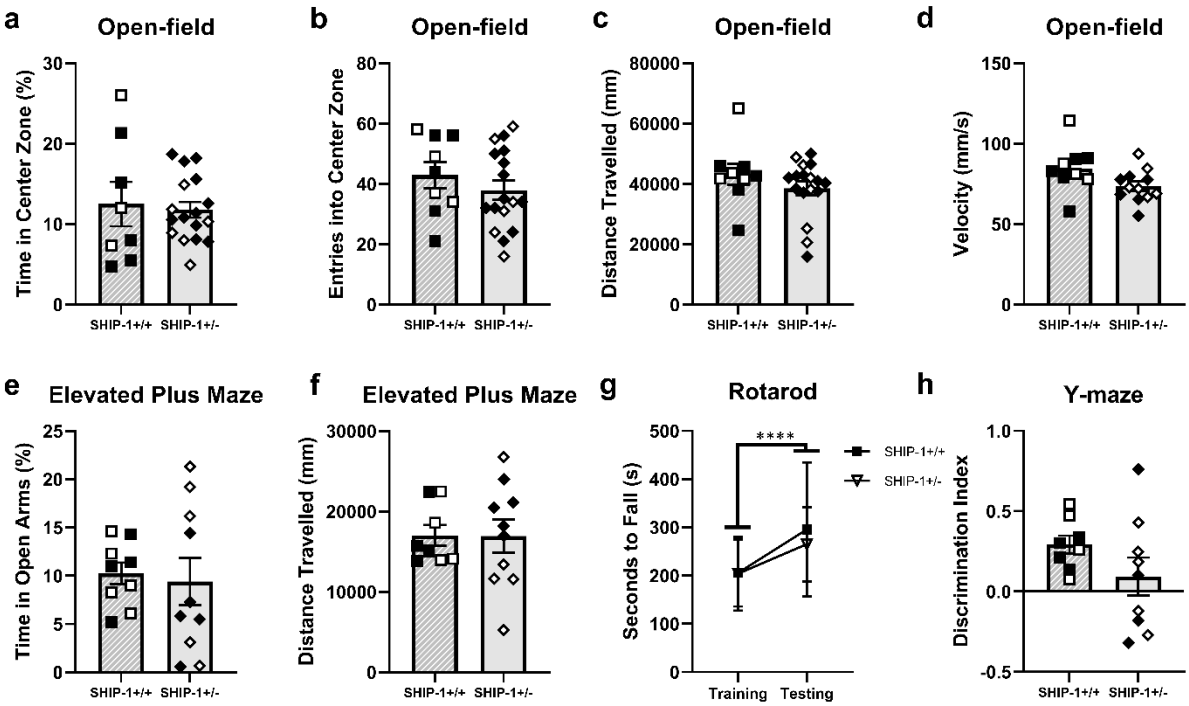
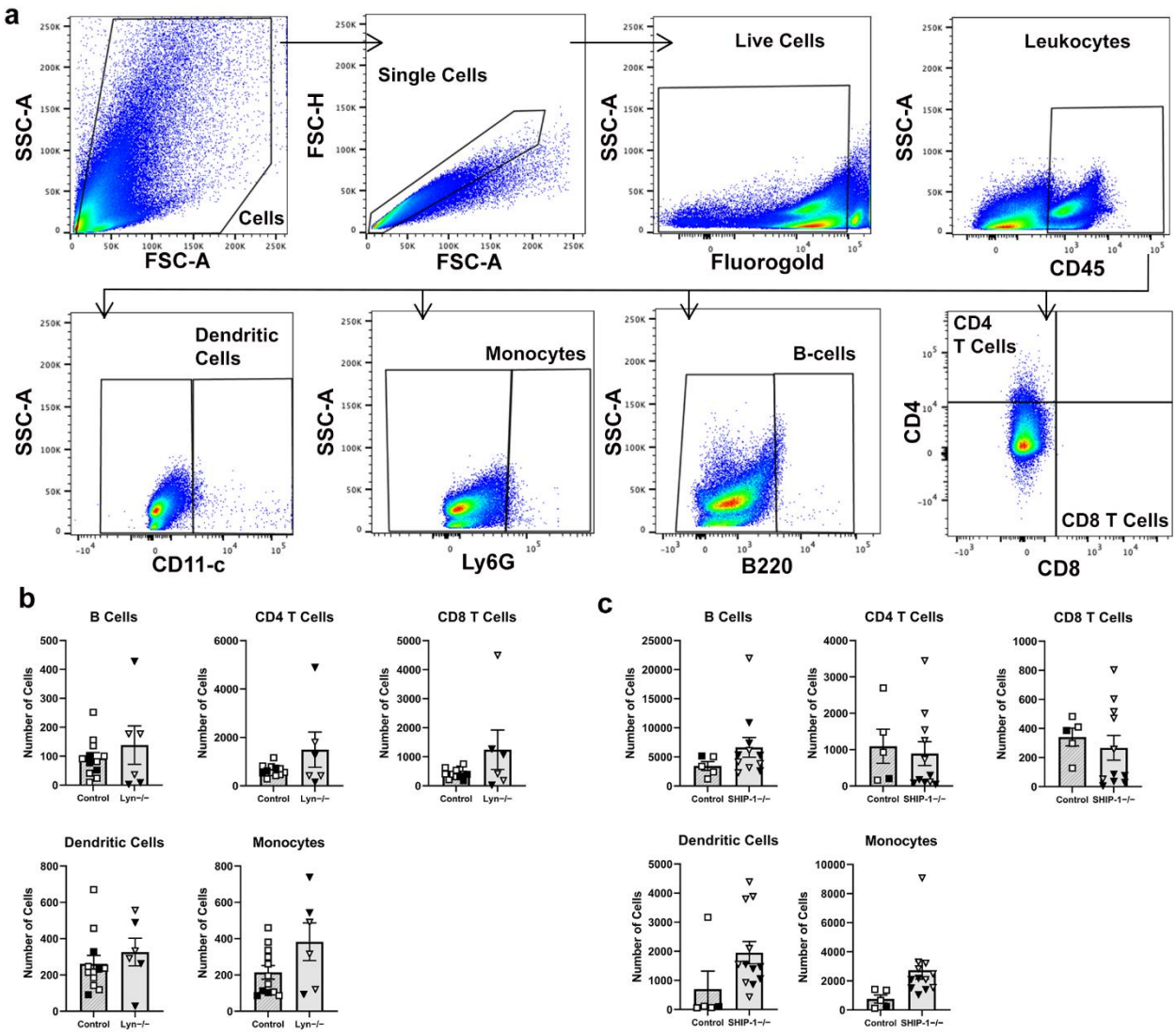


Supplementary Figure S1. Heterozygous SHIP-1+/− mice exhibit no differences in behavior compared to SHIP-1+/+ mice. (a) Time spent in center zone; (b) entries into center zone; (c) distance traveled; and, (d) speed in open-field tests (n= 9 SHIP-1+/+ and 17 SHIP-1+/− mice). (e) Time spent in open arms; and, (f) total distance traveled during Elevated Plus Maze test (n= 9 SHIP-1+/+ and 10 SHIP-1+/− mice). (g) Time (sec) spent on rotarod before falling during consecutive training and testing days (n= 9 SHIP-1+/+ and 10 SHIP-1+/− mice). (h) Discrimination index calculated from time spent in novel arm against time spent in familiar arm during Y-maze test (n = 8 SHIP-1+/+ and 9 SHIP-1+/− mice). Females = solid, males = open. Unpaired t-test and Two-way ANOVA ****p<0.0001.



Supplementary Figure S2. The immune cell composition in the steady-state brains of Lyn−/− and SHIP-1−/− mice is unchanged. (a) Gating strategy to identify cell populations in digested whole brain tissue from Lyn−/− and SHIP-1−/− mice, and their respective controls. Flow cytometric quantitation of the indicated immune cell subsets in digested whole brain tissue from (b) Lyn−/− mice (n = 6 Lyn−/− and 12 control mice); and, (c) SHIP-1−/− mice (n = 12 SHIP-1−/− and 5 control mice). Females = solid, males = open.

Supplementary Table S1. Distribution of animals used in each set of experiments.

Distribution of Lyn−/− mice used in study		
Procedures	Genotype	
	Control (C57BL/6)	Knockout (Lyn-/-)
Behavior	n=18 (m=12, f=6)	n=19 (m=10, f=9)
Histology	n=7 (m=4, f=3)	n=6 (m=3, f=3)
Gene Expression	n=6 (m=3, f=3)	n=6 (m=6, f=0)
Flow Cytometry	n=11(m=8, f=3)	n=11 (m=6, f=5)
Cytokine Flow Cytometry	n=10 (m=5, f=5)	n=10 (m=3, f=7)
Distribution of SHIP-1−/− mice used in study		
Procedures	Genotype	
	Control (SHIP-1+/+ or SHIP-1+/−*)	Knockout (SHIP-1−/−)
Behavior	n=8 (m=4, f=4)	n=23 (m=9, f=14)
Histology	n=8 (m=5, f=3)	n=8 (m=4, f=4)
Gene Expression	n=5 (m=5, f=0)	n=6 (m=4, f=2)
Flow Cytometry	n=10 (m=7, f=3)	n=16 (m=9, f=7)
Cytokine Flow Cytometry	n=9 (m=5, f=4)	n=8 (m=1, f=6)

* Littermate SHIP-1+/+ mice were used as controls for all experiments except for flow cytometry analyses, where littermate SHIP-1+/− mice were used as controls.

Supplementary Table S2. Antibodies used for flow cytometry.

Marker	Clone	Channel	Conc.	Catalogue	Company
CD16/CD32 Fc block	-	-	1:640	553141	Produced in-house
Fluorogold (live-dead stain)	-	BUV525	1:1000	Sc-358883A	Santa Cruz Biotechnology
Brain Analyses					
IBA-1	1022-5	FITC	1:500	Ab15691	Abcam
CX3CR1	SA011F11	PerCP Cy5.5	1:500	149010	BioLegend
CD45	30-F11	BUV395	1:1000	564279	BD Bioscience
TREM2	Polyclonal	Biotinylated	1:300	RDSBAF1729	Labome (R&D Systems)
CD86	GL1	BV421	1:500	564198	BD Bioscience
CD206	IMR5D3	Biotinylated	1:400	MA5016869	Invitrogen
TMEM119	V3RTGOsz	PE-Cy7	1:500	25-6119-82	Invitrogen
CD40	3/23	APC	1:500	558695	BD Bioscience
CD4	GK1.5	FITC	1:600	553729	BD Bioscience
CD14	5A2-8	PerCP Cy5.5	1:500	45-0141-82	
CD8a	53-6.7	APCe780	1:500	47-0081-82	eBioscience
CD11c	HL3	PE	1:500	553802	BD Bioscience
B220	RA3-6B2	PE-Cy7	1:500	25-0452-82	eBioscience
F4/80	T45-2342	BUV737	1:800	748283	BD Bioscience
CCR2	SA203G11	BV421	1:500	150605	Biolegend
Ly6G	1A8	BV510	1:500	127633	Biolegend
CD11b	M1/70	PE-Cy7	1:500	25-0112-82	Invitrogen
CD22.2	G155-178	Biotinylated	1:500	553382	eBioscience
Spleen (Single Stain Set-up Controls)					
B220	RA3-6B2	FITC	1:1000	553088	BD Bioscience
B220	RA3-6B2	PerCP Cy5.5	1:1000	552771	BD Bioscience
B220	RA3-6B2	APC	1:1000	553092	BD Bioscience
B220	RA3-6B2	APCe780	1:1000	47-0452-82	eBioscience

B220	RA3-6B2	PE	1:1000	553090	BD Bioscience
B220	RA3-6B2	PE-Cy7	1:1000	25-0452-82	eBioscience
CD19	1D3	BV450	1:400	48-0193-82	eBioscience
B220	RA3-6B2	Biotinylated	1:1000	553086	BD Bioscience
Secondary					
-	Streptavidin	BV711	1:1000	563262	BD Bioscience
Intracellular Cytokine					
TNF-α	Monoclonal	BV450	1:100	48-7321-82	Thermo Fisher Scientific
IgG Control	-	PE	1:100	554680	BD Bioscience

Supplementary Table S3. Gene assays used for gene expression analyses.

Marker	**Gene Name**	**Gene Assay ID (Thermo Fisher)**
Chemokine (C-C Motif) Ligand 2 (CCL2)	*Ccl2*	Mm00441242_m1
CD16	*Fcgr3*	Mm00438882_m1
CD68	*Cd68*	Mm03047343_m1
CD86	*Cd86*	Mm00444540_m1
CD206	*Mrc1*	Mm01329362_m1
Interleukin 1 beta (IL-1β)	*Il1b*	Mm00434228_m1
Ionized Calcium-binding Adapter Molecule 1 (IBA-1)	*Aif1*	Mm00479862_g1
Glial Fibrillary Acidic Protein (GFAP)	*Gfap*	Mm01253033_m1
Lyn	*Lyn*	Mm01217481_m1
Src Homology 2 Domain Containing Inositol Polyphosphate 5-phosphate 1 (SHIP-1)	*Inpp5d*	Mm00494963_m1
TMEM119	*Tmem119*	Mm00525305_m1
TREM2	*Trem2*	Mm04209424_g1