595.79	22.2	1.589	0.022	96.6	Sox10+/APC+	NAWM	12.3	20.8	15.3	PPMS	2000.5	8.1	Prefrontal
MS7	43.0	1968.1	2011.1	M	433.58	429.54	36.8	1.441	0.037	97.8	Sox10+/APC+	NAWM	11.4	9.3	6.3	SPMS	1990.1	21.0	Frontal cortex
MS8	45.8	1965.8	2011.5	F	ND	522.16	26.4	1.534	0.0264	96.4	Sox10+/APC+	NAWM	12.5	11.4	7.6	SPMS	2002.5	9.0	Prefrontal
MS9	46.9	1965.0	2011.9	F	543.57	535.11	41.0	1.547	0.041	97.1	Sox10+/APC+	NAWM	16.6	4.8	2.6	SPMS	1988.9	23.0	Prefrontal
MS10	48.0	1959.4	2007.4	F	ND	67.36	30.6	1.076	0.031	98.4	Sox10+/APC+	NAWM	6.1	10.1	7.0	SPMS	1984.0	23.4	NA
MS11	49.2	1952.0	2001.2	F	ND	62.01	28.5	1.070	0.029	97.3	Sox10+/APC+	NAWM	20.0	8.8	6.3	SPMS	1977.0	24.2	Posterior
MS12	49.8	1956.0	2005.8	F	ND	35.68	19.4	1.044	0.019	93.6	Sox10+/APC+	NAWM	17.8	25.3	17.0	SPMS	1981.8	24.0	Prefrontal
MS13	50.1	1963.5	2013.6	F	552.12	597.54	17.0	1.554	0.017	90.4	Sox10+/APC+	NAWM	33.7	37.1	28.4	SPMS	1996.6	17.0	Prefrontal
MS14	51.0	1960.7	2011.7	M	262.68	272.61	14.4	1.269	0.014	94.0	Sox10+/APC+	NAWM	33.9	62.6	41.6	SPMS	1988.7	23.0	Prefrontal
MS15	51.3	1948.1	1999.4	F	ND	24.80	13.6	1.033	0.014	91.3	Sox10+/APC+	NAWM	20.8	42.2	27.8	SPMS	1974.4	25.0	Posterior
MS16	55.7	1945.1	2000.8	M	ND	42.71	36.0	1.051	0.036	94.9	Sox10+/APC+	NAWM	20.1	5.8	2.8	SPMS	1957.8	43.0	Prefrontal
MS17	57.3	1946.6	2003.9	F	ND	-8.73	21.8	0.999	0.022	95.5	Sox10+/APC+	NAWM	9.0	14.0	10.0	SPMS	1973.0	30.9	Prefrontal
MS18	57.5	1956.4	2013.9	M	48.62	51.70	29.2	1.057	0.029	94.2	Sox10+/APC+	NAWM	20.7	4.9	3.2	SPMS	2000.9	13.0	Prefrontal
MS19	58.4	1955.0	2013.4	M	ND	33.39	13.6	1.039	0.014	93.4	Sox10+/APC+	NAWM	93.8	19.6	20.1	SPMS	1981.4	32.0	Prefrontal
MS20	62.5	1939.0	2001.5	M	56.37	51.04	14.4	1.056	0.014	93.2	Sox10+/APC+	NAWM	18.1	32.0	27.8	SPMS	1962.5	39.0	Frontal
MS21	69.8	1928.2	1998.0	F	50.18	43.28	18.4	1.051	0.018	93.0	Sox10+/APC+	NAWM	27.4	37.6	22.4	SPMS	1953.0	45.0	Posterior
MS22	70.2	1942.8	2012.9	F	9.91	10.15	15.4	1.018	0.015	94.7	Sox10+/APC+	NAWM	33.0	33.9	29.0	PPMS	1995.9	17.0	Prefrontal
MS23	70.6	1940.6	2011.2	F	16.45	16.43	19.2	1.024	0.019	93.4	Sox10+/APC+	NAWM	25.6	22.2	10.4	SPMS	1984.2	27.0	Prefrontal
MS24	71.7	1929.5	2001.2	F	ND	28.14	14.2	1.036	0.014	93.4	Sox10+/APC+	NAWM	16.4	17.3	12.6	SPMS	1966.2	35.0	Frontal
MS25	72.6	1936.4	2009.0	F	26.79	27.29	12.6	1.035	0.013	94.9	Sox10+/APC+	NAWM	47.1	98.6	64.9	SPMS	1974.0	35.0	Prefrontal
MS26	72.8	1936.5	2009.3	F	24.04	26.15	11.8	1.032	0.012	89.9	Sox10+/APC+	NAWM	32.2	73.7	50.6	SPMS	1963.3	46.0	Prefrontal
MS27	77.0	1930.8	2007.8	F	ND	-16.78	24.0	0.991	0.024	96.8	Sox10+/APC+	NAWM	8.5	11.7	10.1	SPMS	1973.8	34.0	Prefrontal
MS28	77.0	1931.9	2008.9	F	ND	-33.73	24.4	0.974	0.024	96.6	Sox10+/APC+	NAWM	4.3	10.3	9.4	SPMS	1979.0	29.9	NA
MS29	81.0	1928.1	2009.1	F	ND	15.20	27.8	1.023	0.028	97.0	Sox10+/APC+	NAWM	6.8	9.1	6.5	SPMS	1950.0	59.1	NA

Case ID	Age	Date of birth	Date of death	Sex	Δ ^{14}C (‰) purity corrected	Δ ^{14}C (‰)	Δ ^{14}C Error (2SD)	F ^{14}C	F ^{14}C Error (2SD)	FACS Purity (%)	Immuno labeling	tissue	isolated nuclei (10^6)	carbon mass according to measured DNA (µg)	carbon mass measured in graphitization reactor (µg)	Disease type	Date of disease onset	Disease duration	Region
MS30	34.0	1966.6	2000.6	M	494.74	486.53	32.6	1.498	0.033	96.2	Sox10+/APC+	Shadow plaque	7.4	12.5	10.0	Little medical history available, likely PPMS	NA	NA	NA
MS31	45.9	1957.3	2003.3	F	ND	128.25	39.6	1.137	0.040	94.9	Sox10+/APC+	Shadow plaque	5.6	8.6	6.2	RRMS	1997.0	6.0	Posterior
MS32	47.2	1959.0	2006.2	F	ND	171.62	24.2	1.180	0.024	96.5	Sox10+/APC+	Shadow plaque	22.0	15.6	6.1	SPMS	1989.0	17.0	Posterior
MS10	48.0	1959.4	2007.4	F	ND	58.59	36.4	1.067	0.036	98.1	Sox10+/APC+	Shadow plaque	3.2	4.6	3.7	SPMS	1984.0	23.4	NA
MS33	53.0	1958.5	2011.5	M	ND	7.94	40	1.016	0.040	96.7	Sox10+/APC+	Shadow plaque	3.0	3.4	2.8	SPMS	1985.0	26.5	NA
MS34	57.0	1951.7	2008.7	M	ND	-10.98	32.2	0.997	0.032	96.3	Sox10+/APC+	Shadow plaque	4.7	8.6	8.6	SPMS	1979.0	29.7	NA
MS17	57.3	1946.6	2003.9	F	-22.90	-22.35	27.4	0.985	0.027	97.4	Sox10+/APC+	Shadow plaque	7.5	9.7	7.9	SPMS	1973.0	30.0	Prefrontal
MS35	59.0	1953.8	2012.8	M	ND	-2.88	25	1.005	0.025	95.8	Sox10+/APC+	Shadow plaque	7.9	13.5	9.1	SPMS	1990.0	22.8	NA
MS36	66.8	1939.6	2006.3	M	ND	17.32	17	1.025	0.017	96.1	Sox10+/APC+	Shadow plaque	22.0	20.7	15.3	SPMS	1955.0	51.0	Posterior
MS37	75.0	1927.3	2002.3	F	ND	-49.06	31.2	0.959	0.031	96.6	Sox10+/APC+	Shadow plaque	6.1	9.6	6.6	SPMS	1960.0	42.3	NA
MS29	81.0	1928.1	2009.1	F	-17.57	-17.11	29.2	0.991	0.029	96.7	Sox10+/APC+	Shadow plaque	6.2	7.5	5.8	SPMS	1950.0	59.1	NA
MS2	39.0	1972.3	2011.3	F	259.93	261.01	28.4	1.271	0.028	94.5	SOX10+	NAWM	7.8	12.0	9.3	PPMS	1998.3	13.0	Frontal cortex
MS3	39.4	1974.3	2013.7	F	322.42	294.34	32.4	1.304	0.032	78.0	SOX10+	NAWM	7.3	7.3	4.7	SPMS	1999.7	14.0	Prefrontal
MS4	42.0	1971.0	2013.0	M	155.10	167.58	33.8	1.177	0.034	86.3	SOX10+	NAWM	6.4	7.4	5.7	SPMS	1992.0	21.0	Prefrontal
MS6	42.0	1966.6	2008.6	M	439.61	448.76	35.6	1.460	0.036	87.8	SOX10+	NAWM	5.6	5.3	4.3	PPMS	2000.5	8.0	Prefrontal
MS7	43.0	1968.1	2011.1	M	302.36	300.15	36.8	1.311	0.037	98.4	SOX10+	NAWM	14.1	8.3	6.2	SPMS	1990.1	21.0	Frontal cortex
MS9	46.9	1965.0	2011.9	F	351.17	358.35	33.8	1.369	0.034	64.9	SOX10+	NAWM	8.0	9.7	7.0	SPMS	1988.9	23.0	Prefrontal
MS13	50.1	1963.5	2013.6	F	476.68	491.55	30.0	1.503	0.030	71.8	SOX10+	NAWM	8.3	8.1	6.9	SPMS	1996.6	17.0	Prefrontal
MS14	51.0	1960.7	2011.7	M	252.20	235.74	27.8	1.245	0.028	63.1	SOX10+	NAWM	18.1	16.2	11.8	SPMS	1988.7	23.0	Prefrontal
MS15	51.3	1948.1	1999.4	F	30.68	29.27	23.4	1.037	0.023	86.3	SOX10+	NAWM	13.9	14.7	11.1	SPMS	1974.4	25.0	Posterior
MS38	52.0	1948.6	2000.6	F	ND	25.12	21.4	1.033	0.021	92.9	SOX10+	NAWM	6.4	13.1	5.7	SPMS	1979.0	21	Frontal corpus callosum
MS18	57.5	1956.4	2013.9	M	60.86	58.09	18.2	1.066	0.018	80.8	SOX10+	NAWM	11.9	17.7	19.9	SPMS	2000.9	13.0	Frontal
MS21	69.8	1928.2	1998.0	F	-53.14	-34.99	20.6	0.973	0.021	81.8	SOX10+	NAWM	7.2	13.1	12.8	SPMS	1953.0	45.0	Posterior
MS22	70.2	1942.8	2012.9	F	6.05	6.37	19.2	1.014	0.019	92.1	SOX10+	NAWM	22.9	27.8	19.9	SPMS	1995.9	17.0	Prefrontal
MS23	70.6	1940.6	2011.2	F	-0.30	2.56	21.8	1.010	0.022	88.2	SOX10+	NAWM	18.0	17.0	11.7	SPMS	1984.2	27.0	Prefrontal
MS25	72.6	1936.4	2009.0	F	12.53	17.00	18.0	1.025	0.018	77.4	SOX10+	NAWM	18.9	25.1	18.1	SPMS	1974.0	35.0	Prefrontal
MS26	72.8	1936.5	2009.3	F	24.37	24.70	17.6	1.033	0.018	73.8	SOX10+	NAWM	15.6	24.6	20.8	SPMS	1963.3	46.0	Prefrontal
MS39	73.8	1938.3	2012.2	M	ND	30.82	15.2	1.039	0.015	89.3	SOX10+	NAWM	16.0	32.2	28.8	SPMS	1976.2	36.0	Prefrontal
MS40	77.8	1923.3	2001.0	F	ND	38.50	16.8	1.046	0.017	93.3	SOX10+	NAWM	25.0	19.2	8.8	PPMS	1979.0	22	Frontal corpus callosum

NAWM, normal appearing white matter
SPMS, Secondary progressive MS
PPMS, primary progressive MS
RRMS, relapse/remitting MS
NA, not applicable, ND, not determined

Supplementary Table 2 | Description of scenarios used for global fitting of normal appearing white matter oligodendrocytes

Scenario	Description of scenario
1	No turnover throughout life
2	Constant annual turnover rate throughout life. Annual turnover rate estimated.
3	Fixed expansion phase first five years, then constant annual turnover rate throughout life. Annual turnover rate fixed to 0.32%
4	Fixed expansion phase first five years, then constant annual turnover rate throughout life. Annual turnover rate estimated.
5	Fixed expansion phase first five years, constant annual turnover rate fixed to 0.32% up to disease onset, estimated annual turnover rate after disease onset.
6	Fixed expansion phase first five years, estimated annual turnover rate up to disease onset, estimated annual turnover rate after disease onset, set to 2x the pre-onset annual turnover rate.
7	Fixed expansion phase first five years, estimated annual turnover rate up to disease onset, estimated annual turnover rate after disease onset. The two estimations are independent of each other.

All scenarios are based on three connected PDEs to represent three time periods: 1. the first five years 2. from five years to date of disease onset, here set as the time of diagnosis. 3. From date of disease onset to date of death. Turnover rates can be fixed to a specific rate or estimated increasing the complexity of the model.

Supplementary Table 3 | Global fit of NAWM oligodendrocytes- all subjects

Scenario	Estimated annual turnover rate before onset (%)	Estimated annual turnover rate after onset (%)	AIC	Comment
1	NA	NA	287.48	
2	NA	0.88	266.21	
3	NA	NA	257.37	
4	NA	0.58	256.16	
5	NA	0.96	252.79	Best scenario, elevated turnover after disease onset.
6	0.40	0.80	253.58	Second best scenario. Similar estimations as scenario 5
7	0.04	1.14	254.34	

Estimated global turnover rates before and after disease onset. If fixed expansion phase, the estimated turnover rate before onset is between 5 years and age at disease onset. Best scenario based on Akaike information criterion (AIC). NA= Not applicable

Supplementary Table 4 | Individual fit of normal appearing white matter oligodendrocytes based on global scenario 5

Case ID	Age	Age at onset	Disease duration	Estimated annual turnover rate after onset (%)	Residual	Total oligodendrocyte exchange during disease (%)
MS 1	38.0	16.0	22.0	0.52	6.02E-20	11.34
MS 2	39.0	26.0	13.0	0.11	8.82E-19	1.40
MS 3	39.4	25.4	14.0	4.08	4.42E-19	57.14
MS 4	42.0	21.0	21.0	2.93	7.60E-22	61.61
MS 5	42.0	30.3	11.8	7.03	2.91E-20	82.64
MS 6	42.0	33.9	8.1	0.00*	1.40E+03*	*
MS 7	43.0	22.0	21.0	0.93	4.33E-19	19.62
MS 8	45.8	36.8	9.0	1.15	2.61E-18	10.32
MS 9	46.9	23.9	23.0	0.74	5.73E-18	17.06
MS 10	48.0	24.6	23.4	29.71†	1.70E-23†	†
MS 11	49.2	25.0	24.2	1.33	3.01E-20	32.17
MS 12	49.8	25.8	24.0	3481.94*	4.66E+02	*
MS 13	50.1	33.1	17.0	1.26	7.35E-18	21.40
MS 14	51.0	28.0	23.0	3.64	1.73E-18	83.69
MS 15	51.3	26.3	25.0	0.45	2.94E-18	11.30
MS 16	55.7	12.7	43.0	0.50	2.04E-19	21.52
MS 17	57.3	26.4	30.9	0.00*	1.13E+02*	*
MS 18	57.5	44.5	13.0	20.34†	1.14E-22	†
MS 19	58.4	26.4	32.0	55.91†	4.26E-23	†
MS 20	62.5	23.5	39.0	0.63	4.81E-19	24.44
MS 21	69.8	24.8	45.0	0.53	2.16E-17	23.74
MS 22	70.2	53.2	17.0	0.00*	9.55E+01	*
MS 23	70.6	43.6	27.0	0.00	6.27E-19	1.88
MS 24	71.7	36.7	35.0	0.31	9.76E-18	10.96
MS 25	72.6	37.6	35.0	0.32	3.47E-18	11.14
MS 26	72.8	26.8	46.0	0.30	9.51E-19	13.57
MS 27	77.0	43.0	34.0	0.00*	8.33E+02*	*
MS 28	77.0	47.1	29.9	0.00*	2.63E+03*	*
MS 29	81.0	21.9	59.1	0.21	1.44E-17	12.45

Estimated individual turnover rates based on scenario with the best global fit, scenario 5. * Excluded from analysis due to poor fit based on residuals. Subjects with residuals over 1 were excluded. † Excluded from analysis based on unrealistic turnover rate.

Supplementary Table 5 | Individual fit of healthy oligodendrocytes

Case ID	Age	Estimated annual turnover rate (%)
1	32.8	0.416
2	34.6	1.4
3	39.3	0.232
4	41.4	-0.003
5	43.6	0.81
6	51	1.3
7	55.1	-0.23
8	61.1	0.289
9	61.8	0.311
10	68.9	0.185
11	71.4	0.027
12	73.2	0.396
13	74.4	0.349
14	75	0.438
15	77.6	0.333
16	89	0.443
17	92.6	0.291

Estimated individual oligodendrocyte turnover rates from reference data of healthy subjects over 30 years of age[2].

Supplementary Table 6 | Global fit of normal appearing white matter oligodendrocytes- excluding three outliers

Scenario	Estimated turnover rate before onset (%)	Estimated turnover rate after onset (%)	AIC	Comment
1	NA	NA	247.53	
2	NA	0.67	228.55	
3	NA	NA	218.01	
4	NA	0.44	219.07	
5	NA	0.71	215.80	Still best scenario without three outliers. Elevated turnover but lower than the estimation with all subjects.
6	0.31	0.62	215.93	
7	0.02	0.90	215.87	

Estimated global turnover rates before and after disease onset if three outliers are excluded. If fixed expansion phase, the estimated turnover rate before onset is between 5 years and age at disease onset. Best scenario based on Akaike information criterion (AIC). NA= Not applicable

Supplementary Table 7 | Global fit of normal appearing white matter oligodendrocytes- subjects born before 1955

Scenario	Estimated turnover rate before onset (%)	Estimated turnover rate after onset (%)	AIC	Comment
1	NA	NA	118.43	
2	NA	0.30	104.24	
3	NA	NA	103.45	Best scenario.
4	NA	0.27	105.51	
5	NA	0.33	106.12	Estimated turnover rate close to 0.32. Scenario similar to scenario 3.
6	NA	NA	NA	Could not be fitted
7	NA	NA	NA	Could not be fitted

Estimated global turnover rates before and after disease onset only subjects born 1955 and before included (n=15). If fixed expansion phase, the estimated turnover rate before onset is between 5 years and age at disease onset. Best scenario based on Akaike information criterion (AIC). NA= Not applicable

Supplementary Table 8 | Global fit of normal appearing white matter oligodendrocytes- subjects born after 1955

Scenario	Estimated turnover rate before onset (%)	Estimated turnover rate after onset (%)	AIC	Comment
1	NA	NA	149.35	
2	NA	1.35	134.98	
3	NA	NA	134.78	
4	NA	0.95	132.26	
5	NA	1.77	127.64	Best scenario, elevated turnover after disease onset.
6	0.66	1.32	129.83	
7	NA	NA	NA	Could not be fitted

Estimated global turnover rates before and after disease onset only subjects born 1955 and after included (n=14). If fixed expansion phase, the estimated turnover rate before onset is between 5 years and age at disease onset. Best scenario based on Akaike information criterion (AIC). NA= Not applicable

Supplementary Table 9 | Cell proliferation in normal appearing white matter and shadow plaques.

Case ID	age	Ki67/mm^2 NAWM	Ki67/mm^2 Shadow plaque	Ki67/Sox10+/ mm^2 NAWM	Ki67/Sox10+/ mm^2 Shadow plaque	Ki 67+ of all cells NAWM (%)	Ki 67+ of all cells Shadow plaque (%)
MS30	34.0	0.2806	0.4552	0.0058	0	0.0146	0.0262
MS31	45.9	2.5728	1.9019	0.3489	0.2238	0.1173	0.0813
MS32	47.2	0.0141	0.0000	0	0	0.0009	0
MS10	48.0	0.0258	0.0791	0	0	0.0022	0.0061
MS33	53.0	0.1153	0.2651	0.0220	0	0.0078	0.0247
MS34	57.0	0.4332	0.2725	0.0922	0.0210	0.0286	0.0188
MS17	57.3	0.0086	0.0000	0	0	0.0004	0
MS35	59.0	0.1004	0.1617	0.0236	0	0.0074	0.0115
MS36	66.8	0.0968	0.0500	0.0242	0	0.0113	0.0034
MS37	75.0	0.0963	0.0514	0.0088	0	0.0041	0.0028
MS29	81.0	0.0542	0.0262	0.0108	0	0.0039	0.0016

Cell proliferation assessed in normal appearing white matter and shadow plaques with proliferation marker Ki67 combined with oligodendrocyte marker Sox10 (n=11).

Supplementary Table 10 | Cell number quantification in healthy white matter from reference data [2]

Sample	Case ID	Age	mature OL whole corpus callosum (10^9)	OPC whole corpus callosum (10^9)	All cells whole corpus callosum (10^9)	OPC of all cells (%)	Mature OL of all cells (%)	Ratio OPC/mature OL (fraction)	Ratio OPC/mature OL (%)
1	#4327	5.7	6.614	0.519	9.229	5.6	71.7	0.078	7.8
2	#5408	6.8	4.701	0.410	6.079	6.7	77.3	0.087	8.7
3	#1708	8.1	3.742	0.400	5.434	7.4	68.9	0.107	10.7
4	#4337	8.2	5.577	0.314	7.350	4.3	75.9	0.056	5.6
5	#1706	8.6	4.248	0.278	5.426	5.1	78.3	0.065	6.5
6	#1407	9.1	3.351	0.197	4.605	4.3	72.8	0.059	5.9
7	#5161	10.7	4.447	0.366	6.157	5.9	72.2	0.082	8.2
8	#4787	12.9	4.796	0.745	6.177	12.1	77.6	0.155	15.5
9	ND 260	14.0	5.914	0.258	7.839	3.3	75.4	0.044	4.4
10	#5163	14.9	8.158	0.121	10.123	1.2	80.6	0.015	1.5
11	#5168	16.0	6.317	0.425	8.420	5.0	75.0	0.067	6.7
12	ND 168	16.0	4.246	0.123	5.785	2.1	73.4	0.029	2.9
13	ND 182	17.0	4.761	0.138	6.339	2.2	75.1	0.029	2.9
14	ND 210	18.0	6.123	0.272	8.121	3.3	75.4	0.044	4.4
15	ND 212	19.0	3.617	0.134	4.778	2.8	75.7	0.037	3.7
16	ND 124	19.0	4.572	0.040	6.036	0.7	75.7	0.009	0.9
17	ND 162	19.0	4.730	0.072	5.945	1.2	79.6	0.015	1.5
18	ND 172	19.4	5.166	0.121	6.888	1.8	75.0	0.023	2.3
19	ND 184	21.0	4.453	0.113	5.988	1.9	74.4	0.025	2.5
20	ND 192	21.0	5.590	0.137	7.101	1.9	78.7	0.025	2.5
21	ND 127	22.0	3.750	0.092	5.035	1.8	74.5	0.024	2.4
22	ND 178	23.0	3.835	0.124	5.212	2.4	73.6	0.032	3.2
23	ND 188	24.0	6.234	0.244	8.154	3.0	76.5	0.039	3.9
24	ND 275	24.0	4.870	0.371	7.146	5.2	68.2	0.076	7.6
25	ND 257	25.0	3.983	0.120	5.555	2.2	71.7	0.030	3.0
26	ND 175	26.0	3.923	0.157	5.278	3.0	74.3	0.040	4.0
27	ND 236	28.0	5.647	0.246	7.505	3.3	75.2	0.044	4.4
28	ND 107	28.0	5.775	0.069	7.238	1.0	79.8	0.012	1.2
29	ND 146	34.0	4.613	0.163	6.565	2.5	70.3	0.035	3.5
30	ND 180	39.0	3.622	0.108	5.498	2.0	65.9	0.030	3.0
31	ND 147	41.0	4.318	0.271	6.294	4.3	68.6	0.063	6.3
32	ND 217	50.0	3.579	0.098	4.721	2.1	75.8	0.027	2.7
33	ND 207	55.0	4.549	0.188	6.166	3.0	73.8	0.041	4.1
34	ND 163	60.0	5.803	0.210	7.569	2.8	76.7	0.036	3.6
35	ND 138	61.0	3.190	0.712	5.089	14.0	62.7	0.223	22.3
36	ND 156	68.0	4.311	0.483	6.444	7.5	66.9	0.112	11.2
37	ND 174	71.0	4.943	0.393	6.450	6.1	76.6	0.079	7.9
38	ND 216	73.0	3.994	0.232	5.418	4.3	73.7	0.058	5.8
39	ND 154	74.0	4.391	0.279	5.754	4.8	76.3	0.063	6.3
40	ND 189	75.0	3.102	0.104	4.734	2.2	65.5	0.034	3.4
41	ND 203	77.0	3.882	0.243	5.163	4.7	75.2	0.063	6.3
42	ND 261	89.0	4.618	0.196	5.725	3.4	80.7	0.043	4.3
43	ND 191	92.0	4.328	0.126	5.289	2.4	81.8	0.029	2.9

OL, oligodendrocyte
OPC, oligodendrocyte progenitor cells

Supplementary Table 11 | Description of scenarios used for theoretical modelling of oligodendrocyte generated from oligodendrocyte progenitor cells in shadow plaques

Scenario	Description of scenario
1	Healthy oligodendrocyte turnover: Fixed expansion phase first five years, then constant annual turnover rate throughout life. Annual turnover rate fixed to 0.32%
2	All oligodendrocytes are from birth, 100% loss of oligodendrocytes at disease onset, continuous replacement with OPC population dividing 4 times over the time from disease onset to death.
3	All oligodendrocytes are from birth, 100% loss of oligodendrocytes at 10 years before disease onset, continuous replacement with OPC population dividing 4 times over the time from disease onset to death.
4	All oligodendrocytes are from birth, 100% loss of oligodendrocytes at disease onset, momentary replacement with OPC population dividing 4 times.
5	All oligodendrocytes are from birth, 100% loss of oligodendrocytes at 10 years before disease onset, momentary replacement with OPC population dividing 4 times.
6	All oligodendrocytes are from birth, 50% loss of oligodendrocytes at disease onset, momentary replacement with OPC population dividing 3 times.
7	All oligodendrocytes are from birth, 50% loss of oligodendrocytes at 10 years before disease onset, momentary replacement with OPC population dividing 3 times.

All scenarios are based on three connected PDEs to represent three time periods: 1. the first five years 2. from five years to date of disease onset, here set as the time of diagnosis. 3. From date of disease onset to date of death. Turnover rates can be fixed to a specific rate or estimated increasing the complexity of the model. OPC= oligodendrocyte progenitor cell.

Supplementary Table 12 | Measured and estimated ^{14}C oligodendrocytes from shadow plaques.

Case ID	Measured $\Delta^{14}C$ (‰)	Scenario 1 $\Delta^{14}C$ (‰)	Scenario 2 $\Delta^{14}C$ (‰)	Scenario 3 $\Delta^{14}C$ (‰)	Scenario 4 $\Delta^{14}C$ (‰)	Scenario 5 $\Delta^{14}C$ (‰)	Scenario 6 $\Delta^{14}C$ (‰)	Scenario 7 $\Delta^{14}C$ (‰)
MS 10	58.59	373.04	126.06	178.01	217	397.89	218.96	303.38
MS 17	-22.9	22.65	181.15	279.35	413.12	503.4	181.29	223.42
MS 29	-17.57	28.78	217.89	181.87	-23.96*	-18.09*	-18.04*	-15.30*
MS 30	494.74	578.11	NaN	NaN	NaN	NaN	NaN	NaN
MS 31	128.25	196.38	86.48	117.97	104.48	179.25	83.56	118.45
MS 32	171.62	325.91	109.71	150.16	169.43	302.88	177.25	239.53
MS 33	7.94	278.82	108.27	152.68	201.23	369.98	168.68	247.43
MS 34	-10.98	29.55	131.16	195.93	289.82	518.71	122.02	228.83
MS 35	-2.88	69.78	77.11	112.91	146.69	261.21	56.21	109.65
MS 36	17.32	24.8	249.93	205.54	-14.79*	-21.59*	-15.95*	-19.12*
MS 37	-49.06	30.67	285.66	238.06	205.6	-23.94*	89.24	-17.89*

Estimated ^{14}C levels in oligodendrocytes from shadow plaques compared to the measured ^{14}C (n=11). *Values that have atmospheric levels due to shadow plaque formation time is before the rise of the atmospheric ^{14}C curve, thus any turnover cannot be detected in these cases. Case 30 does not have a known date of disease onset and could therefore not be modelled for scenario 2-7.

Supplementary Data: Analysis of cell dynamics in multiple sclerosis white matter

Mathematical modelling of oligodendrocyte turnover in normal appearing white matter

The ^{14}C measurements reflects the average age of a cell population, as it is a cumulative result of all the ^{14}C incorporated over a whole lifespan in a cell population. With mathematical models, we are able to explore turnover dynamics and different biological scenarios that are compatible with our data. We developed further a previously established birth- and death model represented by a linear partial differential equation (PDE)[1]. The solution of the equation is the distribution of cell age at any given age of the individual. The PDE is an age-structured model where the density of cells (n) depends on the age of the subject (t) and the age of cells (a). Cell death is represented by γ in the equation below. The PDE has an initial condition ($f(a)$), representing the initial distribution of cell ages, and a boundary condition ($g(t)$) representing the birth of cells.

$$\frac{\partial n(t,a)}{\partial t} + \frac{\partial n(t,a)}{\partial a} = -\gamma(t,a)n(t,a)$$

$$n(0,a) = f(a), \qquad a > 0$$

$$n(t,0) = g(t), \qquad t \geq 0$$

The total cell number at time t is

$$\int_0^t n(t,a)da.$$

If $K(x)$ denotes the atmospheric ^{14}C level at calendar year x, a cell of age a collected at year y would have a corresponding DNA ^{14}C content $K(y-a)$. Therefore, the measured ^{14}C

concentration in a sample should be the average over all cells, i.e. the integral of the cell density against the atmospheric ^{14}C.

$$C_{average} = \frac{\int_0^t n(t,a)K(y-a)da}{N(t)}$$

Mathematical modelling of oligodendrocyte turnover in healthy individuals estimated that there is an expansion phase the first five years and then a constant turnover of oligodendrocytes throughout life with an annual turnover rate of 0.32% [2]. In order to explore the turnover dynamics of oligodendrocytes in normal appearing white matter in MS patients, we considered a general model where cell death and cell birth rates are a piecewise constant function of the age of the subject, to represent the expansion phase (0 to 5 years), the steady turnover (5 years to age at onset) and the renewal after disease onset. The disease onset is defined as the time of the first noted symptoms that can be related to MS, which can be years before clinical diagnosis.

The birth and death parameters for each time period were either fixed to a specific rate or they were estimated, increasing the freedom and complexity of the model. The initial cell number was set to 10% of the total cell number at 5 years. All cells were assumed to have age 0 at birth of the individual. During the expansion phase (0–5 years) the death rate was set to 0 and the birth rate adjusted so as to have a 10-fold expansion in cell number. During the steady turnover years, the birth rate was set as to keep the total cell number constant. During renewal years, after the disease onset, the birth rates and the death rates were not strictly fixed to make changes in cell numbers possible.

The different scenarios and the parameters estimated can be globally fitted in a least-square sense, to the whole data set, or in some cases individually fitted to each individual subject. First, we systematically tested the models with increasing freedom and complexity (see Supplementary Table 2 for description of turnover scenarios in normal appearing white

matter) globally and evaluated which scenario best fit our data with Akaike information criterion (AIC). The scenario that best fit the data was scenario 5 where there is a fixed expansion phase the first five years, a fixed constant annual turnover of 0.32% before disease onset and an estimated annual turnover rate of 1% after disease onset. Interestingly, the second-best scenario (scenario 6) produced very similar results. This model has a fixed expansion phase, an estimated turnover rate before onset of 0.4% and an estimated turnover rate of 0.8% after onset of the disease (Supplementary Table 3). In order to investigate whether the fit was significantly better with scenario 5 compared to the healthy turnover scenario (Scenario 3), likelihood-ratio test was performed and they were significantly different (P=0.0087).

Based on the best global fitting scenario 5, we estimated the individual turnover rates after disease onset if there is an expansion phase and a constant annual turnover rate of 0.32% before disease onset (Supplementary Table 4). The median individual turnover of oligodendrocytes in NAWM was 0.58 (n=20 CI:0.32-1,26). We found that while there is no correlation between age at onset and individual turnover rate (Fig. 2b, r=-0.099 P=0.68, two-tailed Spearman correlation test), there was a significant negative correlation between disease duration and individual turnover rates (Fig. 2c, r=-0.57 P=0.0081, two-tailed Spearman correlation test), indicating that those with more aggressive disease course have higher turnover rates after onset of the disease. The total oligodendrocyte exchange during the disease was calculated by taking the annual turnover rate times the disease duration in years (Supplementary Table 4). There was no significant correlation between total oligodendrocyte exchange and time from disease onset (Extended Data Fig. 2d, r=-0.0828 P=0.73, two-tailed Spearman correlation test).

Individual turnover of the healthy subjects has been previously calculated and the median individual turnover of oligodendrocytes in healthy was 0.37 (n=34, CI: 0.18-0.81)[2].

As the youngest multiple sclerosis patient at death in our NAWM group was 38 years of age, we selected healthy subjects over 30 years of age at death for our comparison analysis in order to get better age-matched groups. The median turnover in the age-matched healthy group was 0.33 (n=17, CI:0.23-0.44) (Supplementary Table 5). There was a significant difference between the individual turnover rates when comparing the NAWM subject and the healthy subjects over 30 years of age (P= 0.02, Mann-Whitney test). There are 9 NAWM subjects that have over 2-fold the median healthy turnover (over 0.66% annual turnover rate), 7 individuals that have 3-fold (over 0.99% turnover) and 3 individuals that has over 10-fold (over 3.3% turnover) higher turnover than the healthy median. We calculated the average total turnover throughout the disease period for all NAWM subjects: 26.47±24.74% and for the 7 individuals with over 3-fold elevated annual rates: 43.85±30.61%.

The three subjects that have very high turnover rates also stand out in that they seem to have incorporated much ^{14}C from more contemporary atmospheric levels compared to the other subjects born around the same time (Fig. 1d). In order to investigate if these three subjects were solely responsible for the high post-disease onset turnover rate we estimated with the global fit, we performed the global fitting scenarios again without these 3 subjects. We found that the choice of model did not change, but the post onset turnover rate with this model was slightly lower (0.71%, Supplementary Table 6). Thus, the three data points do in part drive the data towards a higher post-onset turnover rate, but scenario 5 was still significantly a better fit without these three subjects (P= 0.0326, likelihood-ratio test) and can therefore not explain all the increase.

The high turnover rates seem to be exclusive to the younger subjects. Therefore, we divided the data set into multiple sclerosis patients born before 1955 (n=15) and patients born after 1955 (n=14) and did global fitting of these data set separately. The best scenario for the older patients was scenario 3 (Supplementary Table 7). Whereas, the best scenario for the

younger patients was scenario 5, with the estimated post-onset turnover rate of 1.8% (Supplementary Table 8).

Mathematical modelling of oligodendrocytes in shadow plaques.

The ^{14}C levels in shadow plaque oligodendrocyte were significantly lower than healthy white matter oligodendrocyte ^{14}C levels (Fig. 3b, P=0.0047, two-tailed Mann-Whitney test). As the subjects in the two groups were not matched for age and time of birth, we modeled a healthy scenario for the shadow plaque subjects to confirm that a healthy scenario is not compatible with our measured data (see Supplementary Table 11 for description of turnover scenarios in shadow plaques).

It would require more than 4 cell divisions of the oligodendrocyte progenitor cells (OPCs) to reconstitute a completely lost oligodendrocyte population, as the OPCs are 20-fold less numerous than the mature oligodendrocytes[2]. Even if only 50% of the oligodendrocytes are lost, roughly 3 cell divisions would be required to reconstitute the lost cells. The oligodendrocytes in the shadow plaques had ^{14}C levels corresponding to the atmospheric curve, indicating a much lower turnover than the healthy oligodendrocytes, if at all any (Fig. 3a).

In order to investigate whether it is possible that proliferating OPCs contribute to newly generated oligodendrocytes in shadow plaques, we systematically tested several theoretical replacement models. In the theoretical models, we estimate the ^{14}C values from mature oligodendrocyte in shadow plaques (n=11) at different set parameters of oligodendrocyte loss and cell replacement. We then compared if these estimated values were compatible with our measured ^{14}C values of the same individuals.

It is possible that the shadow plaques were formed before the first clinical manifestations, we therefore tested all scenarios with the “shadow plaque formation time” set

either from the date of disease onset or ten years before disease onset. Finally, it is not known how long time replacement would occur. We therefore modelled the replacement to be momentary at the set time for shadow plaque formation or continuous from the set time for shadow plaque formation to death.

As some data points had their "shadow plaque formation time" before the rise of the bomb curve, any cell replacement would not be detected regardless of how many cell division. For all data points with their "shadow plaque formation time" set during the elevated atmospheric ^{14}C levels, we found that none of our OPC replacement scenarios are compatible with our measured data (Supplementary Table 12, Extended Data Fig. 8a). Thus, this indicates that major contribution of remyelination in shadow plaques is from old oligodendrocytes and not from oligodendrocytes generated from proliferating OPCs.

The levels of ^{14}C in oligodendrocytes from shadow plaques were significantly lower than the levels in oligodendrocytes from normal appearing white matter when comparing individuals born before the increase of the atmospheric ^{14}C (1955) (P=0.011, two-tailed Mann-Whitney test). This suggest that there has been a reduction of oligodendrocyte generation during disease period in shadow plaques. We therefore estimated the ^{14}C levels in the oligodendrocytes in shadow plaques, if there was a healthy oligodendrocyte turnover up to disease onset (with an expansion phase the first five years and then an annual turnover rate of 0,32%) and then an absence of oligodendrocyte turnover. This scenario reproduced ^{14}C levels close to the measured levels (Fig. 3b, Extended Data Fig. 4). Setting the shadow plaque formation time to 10 years before onset also estimated ^{14}C levels close to the measured data. Thus, if the oligodendrocyte turnover is decreased or absent, it is most likely that it occurred around time of disease onset or even before.

In order to assess the sensitivity of the ^{14}C method we estimated the highest possible oligodendrocyte turnover that could occur undetected during the disease period. We

systematically modeled different turnover rates during the disease period if there was healthy turnover before disease onset. We found that there was a significant difference between the measured levels of carbon in oligodendrocytes in shadow plaques and our modeled scenarios down to 0.1% annual turnover after disease onset (Extended Data Fig. 5, P=0.041, two-tailed Mann-Whitney test). At 0.05% there was no longer a significant difference between the modeled scenario and the measured levels (Extended Data Fig. 5, P=0.132, two-tailed Mann-Whitney test). We calculated the total proportion of oligodendrocytes exchanged during the disease period by taking the annual turnover times the disease duration. The average total exchange of oligodendrocytes during the disease period if the annual turnover after onset was set to 0.1% was 3.1±1.6%. Thus, at a group level, the maximum proportion of generated oligodendrocytes that could go undetected is 3%.

References

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