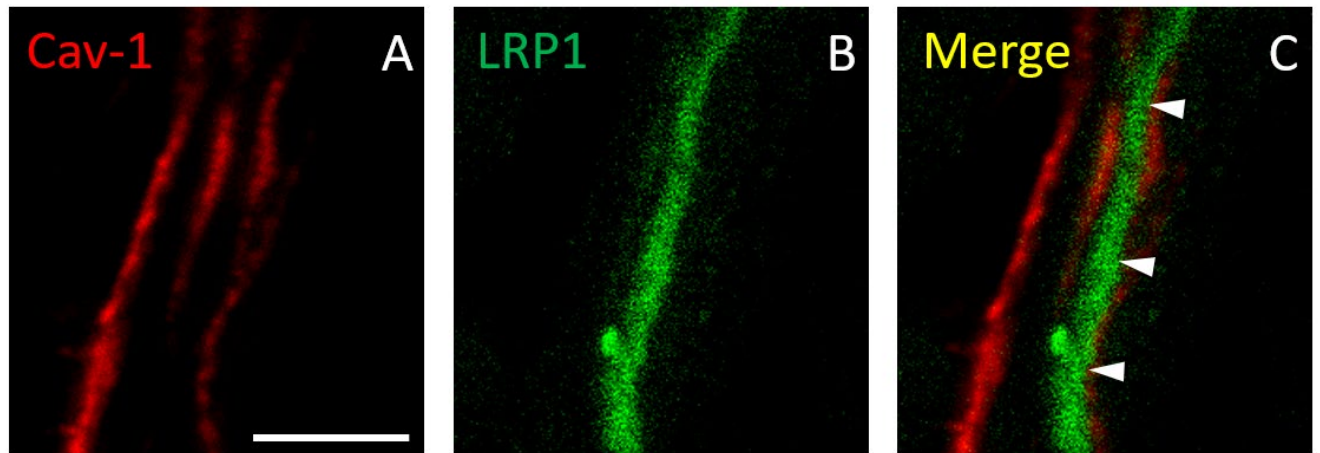
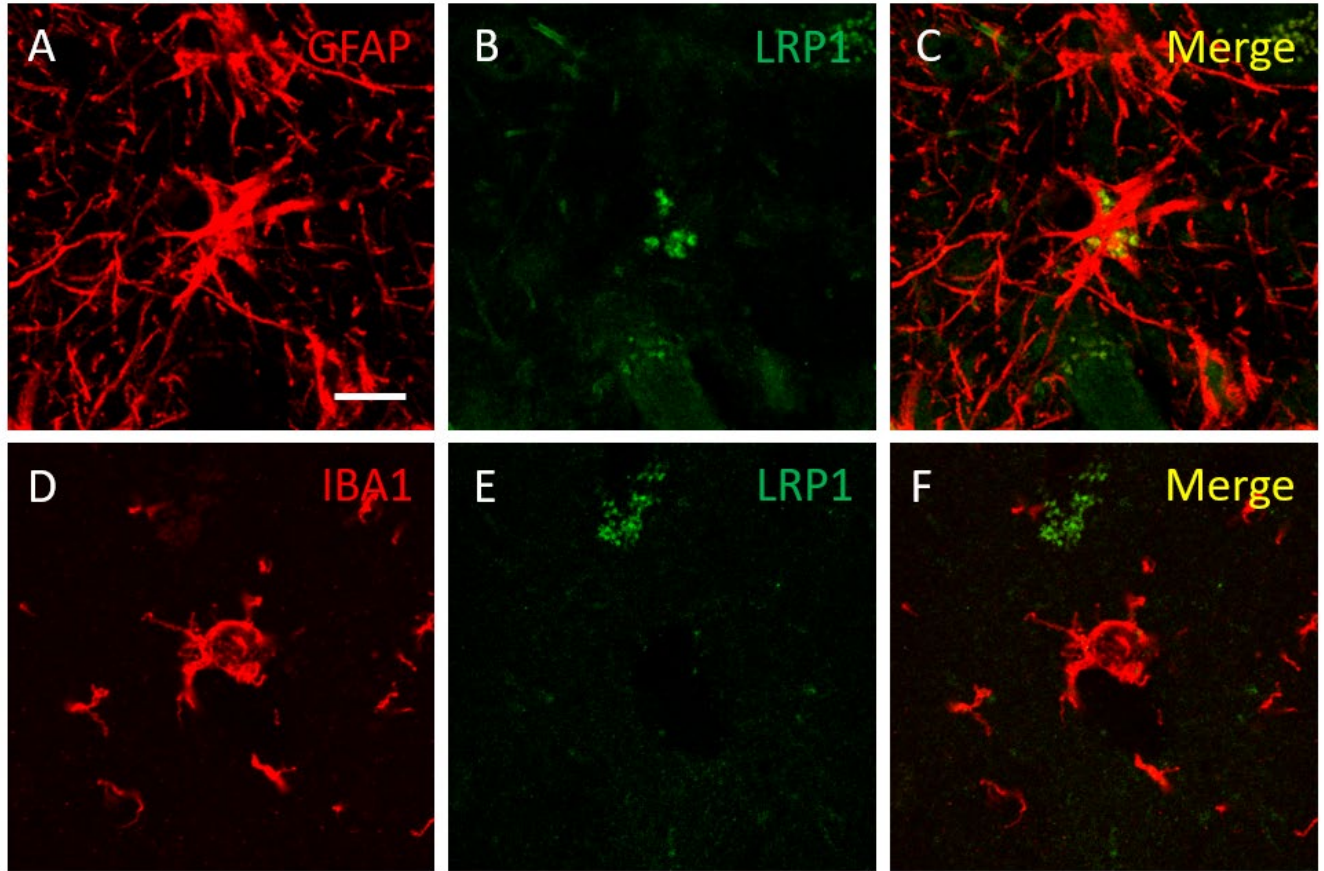


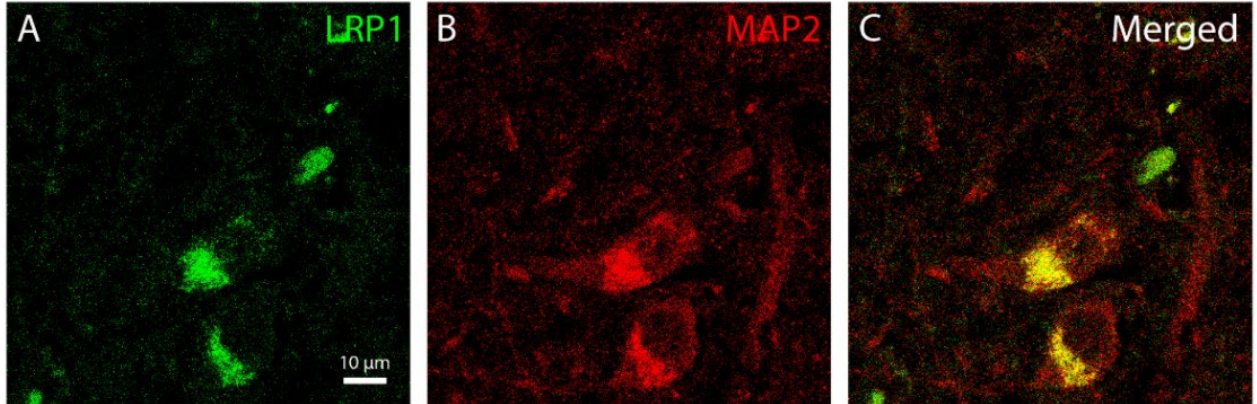
## Supplementary Figures



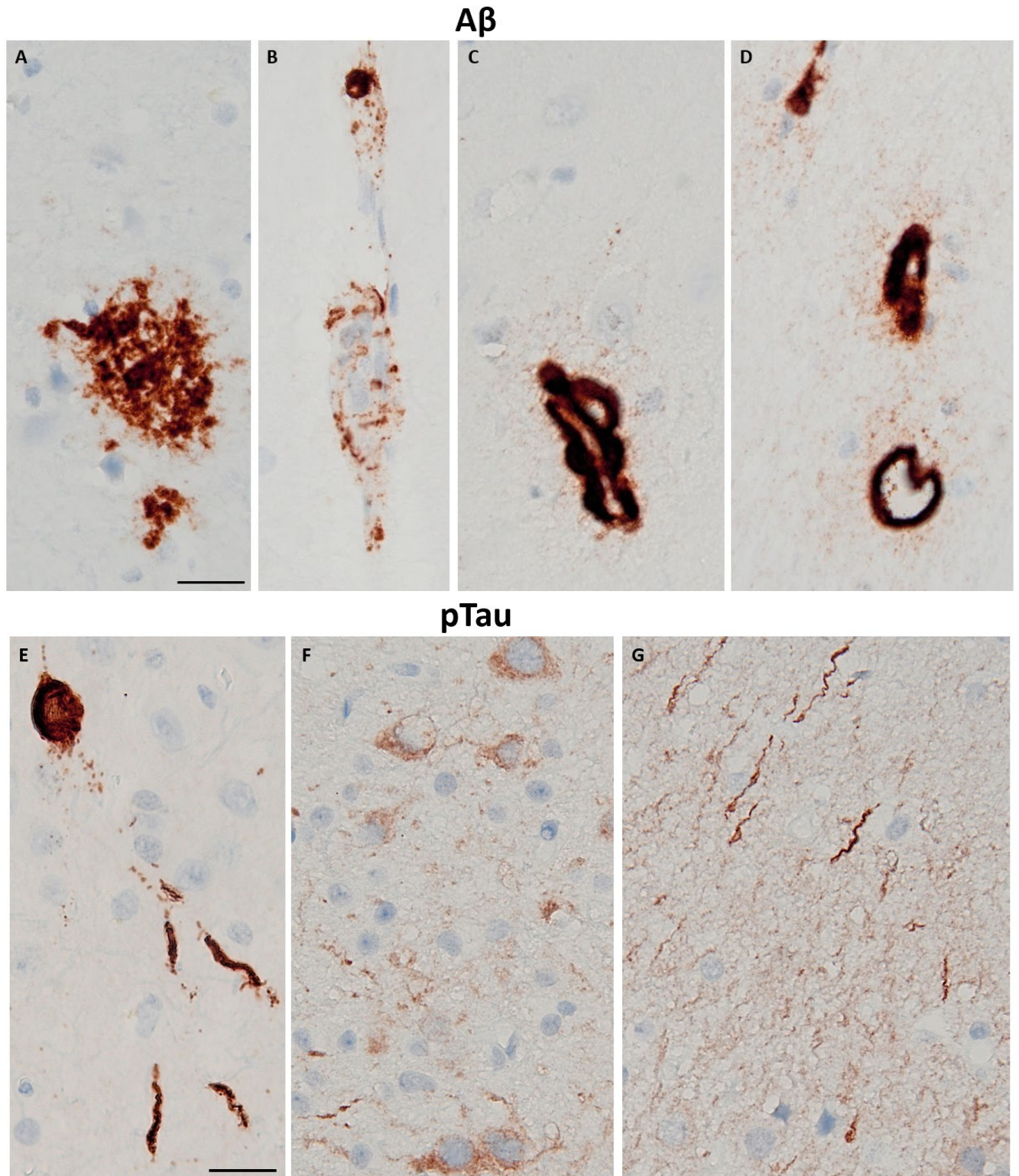
**Supplementary Figure 1. Cellular localization of LRP1 immunoreactivity in brain capillary in the hippocampus human control. (A-C)** Double labelling of LRP1 (green) and caveolin-1 (cav-1, red), which is an integral membrane protein expressed at both the luminal and abluminal side of the brain capillaries, shows that LRP1 is expressed at the abluminal side of the brain capillaries (white arrowheads in **C**). Scale bar: 5  $\mu$ m.



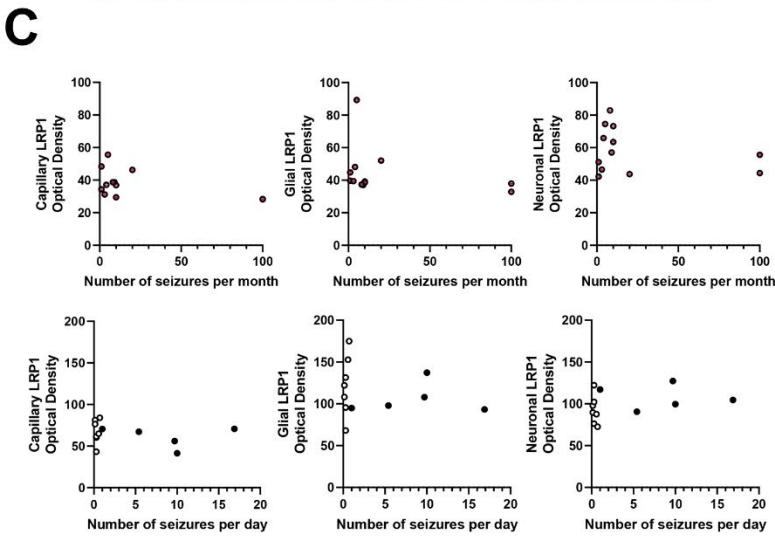
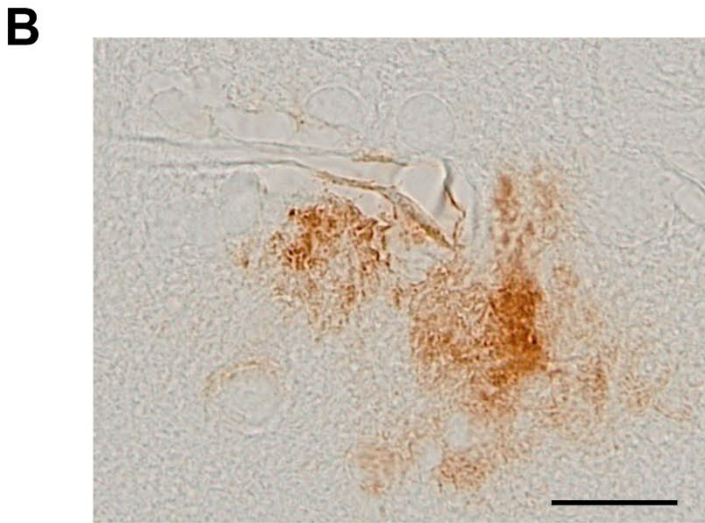
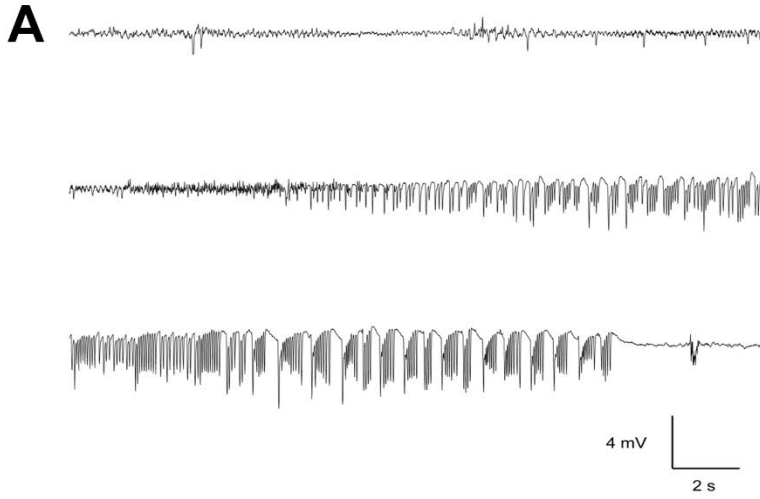
**Supplementary Figure 2. Confocal images of a patient who died after status epilepticus to identify LRP1 immunoreactive cells.** In a patient who died after status epilepticus, LRP1 co-localized with GFAP (A-C), indicating that these LRP1 positive cells were astrocytes. In the same patient, LRP1 did not co-localize with microglial marker IBA1 (D-F). Scale bar: A-F, 10  $\mu\text{m}$ .



**Supplementary Figure 3. Confocal images of human hippocampus to identify LRP1 immunoreactive cells.** In a human control patient, LRP1 co-localized with MAP2 (A-C), indicating that these LRP1 positive cells were neurons. Scale bar: A-C, 10 μm.



**Supplementary Figure 4. A $\beta$  plaque and A $\beta$  depositions surrounding brain capillaries and hyperphosphorylated tau in human epileptogenic brain tissue.** Diffuse plaque in entorhinal cortex (**A**) and capillaries in hippocampal region (**B-D**) in a 60 year old male TLE-HS patient. Hyperphosphorylated tau in neurons and focal tau-positive neuropil threads (**E-G**) in the hippocampus of TLE-HS patients. Scale bar: A-G, 20  $\mu$ m; hematoxylin counterstained.



**Supplementary Figure 5.**

**A. A typical example of an EEG seizure recorded from a rat with spontaneous recurrent seizures**

**B. A $\beta_{1-42}$  depositions surrounding a brain capillary in rat epileptogenic brain tissue.** Representative immunoreactive image for A $\beta_{1-42}$  in a late progressive post-SE rat brain. Scale bar: 20  $\mu$ m.

**C. Correlations between the number of seizures and LRP1 expression.**

The number of seizures did not correlate (Spearman rank  $p > 0.05$ ) with LRP1 expression in capillaries, glial cells or neurons in the hippocampus (CA1) of patients with TLE (top row) nor in rats with recurrent spontaneous seizures (bottom row). Open circles: rats with a non-progressive seizure development, closed circles: rats with a progressive seizure development.

## Supplementary Tables

**Supplementary Table 1. Clinical features of patients (paraffin tissue)**

<b>Pathology</b>	<b><i>n</i></b>	<b>Gender m/f</b>	<b>Age</b>	<b>Age at onset</b>	<b>Duration of epilepsy (years)</b>	<b>Number of seizures (per month)</b>
<b>Control</b>	20	16/4	62 (25-81)	-	-	-
<b>SE</b>	12	6/6	53 (23-87)	-	-	-
<b>TLE-HS</b>	12	7/5	44 (21-66)	24 (1-60)	20 (0-61)	23 (1-100)
<b>AD</b>	10	5/5	77 (73-84)	-	-	-

AD, Alzheimer's disease; SE, status epilepticus; TLE-HS, temporal lobe epilepsy with hippocampal sclerosis; values are given in mean (minimum-maximum).

**Supplementary Table 2. Clinical characteristics of SE patients and controls**

	Case	Pathology	Gender	Age	
1	p, fr	a, b	Control	f	25
2	p	a, b	Control	m	30
3	p	a, b	Control	m	48
4	p	a, b	Control	m	49
5	p, fr	a, b	Control	m	49
6	p	a, b	Control	m	56
7	p	a, b	Control	m	62
8	p	a, b	Control	m	62
9	p	a, b	Control	m	63
10	p	a, b	Control	f	64
11	p	a, b, c	Control	m	65
12	p	a, b, c	Control	m	67
13	p	a, b, c	Control	f	68
14	p	a, b, c	Control	m	69
15	p	a, b, c	Control	m	73
16	p, fr	a, c	Control	m	75
17	p, fr	a, c	Control	f	76
18	p, fr	a, c	Control	m	77
19	p	a, c	Control	m	81
20	p	a, c	Control	m	81
1	p	SE	m	23	
2	p	SE	m	26	
3	p	SE	f	29	
4	p	SE	m	31	
5	p	SE	f	35	
6	p	SE	f	54	
7	p	SE	m	58	
8	p	SE	m	65	
9	p	SE	m	67	
10	p	SE	f	79	
11	p	SE	f	79	
12	p	SE	f	87	

a, age-matched control for SE patients group; b, age-matched control for TLE-HS patients group; c, age-matched control for AD patients group; AD, Alzheimer's disease; SE, status epilepticus; m, male; f, female; TLE-HS, temporal lobe epilepsy with hippocampal sclerosis; p, paraffin; fr, frozen tissue.

**Supplementary Table 3. Clinical characteristics of TLE-HS patients**

Case	Pathology	Gender	Age	HS ILAE type	Duration of epilepsy (years)	Age at onset	Number of seizures (per month)	Antiseizure drugs used	
1	p	TLE-HS	f	21	3	9	12	100	CLB, LAM, LEV
2	p	TLE-HS	f	22	1	7	15	9	LEV, OXC, MDZ
3	p	TLE-HS	m	24	1	16	8	1	LEV, CLB, LCS
4	p	TLE-HS	m	24	1	8	16	100	CNP, LCS
5	p	TLE-HS	m	25	1	19	6	5	LEV, TPM
6	p	TLE-HS	m	55	1	0	55	4	CBZ
7	p	TLE-HS	f	57	1	10	47	1	CNP
8	p	TLE-HS	m	57	1	7	50	20	OXC, LAM
9	p, fr	TLE-HS	f	60	1	54	6	3	CBZ, LEV
10	p	TLE-HS	m	60	1	46	14	10	LAM, LEV, MDZ, CLB
11	p	TLE-HS	m	62	1	61	1	10	PHT, LAM, PB
12	p	TLE-HS	f	66	1	6	60	8	CBZ, CLB
13	fr	TLE-HS	m	49	1	33	16	15	CBZ
14	fr	TLE-HS	f	50	1	35	15	20	CBZ
15	fr	TLE-HS	f	53	1	31	22	15	LAM, CBZ, VPA
16	fr	TLE-HS	m	56	1	32	21	8	CBZ, LEV, CLB

CBZ, carbamazepine; CLB, clobazam; CNP, clonazepam; LAM, lamotrigine; LCS, lacosamide; LEV, levetiracetam; MDZ, midazolam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; TPM, topiramate; VPA, valproic acid; m, male; f, female; HS ILEA type, hippocampal sclerosis International League Against Epilepsy type according to Blümcke et al 2013; TLE-HS, temporal lobe epilepsy with hippocampal sclerosis; p, paraffin; fr, frozen tissue.

**Supplementary Table 4. Clinical characteristics of AD patients**

Case	Pathology	Gender	Age	NIA-AA score	Braak stage	CERAD	Thal Phase	
1	p, fr	AD	f	73	A3B3C3	V	3	3
2	p	AD	m	73	A3B3C3	VI	3	3
3	P	AD	f	76	A3B3C2	V	3	3
4	p	AD	f	76	A3B3C2	V	3	3
5	p	AD	m	76	A2B2C2	IV	2	3
6	p	AD	f	77	A3B3C3	VI	3	3
7	p	AD	f	79	A3B3C2	V	3	3
8	p	AD	m	79	A2B2C2	IV	2	3
9	p	AD	m	81	A3B3C2	VI	2	3
10	p, fr	AD	m	84	A3B2C2	IV	2	3
11	fr	AD	f	89	A3B2C2	V	2	3
12	fr	AD	f	93	A3B2C2	III	2	3

AD, Alzheimer's disease; CERAD, Consortium to Establish a Registry for Alzheimer's Disease; m, male; f, female; NIA-AA score, National Institute on Aging – Alzheimer's Association score; p, paraffin; fr, frozen tissue.

**Supplementary Table 5. List of primary antibodies**

<b>Epitope</b>	<b>Host</b>	<b>Catalog #</b>	<b>Company</b>	<b>Specificity</b>
Human LRP1	Mouse	sc-57351	Santa Cruz Biotechnology	Low-density lipoprotein receptor-related protein 1
Rat LRP1	Rabbit	Ab92544	Abcam	Low-density lipoprotein receptor-related protein 1
Human IBA-1	Rabbit	019-19741	WAKO	Ionized calcium binding adaptor molecule 1 (microglia)
Human GFAP	Rabbit	Z0334	DAKO	Glial fibrillary acidic protein (astrocytes)
Human GLUT-1	Rabbit	RB-9052	ThermoFisher Scientific	Glucose transporter protein-1
Human Cav-1	Rabbit	3238S	Cell signaling	Caveolin-1
Human MAP2	Rabbit	AB5622	Merck	Microtubule-associated protein 2 (neurons)
Human A $\beta$	Mouse	M0872	DAKO	A $\beta$
Rat A $\beta$ <sub>1-42</sub>	Rabbit	GTX134510	GeneTex	A $\beta$ <sub>1-42</sub>
Human phosphorylated tau	Mouse	90206	Innogenetics	phosphorylated tau

## Supplementary Materials and Methods

### *Electrode implantation*

Rats were anesthetized through an intramuscular injection of ketamine (74 mg/kg, Alfasan, Woerden, The Netherlands) and xylazine (11 mg/kg, Bayer AG, Leverkusen, Germany), and positioned in a stereotaxic apparatus. A set of insulated stainless steel electrodes (tips 800  $\mu\text{m}$  apart, 70  $\mu\text{m}$  wire diameter, California Fine Wire, CA, USA) was surgically implanted into the left dentate gyrus under electrophysiological guidance to record hippocampal EEG, while a set of stimulation electrodes was implanted in the angular bundle as described previously (Gorter, van Vliet, Aronica, & Lopes da Silva, 2002). The animals were allowed to recover from surgery for two weeks. Rats were transferred to individual recording cages (40x40x80 cm) and connected to a stimulation and recording system (NeuroData Digital Stimulator, Cygnus Technology Inc, Delaware Water Gap, PA, USA) using an electrical rotating joint and shielded multi-wire cable (Air Precision, Le Plessis Robinson, France).

### *Status epilepticus induction*

After a week of habituation to the new environment, rats received hippocampal repetitive tetanic 50 Hz stimulation delivered as a series of pulse trains at 13-seconds intervals. Each train lasted for 10 seconds and was comprised of biphasic pulses (maximum intensity of 500  $\mu\text{A}$ , with a pulse duration of 0.5 milliseconds). Stimulation was halted when the rats exhibited prolonged forelimb clonus and salivation for several minutes, which usually took place within one hour; if not, stimulation was stopped after 90 minutes. After the electrical stimulation, periodic epileptiform discharges (PEDs) appeared at a frequency of 1-2 Hz that lasted for several hours (status epilepticus).

### *EEG monitoring*

Hippocampal EEG recordings were made for 24 hours per day. Differential EEG signals were 10x amplified via a field effect transistor connected to an amplifier (50x; CyberAmp, Axon Instruments, Burlingame, CA, USA), 1-60 Hz band-pass filtered, and digitized by a computer. EEG signal was sampled at a frequency of 200 Hz per channel by a seizure detection program (Harmonie, Stellate Systems, Montreal, Canada). Trained human observers screened EEG recordings to confirm detected seizures. High voltage amplitude oscillations with a 2-fold amplitude increase that lasted longer than 10 seconds were counted as seizures.

## Supplementary references

Gorter, J. A., van Vliet, E. A., Aronica, E., & Lopes da Silva, F. H. (2002). Long-lasting increased excitability differs in dentate gyrus vs. CA1 in freely moving chronic epileptic rats after electrically induced status epilepticus. *Hippocampus*, 12(3), 311-324. doi:10.1002/hipo.1100