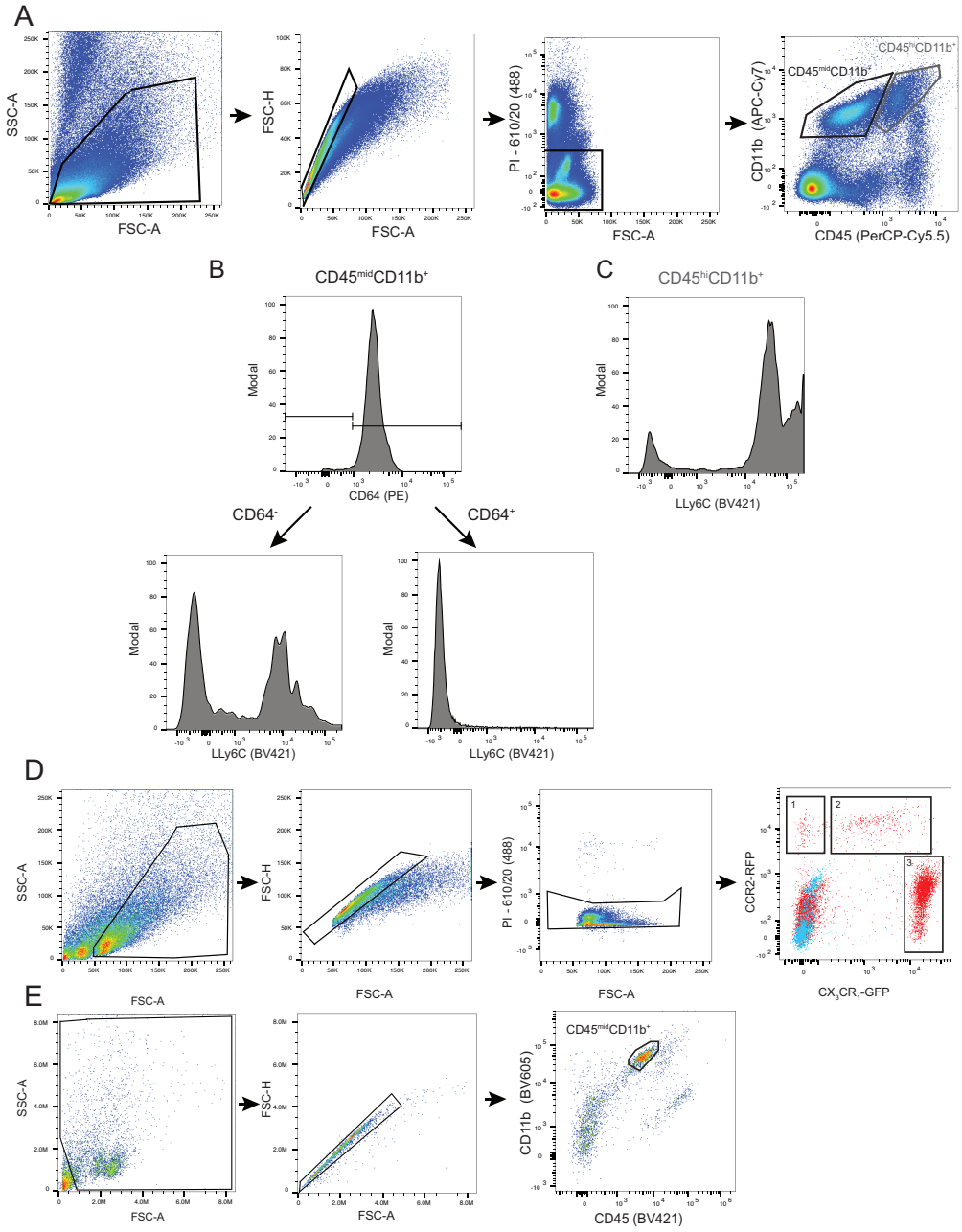

Fig. S1 Gating scheme for brain cells. Live cells were identified by gating on singlets by forward and side scatter characteristics, followed by PI as a live/dead marker. For wild-type and *S100A9*$^{-/-}$ mice myeloid cells and microglia were identified as either CD45^{mid}/CD11b^{+} or CD45^{hi}/CD11b^{+} (A). In the CD45^{mid}/CD11b^{+} population, CD64^{+} cells did not express Ly6C, indicating that these cells were likely microglia or tissue resident macrophages, while some CD64^{-} cells did express Ly6C and include some monocytes and neutrophils (B). The CD45^{hi}/CD11b^{+} population contained a higher proportion of Ly6C^{mid} and Ly6C^{hi} cells (C). In *CCR2*$^{RFP/+}$::*CX$_3$CR$_1$*$^{GFP/+}$ mice, CX$_3$CR$_1$-GFP and CCR2-RFP expression (red) were compared to fluorescence in wild-type cells (blue) and used to identify CCR2^{+}/CX$_3$CR1^{-} monocytes (gate 1), CCR2^{+}/CX$_3$CR1^{mid} intermediate cells (gate 2), and CCR2^{-}/CX$_3$CR1^{hi} microglia/macrophages (gate 3) (D). For ROS measurements, violet dyes were used to identify CD45mid/CD11b+ cells due to the spectrum of dihydrorhodamine (E).

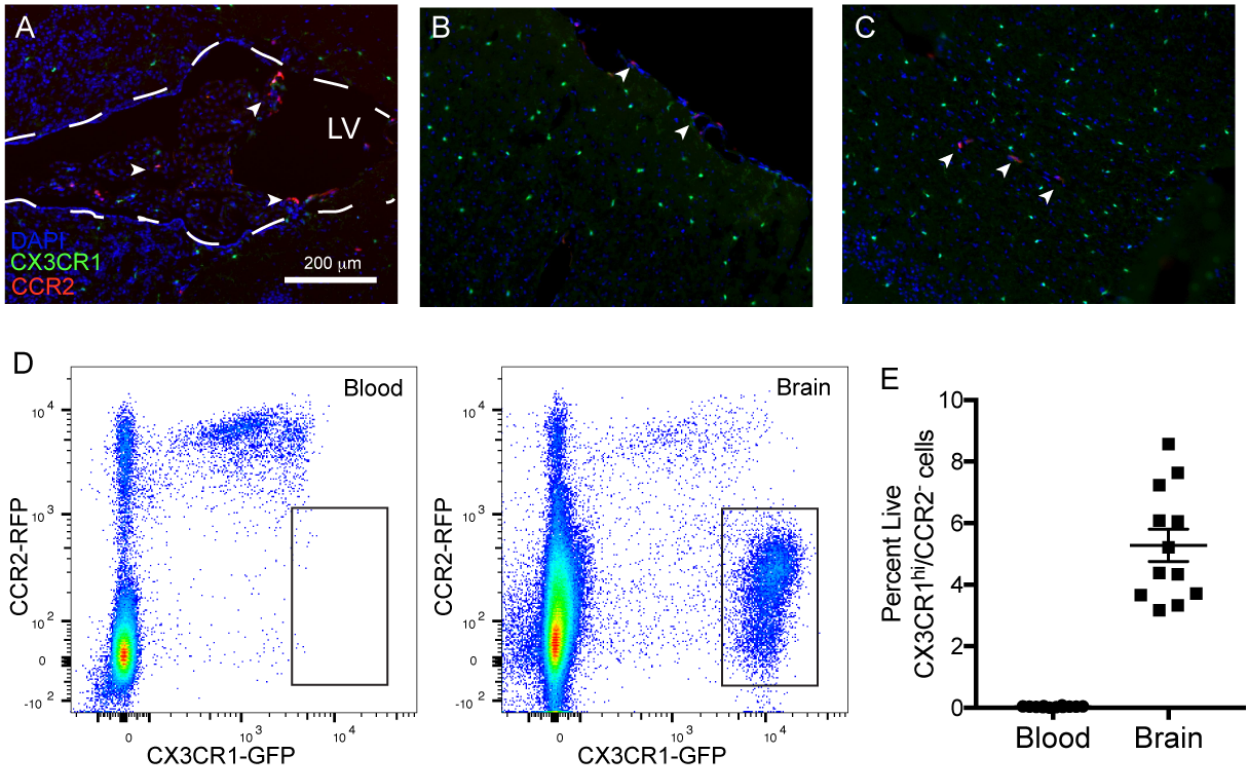

Fig. S2 Fluorescent microscopy for CCR2-RFP and CX_3CR1-GFP shows the presence of RFP+ cells (arrowheads) in expected locations such as choroid plexus (A), meninges (B), and around parenchymal blood vessels (C) 14 days after CLP. We did not observe an parenchymal collections of monocytes in abnormal locations (n = 4 mice). Flow cytometric examination of blood or brain lysates after enzymatic dissociation shows that although CX_3CR_1-GFP is expressed by circulating cells, these cells are nearly uniformly CCR2-RFP positive and exhibit lower GFP expression than do GFP expressing cells isolated from the brain (D, box). Gating on CX_3CR_1-GFP$^+$/CCR2-RFP$^-$ cells nearly completely excludes circulating cells (E).

Table S1 Cause of death of patients whose post-mortem brain tissue was examined.

Age (years)	Sex	Neuropathologic diagnosis	Duration of hospitalization (days)	Terminal events
Subjects with sepsis				
90	M	Alzheimer's Disease	5	Respiratory failure secondary to pneumonia without antecedent hemodynamic instability.
76	F	Alzheimer's Disease	<1	Suspected mesenteric ischemia leading to respiratory arrest with post-intubation cardiac arrest and successful resuscitation followed by shock for 12 hours prior to death.
78	F	Alzheimer's Disease	<1	Urinary tract infection. Hypotensive on presentation with response to a single 250 cc fluid bolus, followed within 12 hours by Kussmaul respirations and respiratory arrest.
49	M	Huntington's Disease	17	Seventeen day hospitalization for recurrent aspiration pneumonia with bronchopleural fistula. Patient became hypotensive 24 hours before death and did not receive resuscitation other than antibiotics due to goals of care.
43	M	None	2	Hemodynamically stable on presentation for management of intraabdominal abscess and colo-enteric fistula. Patient had a sudden cardiac arrest prior to planned surgical management and could not be resuscitated. Autopsy demonstrated ruptured intraperitoneal abscess.
84	F	Alzheimer's Disease	1	Urinary tract infection. Hypotensive on presentation with lactate of 17 after 4 days of illness at home. Received only antibiotics and normal saline at 150 cc/hr due to goals of care.
80	F	None	7	Hypotensive on ICU transfer for multifocal pneumonia, with intermittent vasopressor requirements. Patient had worsening multiorgan failure and care was transitioned to comfort measures less than 24 hours prior to death.
78	F	Progressive supranuclear palsy	6	Presented with pneumonia. Hypotensive on presentation and responded to fluid resuscitation. Patient had worsening hypoxia without hemodynamic instability over the following days prompting transition to comfort care less than 24 hours prior to death.
83	F	None	<1	In shock and respiratory distress on presentation to the emergency department and progressed to cardiac arrest. Patient had been seen and was hemodynamically stable the day prior to presentation. Patient had been treated beginning 5 days prior to presentation for UTI with altered mental status.
Subjects without infection				
45	F	Amyotrophic lateral sclerosis	<1	Sudden respiratory arrest after G-tube placement
82	F	None	<1	Cardiogenic shock after abdominal aortic aneurysm repair.
85	F	None	<1	Unwitnessed in-hospital cardiac arrest during workup of thrombocytopenia
75	F	Progressive supranuclear palsy	<1	Bradycardia and respiratory arrest. Fall with head injury.
43	M	None	<1	Myocardial infarction and arrhythmia
69	M	None	<1	Cardiac arrest during pacemaker placement

Table S2 Probe sequences for in situ hybridization

Probe	Sequence
S100A8-1	5'-CAA TGA GGT /iAmMC6T/GC TCA AGG CC/iAmMC6T/ TCT CCA GT/iAmMC6T/ CAG ACG GCA TTG /iAmMC6T/CA CGA AA-3'
S100A8-2	5'-C/iAmMC6T/G TAG ACA TA/iAmMC6T/ CCA GGG ACC CAG CCC /iAmMC6T/AG GCC AGA AGC /iAmMC6T/CT GCT ACT CC-3'
S100A8-3	5'-GTG GC/iAmMC6T/ GTC TTT GTG AGA /iAmMC6T/GC CAC ACC CAC /iAmMC6T/TT TAT CAC CA/iAmMC6T/ CGC AAG GA-3'
Actin-1	5'-AAG /iAmMC6T/TA GGT TTT G/iAmMC6T/C AAA GAA AGG G/iAmMC6T/G TAA AAC GCA GCT CAG /iAmMC6T/AA CAG TC-3'
Actin-2	5'-CCT T/iAmMC6T/G GGA GGG TGA GGG ACT /iAmMC6T/CC TGT AAC CAT C/iAmMC6T/A TGC CGT GGA /iAmMC6T/AC TT-3'
Scramble-1	5'-CT/iAmMC6T/ GGT GCA TGG AAG G/iAmMC6T/T GTG CTG ACG TGG GA/iAmMC6T/ CAC TTA CTC CCA A/iAmMC6T/G TT-3'
Scramble-2	5'-AAG /iAmMC6T/CT TAG ACG AAC AT/iAmMC6T/ TTG ACG TCT CGA A/iAmMC6T/G CGG GTA AAA G/iAmMC6T/A AAG AG-3'