**Supplemental methods**

*Inoculation with HSV-1 and treatment with acyclovir*

A total of 8 female BalBC mice (8 weeks old, from Jackson Laboratories, Bar Harbor, ME,) were anesthetized with 3% isofluorane. Five mice (#1, 3-6) were intranasally inoculated with 1x106 plaque forming units (PFU) of HSV-1 (strain 17 syn+) and treated with ACV (Auromedics, 20 mg/kg/dose twice daily) starting at 72 hours post-inoculation for 2 weeks. One additional mouse (#2) was included from an initial experiment that resulted in the death of 4 out of 5 mice. This mouse was inoculated with 0.5x106 PFU HSV-1 intranasally, treated with ACV at 24 and 32 hours post-inoculation, and then from day 5, for 2 weeks. Two mice were inoculated with vehicle solution as controls.

*Serum collection*

Retro-orbital bleeds were performed using glass hematocrit capillary tubes (Drummond Scientific) pre-inoculation and at 3, 6, and 8 weeks post-HSV-inoculation. Clotted blood was spun for 15 minutes at 3000 g at 4°C, and supernatant (serum) was collected.

*Brain collection and processing*

At 8 weeks post-HSV-1-induction, mice were anesthetized with 3% isofluorane, perfused with 20 mL of ice-cold PBS via cardiac puncture, and brains were collected into ice-cold PBS. The brains were embedded in optimized cutting temperature (OCT) medium, snap frozen with dry-ice chilled isopentane, and stored at -80°C.

*Immunofluorescent cell-based assay for NMDAR antibody detection*

The presence of NMDAR antibodies in mouse sera was determined using a HEK293 cell-based assay (CBA)7,8. In brief, cells were transfected with the NR1 and NR2B subunits of the NMDAR. Twenty-four hours after transfection, cells were fixed in 4% paraformaldehyde and permeabilized with 0.3% Triton™ X-100 (Sigma-Aldrich, St Louis, MO, USA), and incubated with 1% bovine-serum-albumin (BSA) for 1.5 hours. HEK cells were then incubated with mouse or control serum (1:40 in 1% BSA) at 4°C overnight. The next day, cells were labeled with a rabbit monoclonal NR1 antibody (1:250, Millipore, Billerica, MA, USA) for 1h at room temperature, followed by the corresponding Alexa Fluor© 488 and 594 secondary antibodies against mouse and rabbit IgGs (1:1000, Molecular Probes, Invitrogen, Eugene, OR, USA). Fluorescent signal was captured with a fluorescence microscope using Zeiss Axiovision software8.

*Immunofluorescence and confocal microscopy*

Frozen brains were cut in half. One half was cut into 7 μm thick sections on a cryostat, which were fixed for 1 minute with 4% paraformaldehyde (Electron Microscopy Sciences) at room temperature (RT). For assessment of hippocampal postsynaptic membrane NMDAR density, sections were blocked with 10% goat serum, incubated with human CSF with known NMDAR Abs (diluted 1:20 in blocking serum) overnight at 4°C, washed with ice-cold PBS, permeabilized with 0.5% CHAPS (Sigma Aldrich) in PBS for 1 minute, and incubated with rabbit polyclonal antibody against PSD-95 (diluted 1:150, Clone 18258 Abcam) overnight at 4°C. Slides were then washed with ice-cold PBS and sequentially incubated with Cy3-goat anti-rabbit IgG in PBS (1:800, Jackson Immunoresearch) and then Alexa Fluor© 488 goat anti-human IgG (1:800, 2040-02, Southern Biotech) for 1 hour at room temperature. Coverslips were mounted using Diamond mounting medium and results were visualized on a Nikon i80 epifluorescence microscope. For co-localization of NMDAR and PSD-95,Z-stacks were acquired across 15 areas of the hippocampus on a Zeiss LSM 800 with Airyscan algorithm using a 63x oil objective at 3x zoom, 1016x1016 lateral resolution, to collect 17 optical images across a depth of 3 μm. Imaris 7.6.4 (Bitplane) spot detection and three-dimensional colocalization algorithms were used to quantify the number of postsynaptic NMDAR clusters per Z-stack, which were averaged across the 15 areas.

*Immunoblot analyses*

Comparative NMDAR and PSD-95 protein concentrations in mouse hippocampi were determined with Western blotting similarly to as described before8. Hippocampi were dissected from thawed brain halves after OCT had been washed off, resuspended in 500 μL 0.32 M sucrose, 4 mM HEPES pH 7.4 with protease inhibitors (Roche, 04693124001), minced, and sonicated (Fisher Scientific Sonic Dismembrator 550, speed 3.5) for 20 seconds. The homogenate was spun at 1000 g at 4°C for 15 minutes to remove nuclei, and protein concentration in the supernatant was determined with a BCA assay (Pierce). 10 μg samples were heated to 70°C for 10 minutes in 4X NuPAGE sample loading buffer (Invitrogen) and immunoblotted using 10% SDS gel electrophoresis followed by transfer with a wet blotting apparatus (Invitrogen) to PVDF membranes. Membranes were blocked in 5% non-fat skimmed milk in Tris-buffered saline with Tween 20 (TBST) and incubated overnight in blocking buffer with the following primary and secondary antibodies: NMDAR (1:1000, G8913, Sigma-Aldrich), PSD-95 (1:1000, 124-003, Synaptic Systems, Goettingen, Germany), actin (loading control, 1:2500, A-2668, Sigma Aldrich), and secondary anti-rabbit-IgG-HRP for 1 hour at room temperature, (1:5000-25,000, 7074S, Cell Signaling). Enhanced chemiluminescence (Pierce) was captured on X-ray film (Thermo Scientific). Band density was quantified using ImageJ software; signal was normalized to actin in the same lane. The mean intensity of signal in control mouse hippocampi was defined as 100%, and all other intensities expressed relative to this value.