

## BRIEF COMMUNICATION

# Insights into the sequence of structural consequences of convulsive status epilepticus: A longitudinal MRI study

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### SUMMARY

While acute hippocampal magnetic resonance imaging (MRI) changes have been demonstrated, the long-term structural consequence of status epilepticus remains unclear. Also the timing of previously reported fornix abnormalities in patients with mesial temporal sclerosis (MTS) is unknown. We report longitudinal volumetric MRI and diffusion tensor imaging (DTI) findings of the hippocampus and fornix in a patient following

status epilepticus. Left hippocampal atrophy demonstrated progression beyond 6 months poststatus epilepticus while the right hippocampus and bilateral fornices demonstrated stable volumetric and diffusion abnormalities throughout the study. Our findings provide evidence that status epilepticus can induce permanent hippocampal damage with the delayed timing of the structural changes being consistent with programmed cell death.

**KEY WORDS:** Status epilepticus, Hippocampus, Fornix.

Acute hippocampal edema and transient reversible signal changes on magnetic resonance imaging (MRI) have been well documented following status epilepticus (Tien & Felsberg, 1995; Kim et al., 2001). Whether status epilepticus can cause irreversible damage resulting in mesial temporal sclerosis (MTS) in humans, however, remains controversial (Wasterlain et al., 1993; VanLandingham et al., 1998). While some reports suggest that permanent structural changes may occur in response to status epilepticus (Scott et al., 2002; Pohlmann-Eden et al., 2004), the time course of these changes is not well understood. We have previously reported bilateral abnormalities of the fornix in temporal lobe epilepsy (TLE) patients with unilateral MTS using diffusion tensor imaging (DTI) (Concha et al., 2005). The timing of the fornix abnormalities in relation to TLE and MTS remains unknown. The purpose of this study was to follow the structural properties of the hippocampus and fornix in a patient who presented with

convulsive status epilepticus using longitudinal quantitative MRI performed over an 18 months period.

### MATERIALS AND METHODS

#### Case patient

A 29-year-old right-handed female presented with convulsive status epilepticus. At age 5 years, she experienced a prolonged febrile seizure. Investigations at this time (including lumbar puncture) were normal. The patient was treated with carbamazepine for 2 years after which it was discontinued. The patient remained seizure free until age 13 at which time she experienced a single generalized convulsion. She was restarted on carbamazepine (200 mg twice daily) and remained seizure-free until age 29 when she presented to emergency room with convulsive status epilepticus. She was treated with intravenous phenytoin, lorazepam, and required intubation to protect her airway. Cerebral spinal fluid examination was normal. Twenty-four hours after presentation, the patient was medically stable. Carbamazepine was increased to 400 mg twice daily and she has since remained entirely seizure-free (at 18 month poststatus epilepticus). At 1 month follow-up the patient described short-term memory difficulties that were not present prior to status epilepticus and which had improved somewhat since discharge from hospital. At

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18-month follow-up, the patient continued to express subjective complaints of short-term memory difficulties.

### MRI acquisitions

Images were acquired using a Siemens Sonata 1.5T MRI scanner (Siemens Medical Systems, South Iselin, NJ, U.S.A.) at 24 h (to be accurate, the actual scan was performed between 12 and 24 h), 1, 6, and 18 months poststatus epilepticus. The imaging protocol consisted of: coronal T2 relaxometry with coverage of the hippocampus, axial fluid-attenuated inversion recovery (FLAIR) DTI with coverage of the fornix and hippocampus and whole brain high resolution 3D T<sub>1</sub>-weighted images using a magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence. Image acquisition parameters for T2 and FLAIR DTI were identical to those previously reported (Concha et al., 2005). The 3D T<sub>1</sub>-weighted image was acquired as follows: 1-mm slice thickness with no interslice gap, 144 axial slices, In-plane acquisition resolution =  $1 \times 1 \text{ mm}^2$ , TR = 1,890 ms, TE = 4.38 ms, TI = 1,100 ms, 1 average.

### Data processing

**Hippocampal volume:** The hippocampi were manually outlined by a trained rater (i.e., F Shi). The manual outlining was implemented on consecutive coronal T<sub>1</sub>-weighted MR images perpendicular to the long axis of the hippocampus by using itkSNAP software package (<http://www.itksnap.org/>). The delineation of hippocampus included the cornu ammonis (CA), the subiculum and the dentate gyrus. Details of methods were described previously (Li et al., 2007). The reliability of the hippocampal volume measurement was evaluated by testing the intrarater relative error and repeated-scan relative error. For the intrarater error, the same rater measured the four patient

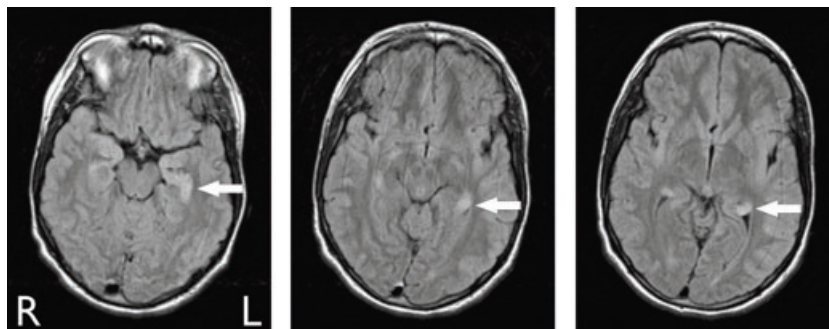
scans and three control scans twice for a total of 14 comparisons (i.e., right and left hippocampi were compared separately). The intrarater relative error (i.e., [first measure – second measure]/max [first measure, second measure]) was  $1.1\% \pm 8.5\%$  (mean  $\pm$  STD). To test the repeated-scan error, three of 10 control subjects were imaged two times with a comparable interscan interval (i.e., range from 8 to 12 months). The repeated-scan relative error was  $6.5\% \pm 7.4\%$  (mean  $\pm$  STD). **Hippocampal T2:** Hippocampal T2 was quantified using manually placed regions of interest (ROI) in two consecutive coronal slices (Concha et al., 2005). **Hippocampal DTI:** The hippocampal mean diffusivity (MD) was calculated using the hippocampal mask that was obtained from the manually outlined hippocampal volume in one). **Fornix DTI:** DTI analysis of the fornix was performed using a DTI tractography based approach, which was reported previously (Concha et al., 2005).

The case data was compared to data acquired in normal control subjects (n = 10, mean age = 29 years, range = 25–33 years) with values outside of two standard deviations of the control subjects considered as abnormal.

## RESULTS

### Left hippocampus

Axial FLAIR imaging 24 h poststatus epilepticus demonstrated striking left hippocampal signal abnormality (Fig. 1). Volume, T2, and MD of the left and right hippocampus in the patient as well as the distribution in normal population (volume [mean  $\pm$  STD] =  $2208 \pm 228 \text{ mm}^3$ , coefficient of variation [CV] = 10.3%; T2 =  $112 \pm 2.5 \text{ ms}$ , CV = 2.3%; MD =  $0.83 \pm 0.04 \times 10^{-3} \text{ mm}^2/\text{s}$ , CV = 5.1%) are demonstrated in



**Figure 1.**

Axial FLAIR images in the acute stage (i.e., between 12 and 24 h) of post–status epilepticus. The left hippocampus showed obvious signal abnormality encompassing the whole hippocampus. While not readily apparent on qualitative imaging, subsequent quantitative T2 evaluation demonstrated that the right hippocampus also had significantly elevated T2 values (see Fig. 2).

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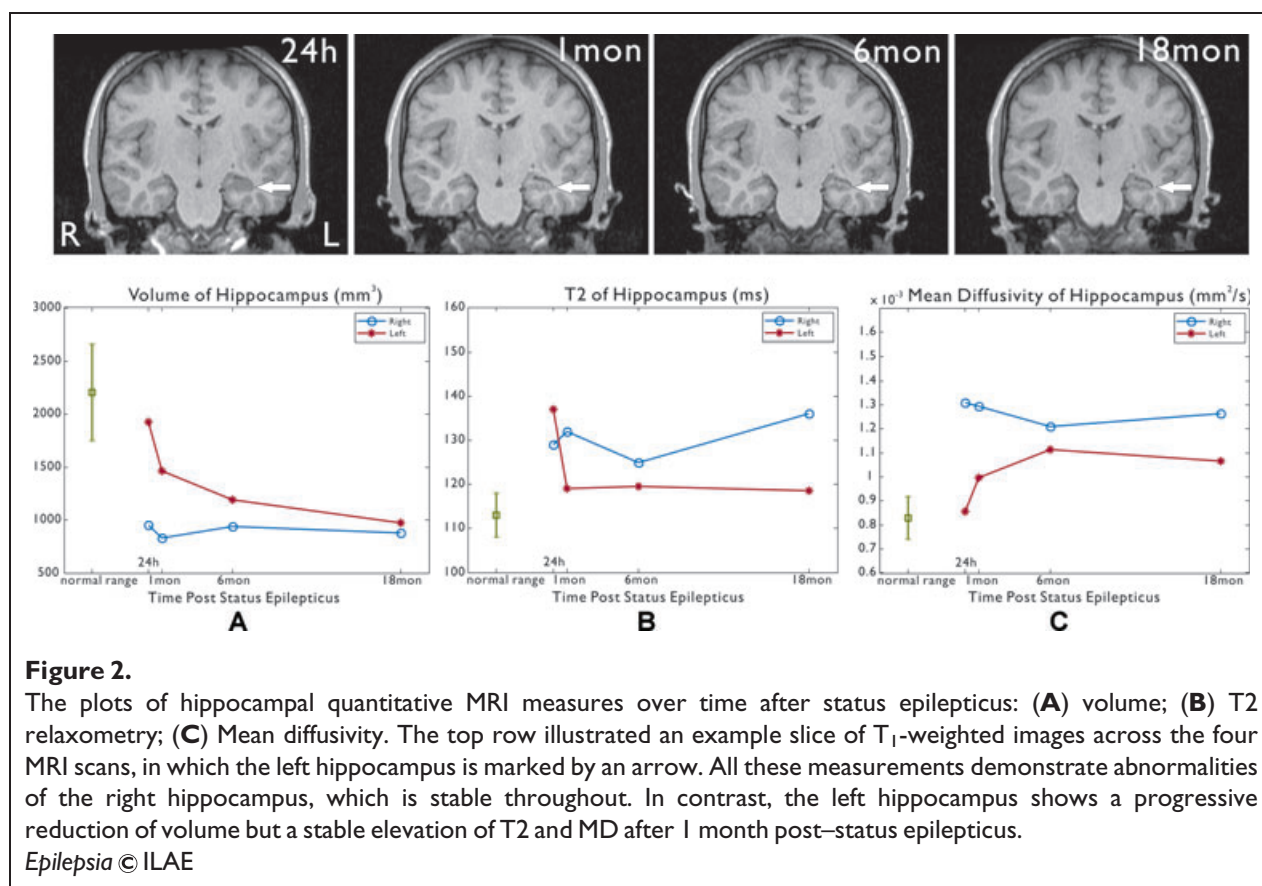


Fig. 2. At 24 h, the left hippocampus demonstrated dramatically increased T2 with volume and MD both within the normal range. At 1 month, volume was reduced with progressive reduction in volume being observed at the remaining time points. T2 relaxometry demonstrated marked abnormality at 24 h with a sharp drop to slightly above the normal range at 1 month. MD, which was initially within the normal range, remained significantly elevated in the remaining scans.

#### Right hippocampus

In contrast to the left, all right hippocampal imaging parameters were abnormal and relatively stable at all time points (reduced volume, elevated T2, and elevated MD) (Fig. 2).

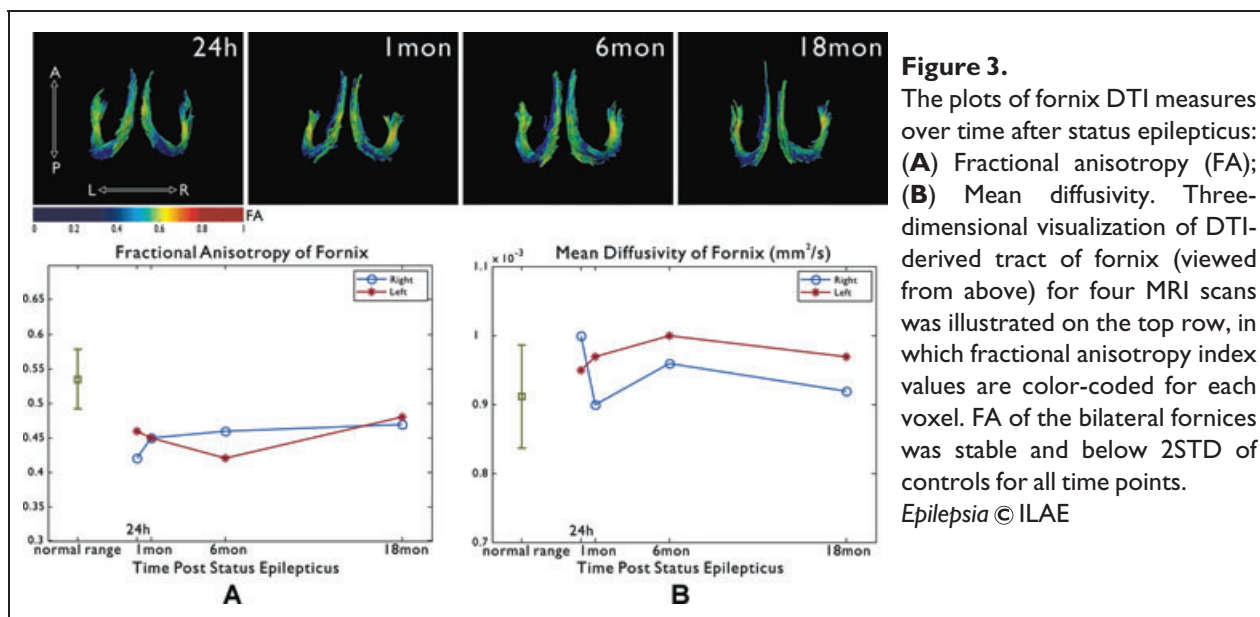
#### Fornix

Both right and left fornix demonstrated significantly reduced fractional anisotropy (FA) at the initial time point, which remained consistently low for the remaining scans (Fig. 3). The FA and MD distribution in normal population (FA =  $0.52 \pm 0.03$ , CV = 5.7%; MD =  $0.91 \pm 0.04 \times 10^{-3} \text{ mm}^2/\text{s}$ , CV = 4.1%) is also demonstrated in Fig. 3.

## DISCUSSION

Transient and reversible hippocampal T2 and diffusion MRI changes have previously been observed acutely following status epilepticus in humans (Tien & Felsberg, 1995; Kim et al., 2001). As well, acute swelling of the hippocampus was observed visually or using MRI volumetry (Wiesmann et al., 1997; VanLandingham et al., 1998). While animal models have suggested that status epilepticus can result in hippocampal neuronal injury (Fujikawa, 1996; Priel et al., 1996; Meldrum, 2002), whether status epilepticus can result in permanent structural changes (i.e., MTS) in humans remains controversial (VanLandingham et al., 1998).

In the reported subject, the right hippocampus demonstrated volume, T2, and MD abnormalities at all time points that were consistent with MTS. As the right hippocampal abnormalities were present at the initial time point and remained stable throughout the study, we assume that right MTS was present prior to status epilepticus. In contrast, considerable evolution of MRI findings of the left hippocampus were observed. Left hippocampal T2 was elevated at 24 h poststatus epilepticus and dropped to just above the normal range for the remaining time points. Left



hippocampal volume and MD were initially within the normal range but were abnormal (reduced volume and increased MD) at 1, 6, and 18 months poststatus epilepticus with volume demonstrating progressive reduction with each subsequent time point. Notably, the discrepancy between T2, MD, and volume findings is not very surprising as various MRI techniques are measuring aspects of some related but distinct pathological phenomena of the hippocampus. Although prestatus epilepticus imaging was not available, based on previous reports, we assume that the marked initial elevation in T2, which dropped dramatically by 1 month, reflected hippocampal edema (Scott et al., 2002). As the initial (presumably swollen) left hippocampal volume was within the normal range and 1 month volume was below two standard deviations of controls, we suspect that the subject likely had left MTS (but to a lesser extent than the right) prior to status epilepticus. The initial normal MD (in contrast to elevated MD for the remaining time points) may have also represented a drop from baseline (consistent with cytotoxic edema) (Kim et al., 2001). As the subject has remained seizure free since the status epilepticus, we assume that by 1 month edema was resolved (Scott et al., 2002; Scott et al., 2003). Reduction of volume beyond 1 month is therefore presumed to reflect further hippocampal atrophy. While it is possible that measurement error could account for some of the differences in volume observed, the difference in volume between 6 and 18 months (18.2%) in comparison with the measured repeated-scan and intrarater errors ( $6.5\% \pm 7.4\%$  and  $1.1\% \pm 8.5\%$ , respectively), strongly suggests that progressive hippocampal atrophy continued beyond 6 months poststatus epilepticus. The idea that the patient has experienced a permanent structural change to

the left hippocampus is further supported by the new memory difficulties that the patient has experienced since status epilepticus.

While Wiesmann et al. have previously reported similar findings of progressive hippocampal atrophy over 58 months poststatus epilepticus, other confounding factors (herpes encephalitis and ongoing seizures) provide possible alternative explanations for the progressive changes observed in this case (Wiesmann et al., 1997). Our finding of progressive hippocampal atrophy following an isolated event of status epilepticus provides further evidence that status epilepticus can result in hippocampal atrophy in humans. The observation of progressive atrophy over a long duration (greater than 6 months in the current case and 58 months in the case of Wiesmann et al.) suggests that status epilepticus can initiate a cascade of intracellular events ultimately resulting in delayed programmed cell death.

Finally, bilateral abnormalities of the fornix (reduced FA) were observed which are consistent with our previous findings (Concha et al., 2005). As we presume that the patient had right and likely also left MTS prior to status epilepticus, it is not possible to determine whether the fornix abnormalities preceded MTS. Several possible explanations exist for the apparently stable fornix abnormalities in the context of evolving hippocampal atrophy. The tractography algorithm used requires a FA threshold be set (i.e., voxels with FA below 0.25 are excluded). Therefore, it is possible that our method underestimated the abnormalities of the fornix by excluding severely damaged voxels, which could have prevented the detection of progressive injury. Another possible explanation is that

the degree of damage to the fornix present prior to status epilepticus limited our ability to detect any further downstream degeneration of hippocampal efferent fibers following status epilepticus.

In summary, our findings suggest that progressive hippocampal atrophy can occur beyond 6 months following status epilepticus in humans.

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Conflict of interest: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. None of the authors has any conflict of interest to disclose.

## REFERENCES

- Concha L, Beaulieu C, Gross DW. (2005) Bilateral limbic diffusion abnormalities in unilateral temporal lobe epilepsy. *Ann Neurol* 57:188–196.
- Fujikawa DG. (1996) The temporal evolution of neuronal damage from pilocarpine-induced status epilepticus. *Brain Res* 725:11–22.
- Kim JA, Chung JI, Yoon PH, Kim DI, Chung TS, Kim EJ, Jeong EK. (2001) Transient MR signal changes in patients with generalized tonicoclonic seizure or status epilepticus: perictal diffusion-weighted imaging. *Am J Neuroradiol* 22:1149–1160.
- Li S, Shi F, Pu F, Li X, Jiang T, Xie S, Wang Y. (2007) Hippocampal shape analysis of Alzheimer disease based on machine learning methods. *Am J Neuroradiol* 28:1339–1345.
- Meldrum BS. (2002) Concept of activity-induced cell death in epilepsy: historical and contemporary perspectives. *Prog Brain Res* 135:3–11.
- Pohlmann-Eden B, Gass A, Peters CN, Wennberg R, Blumcke I. (2004) Evolution of MRI changes and development of bilateral hippocampal sclerosis during long lasting generalised status epilepticus. *J Neurol Neurosurg Psychiatry* 75:898–900.
- Priel MR, dos Santos NF, Cavalheiro EA. (1996) Developmental aspects of the pilocarpine model of epilepsy. *Epilepsy Res* 26:115–121.
- Scott RC, Gadian DG, King MD, Chong WK, Cox TC, Neville BG, Connelly A. (2002) Magnetic resonance imaging findings within 5 days of status epilepticus in childhood. *Brain* 125:1951–1959.
- Scott RC, King MD, Gadian DG, Neville BG, Connelly A. (2003) Hippocampal abnormalities after prolonged febrile convulsion: a longitudinal MRI study. *Brain* 126:2551–2557.
- Tien RD, Felsberg GJ. (1995) The hippocampus in status epilepticus: demonstration of signal intensity and morphologic changes with sequential fast spin-echo MR imaging. *Radiology* 194:249–256.
- VanLandingham KE, Heinz ER, Cavazos JE, Lewis DV. (1998) Magnetic resonance imaging evidence of hippocampal injury after prolonged focal febrile convulsions. *Ann Neurol* 43:413–426.
- Wasterlain CG, Fujikawa DG, Penix L, Sankar R. (1993) Pathophysiological mechanisms of brain damage from status epilepticus. *Epilepsia* 34(Suppl. 1):S37–S53.
- Wiesmann UC, Woermann F, Lemieux L, Free SL, Bartlett PA, Smith SJ, Duncan JS, Stevens JM, Shorvon SD. (1997) Development of hippocampal atrophy: a serial magnetic resonance imaging study in a patient who developed epilepsy after generalized status epilepticus. *Epilepsia* 38:1238–1241.