Supplementary Methods

The methodology and results of animal studies were reported in accordance with the ARRIVE (Animal Research: Reporting in vivo Experiments) 2.0 guidelines.[17] The researchers implemented efforts to minimize animal suffering during the study as listed below:

1. For the non-invasive blood pressure measurements, the animals were introduced to the device by allowing them to walk into the clear tube and acclimate to the environment before placing the nose cone on to the device (~3 minutes). If animals showed significant visible distress at any time during the measurement, they were removed and reintroduced to the device after at least 1 hour or the next day.
2. After induction of anesthesia vital signs monitors were placed to continuously monitor physiological parameters which helped assure anesthetic depth during the experiments. Furthermore, surgical plane anesthesia was assured by toe pinch before incision was made.
3. Protective eye ointment was placed to prevent corneal scarring.
4. For the experiments involving repetitive MRI scanning the rats were monitored by the investigators for at least 1h after anesthesia emergence to assure normal respiration and no distress was present before returning to their home cage.

Histology and Immunohistochemistry

including Masson's trichrome staining, formalin-fixed rat tissue blocks at the level of the ventral hippocampus were embedded in paraffin, cut into 10 μm-thick sections, and stained. The remaining WKY and SHRSP rats were used for immunohistochemistry using an aquaporin-4 (AQP4) antibody (Rabbit Polyclonal, Novus Bio, 1 μg/mL), which is a bidirectional water channel found on astrocytes, and rat endothelial cell antigen-1 antibody (RECA-1, mouse monoclonal,

Abcam, 1 µg/mL). Immunohistochemical slide preparation was performed as follows: After fixation, brains were extracted, and post-fixed in NBF for 24 h at 4ºC, before sequentially cryoprotected in 10%, 20% and 30% sucrose in PBS supplemented with 0.01% sodium azide. The brains were then embedded in OCT, snap-frozen in isopentane super cooled with liquid nitrogen, sectioned coronally at a thickness of 10µm (Histoserv, Inc) and mounted on Apex Superior Adhesive Slides (Leica Biosystems). The sections were stored at -80ºC and air-dried at room temperature overnight prior to staining. All incubations were carried out at room temperature unless otherwise specified. One hippocampal section at the level of ventral (Bregma -5.80) were selected for each animal. Once completely thawed, the sections were rehydrated in PBS, permeabilized for 30 min in PBS/0.3% Triton X-100, incubated for 30 min in Image-iT FX Signal Enhancer (Thermo Fisher Scientific) and blocked for 1h in BlockAid blocking solution/0.3% Triton X-100 (Thermo Fisher Scientific). The sections were then incubated overnight at 4ºC with the primary antibodies. The next day, the sections were incubated for 2h with the secondary antibodies. Following this, the slides were cover slipped with #1.5H coverslips (Thorlabs) using Vectashield Vibrance Antifade Mounting Medium (Vector Laboratories) and allowed to dry overnight before imaging. All primary and secondary antibodies were diluted in BlockAid blocking solution/0.1% Triton X-100 and 3 x 5 min washes in PBS/0.1% Triton X-100 were carried after each antibody incubation. BlockAid Blocking Buffer (Thermo Fisher) with 0.1% triton replaced the primary antibody in negative controls.

Matching of T2- and post-contrast T1-weighted MRI with histological sections

The process of matching the digitized histological sections with their corresponding T2- or CSF contrast enhanced T1w MRI images was based on anatomical pattern recognition and involved several steps. First, the histological section of the ventral hippocampus was displayed in ZEN Blue

3.2 software (Carl Zeiss) and compared side-by-side with the T2w or T1w images displayed using PMOD (PMOD version 4.2) and searched for matching structures. Anatomical landmarks such as the shape of vessels, hippocampal sulcus, hilus and the location of the rhinal vein indentation were used for matching. For each rat, the 2D multi-slice T2w MRI image that best matched to the histological section was chosen. The T1w images were imported into Amira (Amira version 6.4.0, Thermo Fischer Scientific), volume rendered and the 'Slice module' was used to display and rotate the position and orientation of the 3D data to define the 2D slice plane view which best matched the histological data. PVS-like hyperintensities present in the 'best' matched 2D T2w or T1wd images were located, and the corresponding histological data examined to determine the associated immunohistochemical signatures (i.e., AQP4 expression patterns).