Elevated end systolic function in a rat model of temporal lobe epilepsy

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ABSTRACT

Sudden unexpected death in epilepsy (SUDEP) is a common cause of premature death amongst epilepsy patients. It is hypothesized to result from cardiorespiratory dysfunction, but the exact aetiology is unknown. The aim of this study was to determine if functional cardiovascular alterations were present in rats with chronic epileptic behaviour. Naive control rats were compared to a rat model of temporal lobe epilepsy that was induced using a repeated low-dose kainic acid (KA) protocol. The results indicate that end-systolic volume was significantly ($p=0.01$) higher in the epileptic group whilst end-diastolic volume did not reach significance ($p=0.08$). Ejection fraction, stroke volume, cardiac output, heart rate, body weight and heart size were also measured and appeared similar between groups. These initial data support the use cardiac magnetic resonance imaging (cMRI) to investigate cardiovascular changes across disease development of epilepsy-like behaviour, which may offer insight into understanding SUDEP.

INTRODUCTION

Epilepsy is one of the most common neurological diseases with rates of 4-10 per 1000 people worldwide (WHO). Despite good seizure control with antiepileptic drugs, sudden unexpected death in epilepsy (SUDEP) is a primary concern for all patients in this cohort. The incidence of sudden death in young adults with epilepsy is 27 times higher when compared to non-epileptic adults (Thurman, Hesdorffer et al. 2014; Devinsky, Hesdorffer et al. 2016). The exact aetiology is unknown, but human and animal studies suggest that altered cardiac and pulmonary abnormalities are a common finding in SUDEP (Dalager-Pedersen et al. 2005; Zhuo, Zhang et al. 2012; Fazan, Silva et al. 2015; Read, McCann et al. 2015; Devinsky, Hesdorffer et al. 2016).

The biggest risk factor for SUDEP is an increased frequency of generalised tonic-clonic seizures (Devinsky 2011; Hesdorffer, Tomson et al. 2012). Seizures, but also interictal and postictal periods, are known to change autonomic functions that include cardiac arrhythmias, bradycardia, tachycardia, asystole and cardiac repolarization. These events lead to cardiovascular dysfunction, pulmonary oedema and postictal depression of autonomic respiratory reflexes and contribute to sudden unexplained death in epilepsy (Boylan, Flint et al. 2004; Surges, Thijs et al. 2009; Jansen and Lagae 2010).

In animal models of induced epilepsy, cardiomyocyte damage, heart dilation, collagen deposition, arrhythmias, tachycardia, and alterations in ECG have been reported immediately following epilepsy-like behaviour induction and up to 4 weeks post-induction (Metcalf, Poelzing et al. 2009; Bealer, Little et al. 2010; Bealer and Little 2013; Read, McCann et al. 2015). These acute cardiac effects are most likely due to activation of the sympathetic nervous system following seizure (Sakamoto, Saito et al. 2008; Hotta, Koizumi et al. 2009; Little and Bealer 2012; Read, McCann et al. 2015). However, data on progressive epilepsy effects is lacking regarding heart

function, but it is likely that chronic studies will be important for understanding cardiovascular and autonomic changes in this pathology.

We aimed to test the hypothesis that end systolic volume and end diastolic volume would be altered in rats with epileptiform activity at chronic phase following status epilepticus (Pirttimäki, Salo et al. 2016). Profound increases in the left ventricle (LV) end-systolic volume following seizure induction were identified. These data indicate that MRI of cardiac function could be further used to investigate progressive changes co-existing in the central nervous system pathology and periphery.

MATERIALS AND METHODS

Animals

Fifteen male Wistar rats (400-530 g) were used for the study (purchased from Laboratory Animal Centre, University of Eastern Finland). The rats were housed in individual cages and maintained under a 12 h light/12 h dark cycle, with steady temperature (22 ± 1°C) and humidity (50-60%). Water and food were available *ad libitum*. All animal procedures were performed in accordance with the UEF animal care committee's regulations (ESAVI-2013-00833) and in accordance with the guidelines of the European Community Council Directives 2010/63/EU. A subset of rats utilized in this study were reported previously with a brain imaging study (Pirttimäki, Salo et al. 2016).

Induction of epileptogenesis with repeated low-dose kainic acid (KA) protocol

As previously described (Pirttimäki, Salo et al. 2016), epileptogenesis was induced with a systemic

injection of KA (K2389, 50 mg, Sigma-Aldrich, St. Louis, MO) using the repeated low-dose administration protocol (Hellier, Patrylo et al. 1998; Dudek, Hellier et al. 2002; Suarez, Cid et al. 2012). Briefly, rats received an initial dose of 5 mg/kg KA (i.p.). Injections were repeated hourly (for 3-6 h) with either a full or half dose until at least one Class V seizure occurred (total dose range varied between 7.5-20 mg/kg), at which point injections of KA ceased. Seizures were scored according to a modified Racine's scale (Racine 1972; Ben-Ari 1985). The naïve animals did not receive injections, but were strain (Wistar) and age-matched to the KA group.

EEG-fMRI

As previously described in (Pirttimäki, Salo et al. 2016), the rats were anesthetized with isoflurane and EEG electrodes (loops of Ag-wires) were implanted over the somatosensory (S1) cortex (AP -2.12; ML 2.5) bilaterally with the radiofrequency (RF) coil placed over the skull. To follow the development of KA-induced changes in the brain, functional MRI (fMRI) and EEG recordings were done at 1 wk and 1-2 months post-KA administration (the experimental intervention is illustrated in Figure 1.). Epileptiform activity was classified as spiking (duration of 20-70 ms), epileptic discharges (duration less than 6 s, no clear spike-and-wave discharge [SWD]-profile), and seizures (Pirttimäki, Salo et al. 2016). The naïve animals did not undergo KA procedure, but were implanted with EEG electrodes and RF coil 2 months prior to cMRI.

Cardiac MRI

Imaging was performed using a Bruker 7 Tesla PharmaScan (Bruker GmbH, Ettlingen, Germany) operating at 300.5 MHz. A linear 30 mm surface receiver coil (Bruker GmbH) was placed under the rat’s chest and a quadrature volume coil was used for transmission. The rats were anesthetized

with an induction mixture of 4-5 % isoflurane (ISO) and nitrous oxygen (70-% N_2 – 30-% O_2) and placed into the MRI compatible cradle. Animals were breathing spontaneously and transitioned to 1-1.5 % isoflurane. Short axis view (SAX) images covered the whole heart from apex to aorta (each slice thickness 1.5 mm) and included the entire cardiac cycle. Function of the LV was measured using FISP-cine sequence (TR = 8 ms, TE = 2 ms, FOV = 4.5 x 4.5 cm^2, matrix size 192 x 192, 8-11 slices, slice thickness 1.5 mm, 12-14 frames depending on heart rate) based on electrocardiogram (ECG) and respiratory gating. Blood oxygen saturation, heart rate, and spontaneous breathing rate were monitored throughout the experiment using a pulse oximeter and pressure-sensitive sensor (MR-compatible Small Animal Monitoring and Gating System, SA Instruments, Inc., Stony Brook, NY). ECG and heart rate (HR) was measured from the front paws using 6 mm gold disk electrodes (SA Instruments). Body temperature was monitored with a rectal probe and maintained at 37 ± 1°C by a water-circulating heating pad.

Data analysis

Age and strain matched control animals (naïve, n=9) were compared to the KA-treated rats (n=6). Two independent researchers who were both blinded to the animal cohort did initial off-line data analysis. No differences were found between the two raters, so these data were pooled together for an average. The LV was segmented for both end systole and diastole with region-of-interests (ROIs) subtraction using the medical image analysis tool Aedes (http://aedes.uef.fi). End-systolic and end-diastolic volumes (ESV, EDV), stroke volume (SV), ejection fraction (EF), cardiac output (CO) and size (cardiac muscle volume and mass) for the LV were then calculated.

Statistics

To identify possible differences across groups, a Multivariate Analysis of Covariance (MANCOVA) was run with body weight as a covariate. Initial type II sum of squares testing using Pillai's Trace determined that KA was a significant variable for the two response measures tested (ESV and EDV). The other variables were not included due to their strong intercorrelation and so as to create a parsimonious model. The high correlations are not surprising since ESV and EDV are part of the EF and SV calculation (EF=SV/EDV; SV=EDV-ESV). An additional MANCOVA was run with LV muscle volume, instead of body weight, as a covariate to identify if these variables predict ESV and EDV. Descriptive statistics are shown as mean ± standard deviation (SD). Significance was selected *a priori* to be $p<0.05$.

RESULTS

To study physiological cardiac changes during a chronic state of KA-induced temporal lobe epilepsy, MRI of cardiac function was performed 67-89 days after induction of SE and compared to naïve rats. ESV, EDV, SV, EF, CO, and heart muscle volume were measured via cMRI. The descriptive statistics for these parameters are presented in *Table 1*.

The KA administration group had elevated ESV ($p=0.01$; effect size 1.34), but not EDV ($p=0.08$; effect size 0.90), although EDV approached significance and the effect size suggests meaningful physiological differences (*Table 1*, *Figure 2A* and *B*). As expected, a relationship was found between heart muscle volume and body weight (Pearson's correlation $r=0.59$, $p=0.02$). Re-running the MANCOVA on ESV and EDV with muscle volume as a covariate instead of body weight had similar results. Pillai's trace shows that the intervention is significant ($p=0.045$) for KA, with post hoc testing again showing the difference to be significant only for ESV ($p=0.011$). Therefore, we are confident that KA administration had a physiologically relevant change on the heart function.

SV and EF tended to be dissimilar between groups, and this is expected since ESV (p=0.01) and EDV (p=0.08) are used in these calculations.

One rat was imaged early (11 days with SE) due to continuous epileptiform activity (Pirttimäki, Salo et al. 2016). The body weight was lower for this animal (228 g), but was within 2 standard deviations of the mean. Additionally, significance was similar with or without this animal, so it remained in the data set. The average weight of the KA group was 417 g (range: 228-523 g), which was similar to 465 g in control group (range: 406-500 g), although we still accounted for possible differences by running body weight as a co-variate.

The response of individual subjects to the KA-induced status epilepticus and how the epileptiform activity started to progress varied (*Table 2*). Racine score did not correlate with the recorded post-injury epileptiform activity including spiking, spike-and-wave discharges and seizures (Class I-V: r=0.74, p=0.15; Class V: r=0.47, p=0.42; rat number 5 not included in these) suggesting that electrophysiological recordings are necessary to reveal pathological electrical activity of the neurons otherwise not visible to the researcher during behavioural observations.

DISCUSSION

This investigation quantified *in vivo* cardiovascular function following chronic epilepsy-like behaviour in rats. Here we used cardiac MRI to measure heart function in a rodent model of epilepsy and demonstrated cardiovascular changes following 3 months of temporal lobe seizure activity. Our data reveal elevated ESV in KA administered rats compared to naïve animals, thus establishing this model as a way to investigate long-term effects of spontaneous epilepsy-like seizure behaviour on cardiovascular dysfunction. In particular, MRI is non-invasive and can be utilized across disease development and progression. Therefore, these experiments provide a

177 foundation for future studies investigating heart function with chronic seizures, including
178 pharmacological and behavioural interventions to curb both seizure activity and autonomic
179 dysfunction associated with this pathology.

180 While a direct correlate to human SUDEP is not available in animal models, identifying
181 similar cardiovascular changes with epilepsy-like behaviours in rodents is a first step to further
182 understanding the mechanism of this fatal occurrence. For instance, an eloquent series of
183 experiments has been performed showing cardiovascular changes up to 28 days post temporal lobe
184 seizure induction (Sakamoto, Saito et al. 2008) with accompanying changes in autonomic tone.
185 This is complemented by other studies using a non-spontaneous, audiogenic seizure model, the
186 Wister Audiogenic Rat (WAR), which found that rats are hypertensive, have higher heart rates at
187 rest (Fazan, de Oliveira et al. 2011) and at one year of age show elevated ESV (Fazan, Silva et al.
188 2015). The domoic acid model of seizure showed lower left ventricular developed pressure and
189 coronary blood flow at 14 days with either systemic or central administration (Vranyac-
190 Tramoundanas, Harrison et al. 2011). By continuing to characterize cardiovascular changes in
191 various animal models of seizure, it will offer scientists insight into the mechanistic development
192 and possible amelioration of such dysfunction.

193 Here we report an investigation of systemic KA administration resulting in spontaneous
194 seizures that can continue chronically across the lifespan. Systemic KA is feasible to administer
195 and has lasting brain alterations that induce chronic, spontaneous seizure activity allowing the
196 epilepsy-like phenotype to be studied long-term (reviewed in: (Levesque and Avoli 2013). The
197 acute systemic effects of KA administration do have immediate physiological changes, but they
198 typically only last during KA dosing (Hellier and Dudek 2005). Altogether, KA has been
199 established as an appropriate way to study long-term nervous system alterations in epilepsy-like

behaviours and we suggest it is also suitable for uncovering cardiovascular changes induced by long-term spontaneous seizures.

While anaesthetics do suppress the cardiovascular system and could influence our findings, we found that reduced consciousness was appropriate for use in the MRI chamber. Quantifying left ventricular function with cardiac MRI in rodents has proven reproducible with isoflurane (Joubert 2017), the same anaesthetic used in this report. Additionally, our results demonstrating elevated ESV following ~3 months of spontaneous seizure activity are consistent with clinical human studies that found left ventricular alterations in epileptic patients. These results include decreased EF (Bilgi, Yerdelen et al. 2013; Al-Najafi and Rosman 2015), higher ESV (Bilgi, Yerdelen et al. 2013; Kibar, Unver et al. 2014), end systolic diameter (Bilgi, Yerdelen et al. 2013), and increased EDV (Kibar, Unver et al. 2014). Continuing to use cardiac MRI for non-invasive measures in a KA epileptic-like model may provide additional information regarding development of ESV in this population, and could be used to follow cardiomyocyte damage and progression (Musthafa, Dragneva et al. 2013).

CONCLUSION

Importantly, using this technique alongside brain fMRI and EEG would allow long-term monitoring of cardiac dysfunction. Ultimately, future studies could point us towards a clearer mechanistic understanding of SUDEP and may provide possible therapeutic interventions to reduce its prevalence.

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Figure 1

Experimental interventions.

Timeline illustrating the time-points for the follow-up experiment of kainic acid (KA)-induced epileptogenesis. A week before KA treatment, baseline video-electroencephalogram (vEEG) recording and resting-state functional magnetic resonance imaging (rs-fMRI) were performed. Follow-up brain imaging sessions were approximately 1 week and 1–2 months after the injury depending on the MRI-scanner availability. Cardiac MRI reported here was performed a month after the last resting state fMRI scan.

**Note: Auto Gamma Correction was used for the image. This only affects the reviewing manuscript. See original source image if needed for review.*

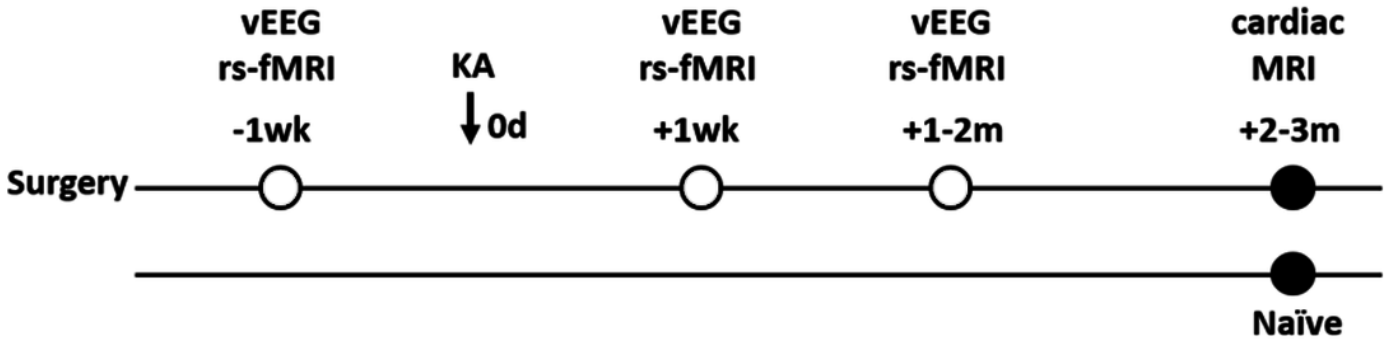
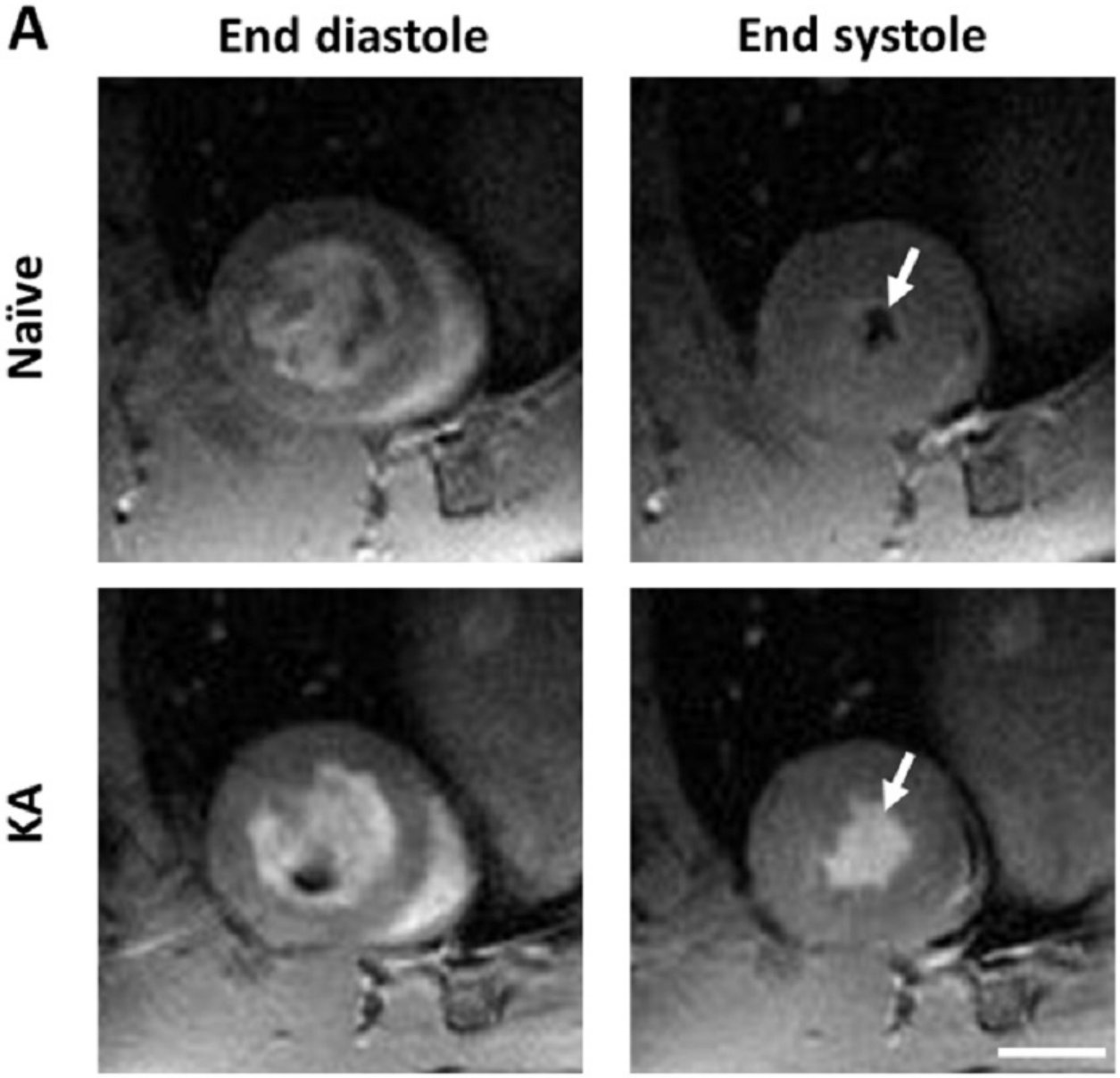
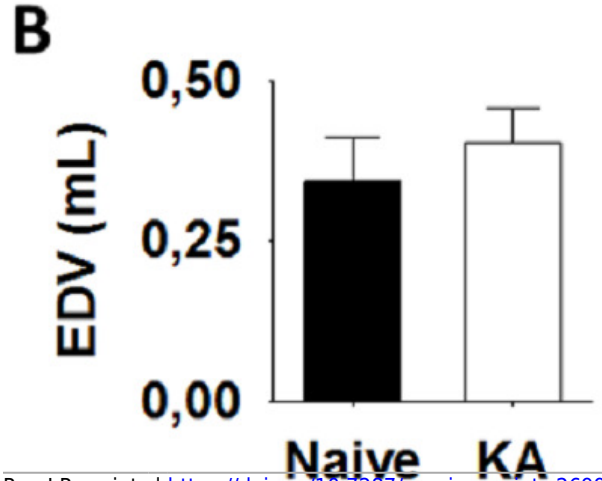


Figure 2

KA-rats have increased end-systolic volume.

(A) Representative MRI images from end diastolic (left) and end systolic cardiac cycle from a naïve control (top) and from a rat administered KA. White arrows indicate the left ventricles during end systole cycle. Scale bar 500µm. **(B)** Bar graphs showing the mean (±SD) for the end diastolic volume and **(C)** for the end systolic volume in control (n=9) and in KA-group (n=6). *=$p<0.05$.


A
End diastole
End systole
Naïve
KA


B
EDV (mL)
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0,25
0,00
Naive
KA

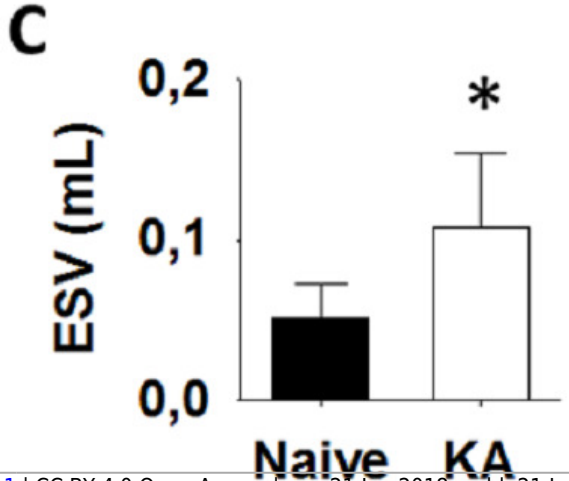
C
ESV (mL)
0,2
0,1
0,0
*
Naive
KA

Table 1(on next page)

Descriptive statistic.

Comparison of the mean values obtained by functional cardiac imaging. Data is presented as mean ± SD. Naïve (n=9) and KA (n=6) rats were compared for ESV (p=0.01) and EDV (p=0.08).

1

	EDV (ml)	ESV (ml)	SV (ml)	EF (%)	HR (BPM)	CO (ml/min)	LV vol (ml)	LV mass (g)
Naïve	0.343± 0.069	**0.051± 0.021**	0.293± 0.065	85±6	372±23	108.4± 22.5	0.58± 0.074	0.61± 0.078
KA	0.405± 0.051	**0.108± 0.046***	0.297± 0.032	74±9	388±28	115.6± 13.3	0.60± 0.126	0.63± 0.13

2

3

Table 2 (on next page)

Descriptive statistics of KA-induced epileptiform activity.

The total number of Racine score count is for seizures between Classes I-V and in brackets is the number of Class V seizures only. The total number of epileptic events including spiking, spike-and-wave discharges and seizures is counted from the two preceding EEG time points. SE=status epilepticus. Time from KA refers to the time point of cMRI. Body weight as measured at the time of cMRI.

1

Animal ID	Racine Scoring	Epiletic events	Time from KA	Body weight, g
1	39 (5)	36	83d	487
2	0 (0)	4	67d	523
3	59 (20)	30	89d	410
4	26 (3)	35	81d	417
5	26 (3)	SE	11d	228
6	19 (1)	8	81d	438

2