**Supplementary figure 1**. **mGcm1 and mGcm2 expression**. (**A**) Immunolabelling of CNS primary cultures for mGcm1 (grey), microglia (CD45, red) and DAPI (blue), N=3; scale bar 10 μm. (**B**) RNA ISH of brain sections on P14, 2 and 18month-old brain sections from control and cko animals: *Cx3cr1* (red), *mGcm2* (green) and DAPI (blue), N=3; scale bar: 10 μm. (**C**) RNAscope labelling on control and cKO brain sections at 18 months: *Cx3cr1* (red), *mGcm1* (green), DAPI (blue), N=3; scale bar: 10 μm. (**D**) Immunolabelling of resident macrophages from lung and adipose tissues at 24month-old animals: mGcm2 (grey), CD45 (red) and DAPI (blue). Scale bar: 100 μm. *Cx3cr1-Cre$^{+/-}$;mGcm2$^{flox/}$* (control) and *Cx3cr1-Cre$^{+/-}$, mGcm2$^{flox/flox}$*(cKO)
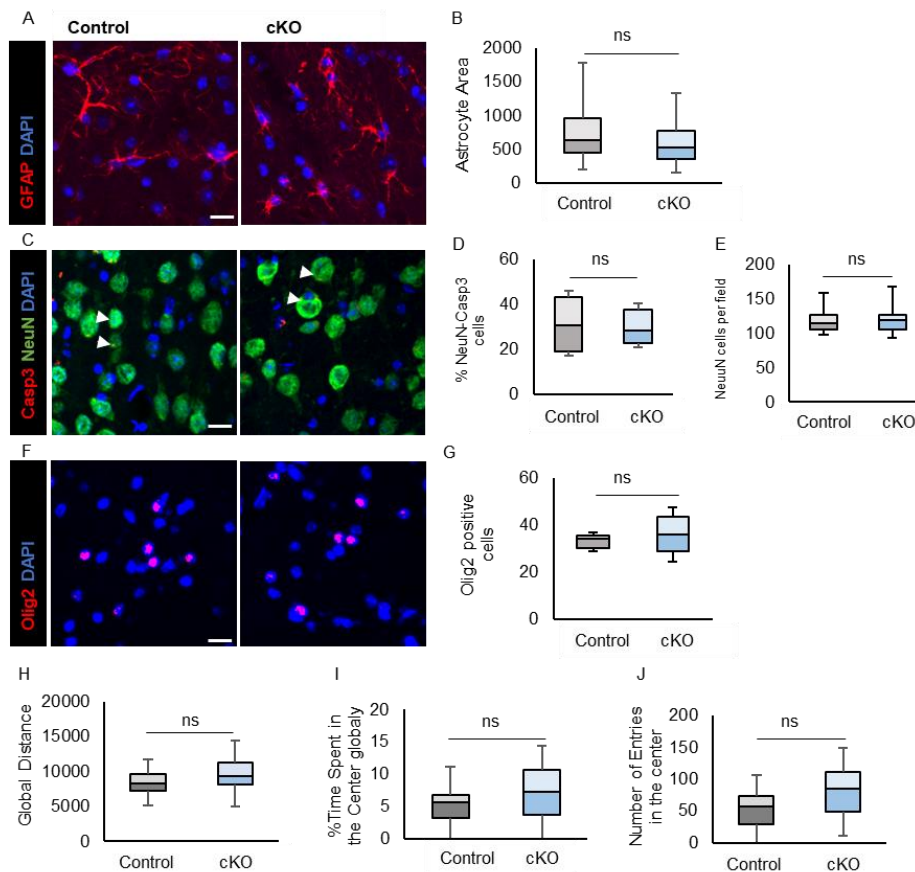
Supplementary figure 2. Characterisation of cell populations in the cortex of 24month-old animals. (**A**) Immunolabelling of astrocytes from control and cKO animals for GFAP (red). (**B**) Quantification of the GFAP area. (**C**) Immunolabelling of neurons with the pan neuronal marker NeuN (green) and the cell death marker Caspase3 (red). (**D**) Quantification for double positive NeuN-Caspase3 cells to calculate the neuronal cell death and (**E**) the total neuronal number. (**F**) Immunolabelling for oligodendrocytes with Olig2 and (**G**) quantification of oligodendrocytes in control and cKO animals. (**H,J**) Open field test for control and cKO animals at 18 months. The animals were evaluated for the total distance covered (**H**), the percentage of time spent in the centre (**I**) and how many times they entered in the centre (**J**). p-value: *<0.05, **<0.01, ***<0.001, and ns for not significant. N=5-13; scale bar: 50 μm. Statistical significance was determined by one-way ANOVA followed 2-tailed, unpaired t-test. *Cx3cr1-Cre$^{+/-}$;mGcm2$^{flox/}$* (control) and *Cx3cr1-Cre$^{+/-}$, mGcm2$^{flox/flox}$*(cKO)
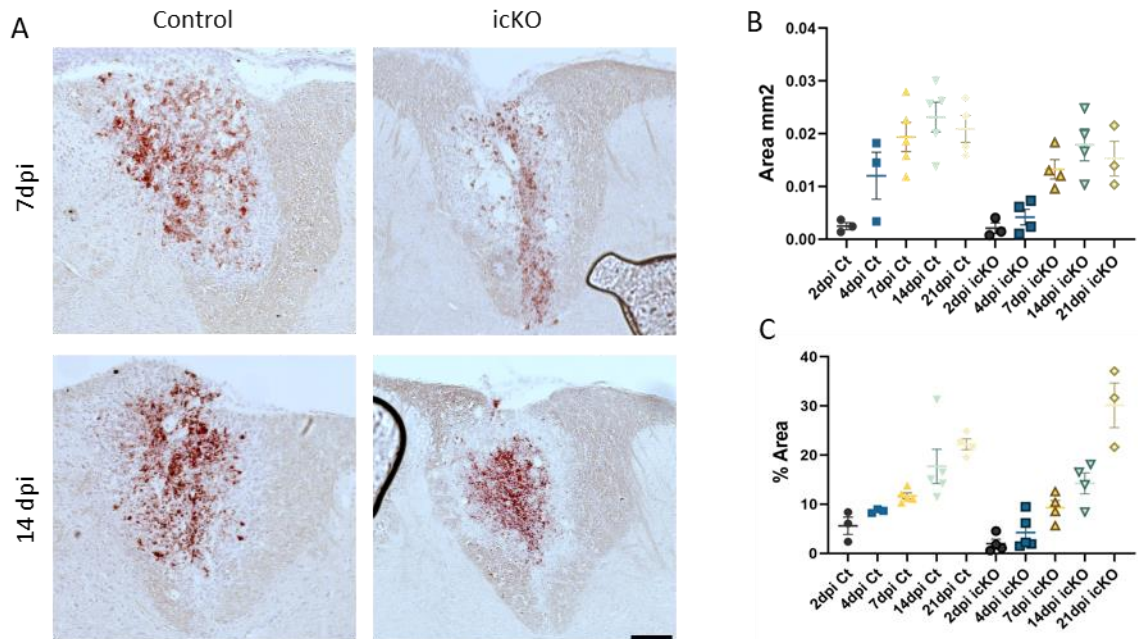
Supplementary Figure 3. The density of macrophages containing myelin debris is not altered in LPC demyelinated lesions of *mGcm2* icKO mice. (A) Oil-Red O staining of macrophages with myelin debris in control and *mGcm2* icKO LPC lesions, at 7 and 14 dpi. **(B)** Quantification of Oil-Red-O+ area in LPC lesions from 2 to 21 dpi, in control and *mGcm2* icKO animals. **(C)** Percentage of Oil-Red-O+ area in LPC lesions from 2 to 21 dpi in both experimental groups. Note that the clearance of myelin debris by macrophages in demyelinated lesions is not altered in *mGcm2* icKO with respect to control mice. Scale bar: **(A)**, 100μm.
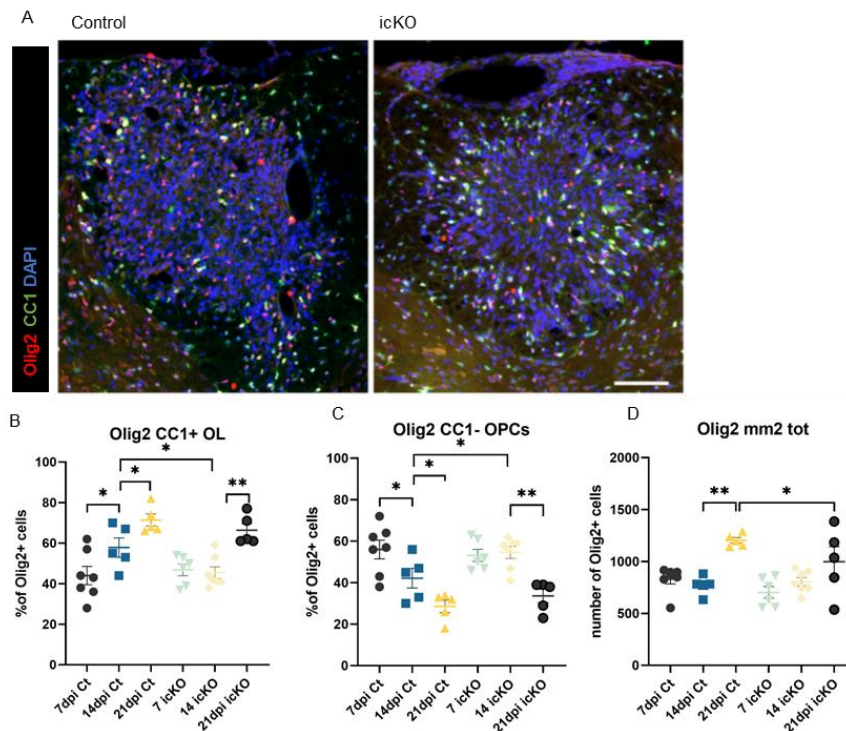
Supplementary Figure 4. Loss of *mGcm2* function in microglia delays oligodendrocyte differentiation in demyelinated lesions. (**A**) Immunolabelling with Olig2 (red) and CC1 (green) in LPC lesions of the spinal cord at 14 dpi, in control and *mGcm2* icKO mice. Nuclei are counterstained with DAPI. (**B,C**) Graphs indicating the percentage of Olig2/CC1-double positive differentiated oligodendrocytes and Olig2-positive/CC1-negative OPCs in demyelinated lesions from 7 to 21 dpi, in control and *mGcm2* icKO mice. (**D**) Quantification of the number of total Olig2-positive oligodendroglia in LPC lesions at 7, 14 and 21 dpi, in control and *mGcm2* icKO animals. Two-way ANOVA followed by Tukey's multiple comparison tests were used for statistical analysis. *p< 0.05, **p< 0.01. Scale bar: (**A**), 100 μm.
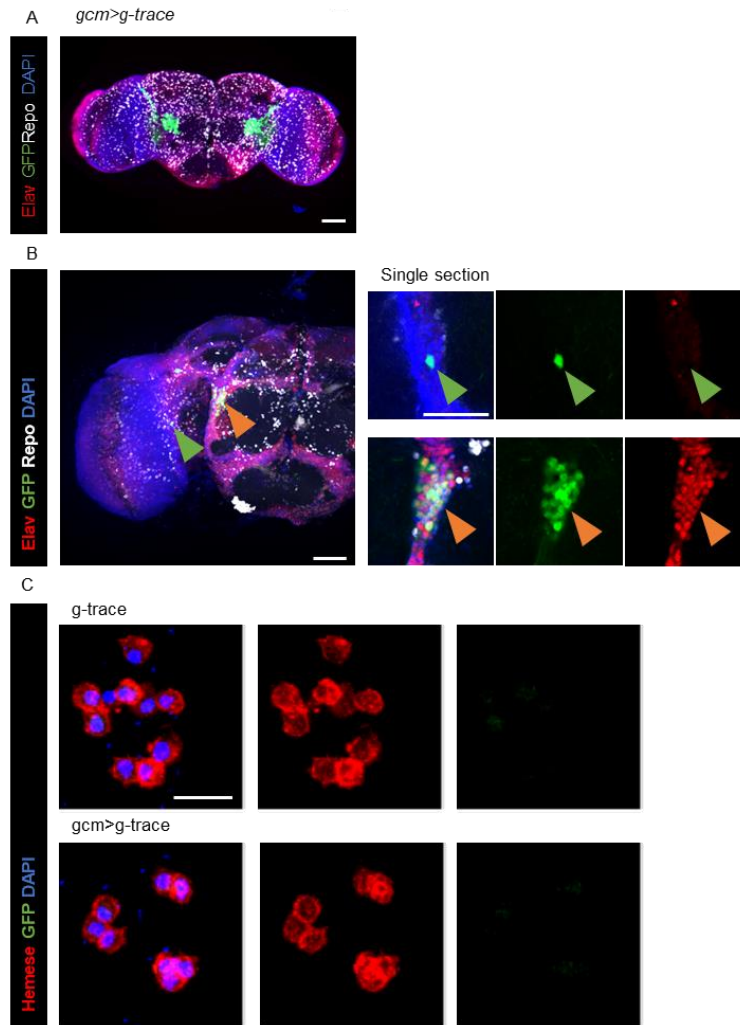
Supplementary Figure 5. An inducible system tracing *gcm* expression. (**A**) Immunolabelling of adult *Drosophila* brain with *gcm* tracing (*gcm>g-trace*=GFP) in green, Repo (white), Elav (white) and DAPI (blue). (**B**) Immunolabelling of adult *Drosophila* brain with *gcm* tracing (*gcm>g-trace*) in green, Repo (grey), Elav (red) and DAPI (blue), Scale bar: 20 μm. (C) Immunolabelling of hemocytes from gcm>g-trace strain. The pan-hemocyte marker Hemese (red), g-trace (green), DAPI (blue). Animals were raised at 18°C and shifted at 29°C at second instar larval. scale bar: 20 μm.

Host	Target	Dilution	Reference
mouse	anti-Arginase1	1/200	sc-271430
rat	anti-CD11b	1/400	MCA-74G
rat	anti-CD45	1/50	MCD-4500
rat	anti-CD68	1/400	MCA-1957
rat	anti-F4/80	1/100	MCA-497
rabbit	anti-Gcm1	1/50	B. Nait-Oumesmar
rabbit	anti-Gcm2	1/200	ab201170
rabbit	anti-Iba1	1/300	1919741
mouse	anti-iNOS	1/100	ab210823
mouse	anti-GFAP	1/100	PCN
mouse	anti-NeuN	1/100	ab279296
rabbit	anti-Casp3	1/200	mAb #9664
mouse	anti-MOG	1/20	clone C18C5, C. Linnington
rabbit	anti-Olig2	1/400	AB9610
mouse	anti-APC	1/100	OP80
mouse	anti-HLA	1/100	CR3/43
mouse	anti-Repo	1/20	8D12 (DSHB)
rat	anti-Elav	1/100	7E8A10 (DSHB)
mouse	anti-Hemese	1/40	I. Ando
mouse	anti-L4	1/50	I. Ando
chicken	anti-GFP	1/500	703095155
donkey	anti-mouse-Cy3	1/500	715-165-151
donkey	anti-rabbit-Cy3	1/500	711-165-152
goat	anti-rat-Cy3	1/500	112-165-167
goat	anti-mouse-Alexa647	1/500	115-605-166
goat	anti-rabbit-Cy5	1/500	111-175-144
goat	anti-rat-Cy5	1/500	112-175-144
donkey	anti-chicken-FITC	1/500	A11039
goat	anti-rat-Alexa568	1/1000	A11077
donkey	anti-rat-Alexa488	1/1000	A21208
donkey	anti-rat-Alexa647	1/1000	AB150155
donkey	anti-rabbit-Alexa568	1/1000	A10042
goat	anti-mouse-Alexa488	1/1000	1070-02
donkey	anti-mouse-Alexa488	1/1000	A21202
goat	anti-mouse-FITC	1/100	A21141

Supplementary Table 1. Primary and secondary antibodies

MS cases	Age	Sex	PMD	Disease duration	Disease course	Lesions analyzed			
						Active	Chronic active	Chronic inactive	Shadow plaques
MS94CLA6	42	F	11	6	PP	1			
MS100CLC2	46	M	7	8	SP			1	
MS121CLC5	49	F	24	14	PR	1		1	
MS106L6C8	39	F	18	21	PP		1		
Control									
C26CLA5	79	F	18		Cardiac failure				

Supplementary Table 2. MS and control cases used to study hGCM2 expression

	Target	Taqman probes
	Hprt	HPRT TaqMan® Gene Expression Assays (Mm03024075_m1)
	mGcm2	GCM2 TaqMan® Gene Expression Assays (Mm00492312_m1)
M1	iNOS	NOS2 TaqMan® Gene Expression Assays (Mm00440502_m1)
M1	TLR2	TLR2 TaqMan® Gene Expression Assays (Mm00442346_m1)
M2a	Arg-1	ARG1 TaqMan® Gene Expression Assays (Mm00475988_m1)
M2b	Il-4ra	IL-4a TaqMan® Gene Expression Assays (Mm01275139_m1)
M2c	CD163	Cd163 TaqMan® Gene Expression Assays (Mm00474091_m1)

Supplementary Table 3. Taqman probes used for qRT-PCR analysis of LPC lesions