Fluoxetine restores spatial learning but not accelerated forgetting in mesial temporal lobe epilepsy

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Learning and memory dysfunction is the most common neuropsychological effect of mesial temporal lobe epilepsy, and because the underlying neurobiology is poorly understood, there are no pharmacological strategies to help restore memory function in these patients. We have demonstrated impairments in the acquisition of an allocentric spatial task, in patients with unilateral hippocampal sclerosis. We also show that patients have accelerated forgetting of the learned spatial task and that this is associated with damage to the non-dominant hippocampal formation. We go on to show a very similar pattern of chronic allocentric learning and accelerated forgetting in a status epilepticus model of mesial temporal lobe epilepsy in rats, which is associated with reduced and abnormal hippocampal neurogenesis. Finally, we show that reversal of the neurogenic deficit using fluoxetine is associated with reversal of the learning deficit but not the accelerated forgetting, pointing to a possible dissociation in the underlying mechanisms, as well as a potential therapeutic strategy for improving hippocampal-dependant learning in patients with mesial temporal lobe epilepsy.

Keywords: epilepsy; epilepsy memory impairment; neurogenesis; mesial temporal sclerosis; spatial memory
Abbreviation: BrdU = 5-bromo-2’-deoxyuridine

Introduction
Mesial temporal lobe epilepsy is the most prevalent form of drug refractory epilepsy, and memory dysfunction is its most common neuropsychological effect (Duncan and Thompson, 2003). Over half of patients with epilepsy rate their memory problems as moderate to severe (Corcoran and Thompson, 1992), contributing significantly to their adverse quality of life (Fisher et al., 2000).
Currently, there are no pharmacological strategies to help restore memory function in these patients, making it a significant unmet therapeutic need.

The hippocampus has a major role in all stages of episodic declarative and spatial memory processing, including acquisition, consolidation and recall (O’Keefe and Nadel, 1978; Riedel et al., 1999; Morris, 2006). Mesial temporal lobe epilepsy may thus affect episodic (Howard et al., 2010) and semantic memories (Messas et al., 2008), in both verbal (Bell and Davies, 1998; Richardson et al., 2004) and spatial domains (Kessels et al., 2001), including spatial working and reference memory (Abrahams et al., 1999; Astur et al., 2002; Crane and Milner, 2005; Barkas et al., 2010). Damage incurred by left-sided mesial temporal lobe epilepsy is characterized by material-specific verbal memory deficits (Hermann et al., 1997). Analogous findings with right mesial temporal lobe epilepsy and non-verbal memory are less consistent, except for patients with hippocampal sclerosis, where specific visual memory deficits have been found (Gleissner et al., 1998a). This inconsistency may be partly dependent on the characteristics of the spatial cues, in particular how easily they can be verbalized (Barkas et al., 2010).

Our understanding of the functional memory deficits in mesial temporal lobe epilepsy is not only influenced by the characteristics of the cues, but also by the temporal nature of the testing and retesting. Many tests of memory impairment in patients with mesial temporal lobe epilepsy measure the learning of the stimulus material and only its short-term retention. Yet, there is evidence that both short-term working memory and long-term reference memory can be impaired in patients with hippocampal damage (Abrahams et al., 1999). Indeed, recent animal research has gone further in suggesting that the two types of memory can be dissociated (Sanderson et al., 2009; Rust et al., 2010), and the epilepsy literature is increasingly showing an inability to retain learned memories over a long period of time, a phenomenon referred to as accelerated forgetting (Blake et al., 2000; Cronel-Ohayon et al., 2006; Bell and Giovagnoli, 2007; Butler and Zeman, 2008).

An extreme form of accelerated forgetting has been described in transient epileptic amnesia (Butler et al., 2007). This accelerated long-term forgetting has been measured over periods of a day (Martin et al., 1991; Muhlert et al., 2010), to weeks (Blake et al., 2000), despite normal learning and initial retention, and is confined to declarative memories—consistent with pathophysiology within the medial temporal lobes. Accelerated long-term forgetting is clinically important as it corresponds to patients’ subjective memory complaints (Butler et al., 2009), and yet is undetected on standard memory testing, which typically test memory retention for up to just 30 min (Muhlert et al., 2010). Despite the postulation that seizure activity might interfere with memory consolidation in transient epileptic amnesia (Butler et al., 2007), the mechanisms underlying poor working and long-term memory in mesial temporal lobe epilepsy and transient epileptic amnesia are unknown.

Spatial learning to locate a goal is believed to involve different strategies. For example, allocentric navigation, where the participant creates a cognitive map by learning the spatial relationships between the distal environmental cues and the goal; egocentric navigation, where participants use a set route to locate a goal by learning the spatial relationship between the goal and their own body; and proximal cue based navigation where subjects use a single cue, proximal to a goal location, to guide them. Morris water maze task studies in both rodents (Morris et al., 1982) and humans (Goodrich-Hunsaker et al., 2010), and functional MRI (Hartley et al., 2003;Rauchs et al., 2008) indicate that the hippocampus is necessary for allocentric but not egocentric and cued navigation.

The hippocampus is also the site of ongoing neurogenesis throughout life, and while early studies showed conflicting roles for neurogenesis in spatial learning and memory (reviewed in Leuner et al., 2006; Abrous, 2007), more recent studies using paradigms that involve a higher cognitive demand, have demonstrated roles for neurogenesis in both the acquisition (Dupret et al., 2008; Clelland et al., 2009) and retrieval (Trouche et al., 2009) of spatial relational memory. Status epilepticus permanently alters hippocampal neurogenesis (Benzzon et al., 1997; Parent et al., 1997; Gray and Sundstrom, 1998), such that it is chronically impaired both in level (Hattiangady et al., 2004) and connectivity (Jessberger et al., 2007a, b). Studies in patients with mesial temporal lobe epilepsy have confirmed this neurogenic impairment, which is associated with impaired learning and memory performances (Coras et al., 2010). Thus, impaired neurogenesis may be one possible mechanism for the learning and memory deficits seen in patients with mesial temporal lobe epilepsy.

The restoration of neurogenesis is therefore of particular interest in injury and disease models that show reduced neurogenesis and impaired cognitive ability on hippocampal dependent tasks. The antidepressant fluoxetine is a powerful stimulant of hippocampal neurogenesis (Malberg et al., 2000) and improves memory deficits in patients with mild cognitive impairment (Mowla et al., 2007), and after traumatic brain injury (Horsfield et al., 2002). In animal models, fluoxetine-induced neurogenesis is associated with improved allocentric spatial learning and memory after ischaemic injury (Li et al., 2009), and restoration of deficits in spatial working memory after anti-mitotic treatment (ElBeltagy et al., 2010; Lyons et al., 2011a).

Herein, we characterize the patterns of spatial learning and accelerated forgetting in patients with hippocampal sclerosis and in a rodent status epilepticus model of mesial temporal lobe epilepsy, where we also ask if fluoxetine restores any of the observed deficits.

**Materials and methods**

**Human studies**

There is a close correlation between the mechanisms of human and rodent spatial learning and memory (Kesner and Hopkins, 2006) as assessed using real and virtual Morris water maze tasks (Astur et al., 2002; Sutherland and Hamilton, 2004; Hamilton et al., 2009; Goodrich-Hunsaker et al., 2010). Our clinical studies used a verbalizable cued virtual environment as we have previously shown that selective resection of the non-dominant hippocampal formation results in a failure to learn an allocentric task in a non-verbalizable abstract environment.
(Barkas et al., 2010). Ethical permission was obtained from the South East Anglia and Isle of Wight Research Ethics Committee (07/Q1701/6). Patients with mesial temporal lobe epilepsy and unilateral (left \( n = 6 \); right \( n = 6 \)) hippocampal sclerosis on MRI scanning and patients who had undergone a unilateral trans-sylvian selective amygdalohippocampectomy (left \( n = 3 \); right \( n = 8 \)) were recruited from the Wessex Neurological Centre, Southampton General Hospital and compared with age matched healthy controls (\( n = 12 \)). Subjects with other conditions possibly contributing to cognitive impairment were excluded. Patient characteristics are shown in Tables 1 and 2.

A virtual Morris water maze task environment was designed using NeuroInvestigations; Virtual Navigation Software, Morris Water Task version 3.0 (Barkas et al., 2010) (Fig. 1). The environment consisted of a circular pool with a hidden escape platform beneath the opaque water. Participants could move around the pool using the arrow keys on the computer keyboard. In order to complete a trial, participants had to locate the platform. The pool was surrounded by objects and participants could learn the fixed spatial relationship between the objects and the platform to solve the task (Fig. 1 and Supplementary material).

Over a series of 16 training trials, participants were asked to find the hidden platform and learn its position in relation to the objects around the pool. The rate at which the distance travelled to find the platform decreased was taken as a measure of how easily the task was learned. A probe trial was then given in which, unknown to the participants, the platform was removed. Time spent in the platform quadrant was taken as a further measure of how well participants had learned the platform’s position. A further three training trials followed to moderate any extinction effects of removing the platform.

Three to six weeks after the first session, participants returned for an identical 60 s probe task. Participants had not been told what to expect in the second session. Time spent searching in the platform quadrant was taken to measure the participants’ memory of the platform position.

### Animal studies

#### Kainate injections

Fifty-six male Lister Hooded and 27 Long Evan young (6-week-old) adult 300 g male rats (fluoxetine experiments) were used in this study. Experiments were carried out in accordance with the current British Home Office guidelines, and with consent of the University of Southampton Bioethics Committee.

We used a kainate-induced status epilepticus model of mesial temporal lobe epilepsy (Williams et al., 2009) without intracranial electrode monitoring or telemetry. Rats allocated to the kainate condition were given hourly doses of 4 mg/kg of kainate (Tocris) dissolved in sterile 0.9% saline (Macropharma) by intraperitoneal injection, until they entered status epilepticus or until they had received a maximum of three injections. Once status epilepticus was achieved, seizures were terminated with 10 mg/kg diazepam after 1 h. Only animals achieving Class 5 seizures on the Racine scale were used for further study (Racine et al., 1972). Control rats received an equal volume of sterile 0.9% saline.

For fluoxetine experiments, male Long Evan rats were used instead of Lister Hooded because of a high-mortality rate in the Lister Hooded animals after kainate. All animals underwent behavioural testing 3 months after kainate-induced status epilepticus.

#### 5-Bromo-2′-deoxyuridine labelling

Lister Hooded rats were given an intraperitoneal injection of 5-bromo-2′-deoxyuridine (BrdU) on three consecutive days at a dose of 50 mg/kg 24–26 days prior to sacrifice. For fluoxetine experiments, Long Evan rats were given BrdU 35 days prior to sacrifice and 15 days after commencing fluoxetine or sham treatment (Fig. 8E).

#### Fluoxetine experiments

In an attempt to reverse the chronic decrement in neurogenesis in kainite-treated rats, 20 mg/kg of fluoxetine (Sigma) were placed in the water supply of eight rats, 2 months after kainate injection, 30 days before behavioural training and continued until sacrifice (a total of 50 days treatment; Fig. 8E). Water bottles were replaced with fresh drinking water every day, with the correct concentration of fluoxetine made up to deliver 20 mg/kg per animal per day. Animals

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### Table 1 Patients details

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### Table 2 Patients with unilateral hippocampal sclerosis

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<td>Partial epilepsy with right sclerosis</td>
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<td>Partial epilepsy with right sclerosis</td>
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<td>7</td>
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<td>Partial epilepsy with right sclerosis</td>
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<td>8</td>
<td>Right</td>
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<td></td>
<td>Incidental cerebral aneurysm</td>
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<td>Partial epilepsy with left sclerosis</td>
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<td>Partial epilepsy with right sclerosis</td>
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were weighed on a weekly basis. There were no significant differences between animals in terms of their water intake or fluoxetine doses received. These were compared to nine age matched kainate rats without fluoxetine and 10 sham controls. BrdU injections were timed so that the labelled cells would capture the initial response to fluoxetine and be between 2 and 3 weeks old at the time of behavioural training, the time at which newly born granule cell neurons functionally integrate into circuitry underlying learning (Tashiro et al., 2007) (Fig. 8E).

**Morris water maze task testing**

A standard 2 m Morris water maze was used (Supplementary material) to assess the learning and retention of both a hippocampal and non-hippocampal spatial navigation task. For the non-hippocampal dependent task, the platform position alternated between trials either 20 cm west or east of the centre of the pool, marked by a 10 cm diameter red sphere hung 30 cm above it.

**Effects of kainate on spatial learning**

**Hippocampal dependent task (allocentric navigation)**

Rats received four training trials a day for 4 days to locate the hidden submerged platform. They were released from one of four different cardinal locations and allowed to swim for up to 60 s. Escape latencies were recorded. The rat remained on the platform for 20 s before being removed from the pool. There was ~5 min between training trials. On the fifth day, the rats received two training trials followed by a probe trial with no platform. Time spent within a 30 cm radius of the platform position was recorded. After 3 days, rats were given a second probe trial and sacrificed within 2 h.

**Non-hippocampal dependent task (egocentric and cued navigation)**

Procedural details were the same as in the hippocampal dependent task except a beacon marked the position of the platform and the platform position was always to the left of the rats starting position. For the probe trials, the beacon and platform were removed from the pool. Half of the rats received the hippocampal dependent task first, while the rest received the non-hippocampal task first.

**Extended training and group accelerated forgetting experiments**

Procedural details were as for the hippocampal dependant task except rats were trained on 12 consecutive days. On the 13th day, the rats were given two training trials then half of the rats were given a probe trial while the other half were returned to their cages and tested with a single probe trial 10 days later.

**Fluoxetine experiments**

Procedural details were as for the hippocampal dependant task except that after the first probe trial the platform was replaced and the rats received a further three training trials to reduce effects of probe trial. Ten days later, the rats were given a further probe trial.

**Histology**

Animals were given an intraperitoneal overdose of pentobarbitone (30 mg in 0.1 M saline) and perfused transcardially with 50 ml 0.9% saline followed by 50 ml 4% paraformaldehyde (pH 7.2). The brains were immediately removed and post-fixed in paraformaldehyde, cryo-protected as previously described (Zaben et al., 2009) (Supplementary material), and serially coronally cryosectioned at 30 µm intervals. Separate systematic randomized samples of every 24th section were stained for thionin, doublecortin and BrdU, as previously described (Zaben et al., 2009) (Supplementary material). Immunopositive cells were exhaustively counted in a stereological sample of sections from each animal using the stereoinvestigator system (Microbrightfield Inc.) and total counts per animal calculated using the Calvaleri principle. Neurolucida (Microbrightfield Inc.) was used to measure the length of each major dendritic process extending from the cell body, and the angle of that process orthogonal to the subgranular zone.

**Statistical analysis**

Training trials were analysed using a Group × Trials Analysis of Variance (ANOVA) performed on distance travelled (humans) and escape latencies (animals). Probe trials were analysed by a Group × Probe ANOVA performed on the time spent either in

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**Figure 1** Virtual water maze. (A) Layout of pool, platform position and objects on the walls surrounding pool. (B) First person view from centre of pool toward the north west corner of the virtual water maze environment.
platform quadrant (humans) or platform area (animals). For animals, the drop in performance overnight between trials was also analysed using a Group × Trials × Days mixed design ANOVA performed on escape latencies during the last session of the day and the first session of the following day (Pearce et al., 1998).

Results

Human studies

Both surgically resected and hippocampal sclerosis patients show less efficient allocentric spatial learning

We have previously reported that selective resection of the hippocampal formation in patients with intractable epilepsy results in impaired allocentric spatial learning in a contextualized virtual water maze (Barkas et al., 2010). Herein, we extend our investigations to patients with unilateral hippocampal sclerosis and more fully characterize spatial learning and memory. The patient groups learned slower than the control group (Fig. 2A); \( F(2,32) = 3.57, P < 0.05 \). Dunnett post hoc testing showed that the path lengths of both patient groups were significantly longer than the controls (\( P < 0.05 \)), suggesting impairment in spatial learning for both patient groups (Fig. 2Aii). There was no effect of lateralization.

Probe 1 showed that despite the overall allocentric learning impairment in patients with surgery and hippocampal sclerosis, by the end of training all participants had learnt the task to criterion (spending significantly > 25% of time in platform area; Fig. 2B). Post-probe training trials showed no effect of probe trial.

Both surgically resected and hippocampal sclerosis patients show accelerated forgetting

In Probe 2, performance was poorer for both hippocampal sclerosis and surgery patients compared to controls and to their own performance in Probe 1 (Fig. 2B): \( F(2,32) = 3.67, P < 0.05 \). Simple main effects (Keppel, 1973) revealed that the groups only differed on Probe 2 \( F(2,64) = 10.67, P < 0.01 \). Dunnett post hoc testing revealed that both patient groups performed worse than controls on Probe 2 (\( P < 0.05 \)). This suggests that the hippocampal sclerosis and surgical groups were impaired in remembering the position of the platform only after a prolonged interval—consistent with the phenomenon of accelerated forgetting (Butler et al., 2007).

Allocentric spatial accelerated forgetting is lateralized to the non-dominant hippocampal formation

When the hippocampal sclerosis and surgical patients were separated into left and right-sided groups the impairment was restricted to the right-sided groups (Fig. 2C): \( F(4,30) = 3.64, P < 0.05 \). Simple main effects revealed that groups differed only on Probe 2 \( F(4,60) = 3.21, P < 0.01 \). Dunnett post hoc testing revealed that only the right-sided hippocampal sclerosis and surgery patients performed worse than controls (\( P < 0.05 \)).

Taken together these results suggest that hippocampal damage, either from hippocampal sclerosis or hippocampal sclerosis followed by selective hippocampal formation resection, is associated with defective allocentric spatial learning and furthermore that right-sided damage is associated with accelerated forgetting of the memory over time.

Animal studies

Allocentric navigation deficits are present 3 months after status epilepticus with a significant decrement in overnight performance during training

Allocentric learning and memory

In a Morris water maze task, both control and kainate-treated animals were trained to locate a hidden platform and kainate animals performed worse than controls in the latter sessions of training (Fig. 3Ai); \( [\text{Group} \times \text{Trial interaction}, F(17, 289) = 1.86, P < 0.05] \). Simple main effects revealed that kainate rats had longer latencies than controls on Trials 10, 14 and 15 \( [F(1,306) > 4.21, P < 0.05] \).

Grouping performance by trials in a day (Fig. 3B) revealed that kainate rats perform poorly in the initial trials of each day, suggesting kainate animals performed worse than controls in the latter sessions of training (Fig. 3Ai); \( [\text{Group} \times \text{Trial interaction}, F(17, 289) = 1.86, P < 0.05] \). Simple main effects revealed that kainate rats had longer latencies than controls in Trials 10, 14 and 15 \( [F(1,306) > 4.21, P < 0.05] \).

The pattern of results in Fig. 3Ai suggests that in the last trial of the latter sessions (Trials 8, 12, 16 and 18) kainate animals were performing as well as controls. However, in the initial trials of the following sessions, kainate animals performed poorly. Comparing the performances in the last trial of each day and the first trial of the next (Fig. 3Bi (controls) and Fig. 3Bii (kainate animals)) confirmed that kainate animals had poor overnight retention compared with controls \( [\text{Group} \times \text{Trial} \times \text{Day interaction}, F(3,51) = 2.91, P < 0.05] \). Simple main effects revealed kainate animals had shorter latencies in Trial 4 than Trial 1 of the following day on several days \( [F(1,68) > 4.37, P < 0.05] \). Taken together, these results suggest that the kainate animals learned the task more slowly and that the memories formed by the end of the day were more brittle and therefore more prone to deteriorate overnight.

Allocentric memory was further assessed in two probe trials, given immediately and 3 days after training (Fig. 3C). Controls performed better than kainate animals in both probe trials \( [F(1,17) = 6.71, P < 0.05] \). Poor performances in both probe trials confirm that the kainate group had learned the task less well than the controls.

Thus, the pattern of allocentric spatial learning and memory deficits seen in rats 3 months after intraperitoneal kainate is similar to the pattern seen in human patients with hippocampal sclerosis. However, it is difficult to show signs of accelerated forgetting as kainate rats had not learnt the task to the same level as the controls by the end of training.

Cued learning and egocentric navigation

Three months post-status epilepticus non-hippocampal dependant cued navigation was normal and egocentric memory decayed at the same rate as controls (Fig. 4A and B).
Impaired allocentric learning, overnight performance and accelerated forgetting with prolonged training

In order to test for accelerated forgetting by ensuring training to criterion, kainate animals and controls were given extended training (50 trials). To counter any effects of extinction by repeated probe trials, rats received only one probe trial either immediately after training or 10 days after training. Kainate animals had longer escape latencies than controls over the first seven sessions of training (Fig. 5A) \[\text{Group} \times \text{Trials interaction}, F(49, 1715) = 2.08, P < 0.01\]. Simple main effects revealed kainate animals had longer escape latencies than controls in Trials 5, 6, 8, 10, 13, 17 and 25 \[F(1,1750) = 5.98, P < 0.05\]. Trials in the middle of a
session differed only in the early sessions (Sessions 2 and 3) whereas differences in Trial 1 continued longer into training (Sessions 2, 4, 5 and 7).

These results suggest that kainate animals were again most impaired in being able to use the spatial information learned the previous day. A Group × Trial × Day analysis of escape latencies in Trial 4 and Trial 1 of the following day produced a significant interaction \( F(11, 385) = 2.01, P < 0.05 \). Simple main effects revealed that kainate animals had shorter escape latencies in Trial 4 than Trial 1 \( F(1, 420) = 4.62, P < 0.05 \) (Fig. 5Bi and Bii) in Sessions 2, 4, 7 and 8, while for the controls this was never true.

Control and kainate animals perform similarly well in Probe 1, given immediately after training. Kainate animals perform poorly compared to controls only in Probe 2 given 10 days after training (Fig. 5C); [Group × Probe interaction, \( F(1, 33) = 4.47, P < 0.05 \)]. Simple main effects revealed kainate animals were worse than controls only on Probe 2, \( F(1, 33) = 7.79, P < 0.01 \).

**Reduced neurogenesis 3 months after status epilepticus**

Cell population proliferation and survival over the 25 days prior to sacrifice, as measured by the S-phase marker BrdU, showed no differences compared to controls at 3 months (Fig. 6A).
A significant reduction in neurogenesis was identified by lower numbers of doublecortin-positive newly born neurons at 3 months post-kainate (Fig. 6B). There was also evidence of abnormal neurogenesis at 3 and 5 months with many doublecortin-positive neurons in ectopic hilar locations and abnormal patterns of dendritic branching into the hilus or horizontally across the subgranular zone (Fig. 7A and B) as has been previously described (Hattiangady et al., 2004). Light microscopic analysis of stereologically sampled thionin stained sections showed no gross hippocampal lesions.

Fluoxetine reverses the neurogenic deficit after kainate
In our study, only one animal (kainate and fluoxetine treated) was noted to have had a clinical seizure on Day 8, after training had ended. No animal had clinical seizures during the probe trials. Fluoxetine restored the numbers of newly born doublecortin-positive granule cell neurons to normal at sacrifice (Fig. 8A). In addition, it restored the dendritic branching pattern and morphology of the doublecortin-positive neurons to normal (Fig. 8B and C).

Fluoxetine reverses the learning deficit but not the overnight decrement or accelerated forgetting
Escape latencies for all groups decreased with training but were shorter for controls and kainate+fluoxetine treated animals than for kainate animals (Fig. 9Ai and Aii) [Group, $F(2, 23) = 5.58$, $P < 0.05$]. Dunnett post hoc testing revealed longer escape latencies compared to controls only in kainate animals ($P < 0.05$),...
suggesting that fluoxetine had restored performance in the kainite-treated group.

However, comparison of the last learning trial on one day and the first trial of the next (Fig. 9Bi–iii) revealed poor overnight retention in both the kainate and kainate + fluoxetine treated groups, compared with the control animals; Group (n = 2) × Trial (n = 50) ANOVA on escape latencies; Group, F(1, 35) = 10.25, P < 0.01; Trial, F(49,1715) = 47.64, P < 0.01; Interaction, F(49, 1715) = 2.08, P < 0.01. Simple main effects revealed controls had shorter latencies than kainate animals in Trials 5, 6, 8, 10, 13, 17 and 25, F(1,1750) = 5.98, P < 0.05. Error bars for controls (n = 19) and kainite animals (n = 18) are mean ± 1 SE. (Aii) Group escape latencies meaned across all training trials. Main effect of Group across all training trials revealed escape latencies for controls were shorter than for kainate animals, F(1, 35) = 10.25, P < 0.01. (Bi and Bii) Group mean escape latencies in Trial 4 and Trial 1 of following day suggest there is little drop in performance overnight for controls, but there is for kainate animals between several training days. Group (n = 2) × Trial (n = 2) × Day (n = 12) ANOVA on escape latencies; 3-way interaction, F(11, 385) = 2.01, P < 0.05. Simple main effects revealed shorter latencies in Trial 4 than in Trial 1 of the following day for Days 1 and 2, 3 and 4, 6 and 7, and Days 7 and 8, F(1, 420) > 4.62, P < 0.05. (C) Group mean time in platform area in probe Trials 1 and 2. Kainate animals spent less time in the platform area than controls only during probe Trial 2. Group (n = 2) × Probe (n = 2) ANOVA on time in platform area; Group, F(1,33) = 3.35, P > 0.05; Probe F(1, 33) = 11.79, P < 0.05; interaction, F(1, 33) = 4.47, P < 0.05. Simple main effects revealed an effect of group on Probe 2, F(1, 33) = 7.79, P < 0.01 but not on Probe 1, F < 1. Kainate animals were also found to spend less time in the platform area in Probe 2 than Probe 1, F(1, 33) = 15.39, P < 0.01. This was not true for controls, F < 1. KA = kainate animals.

Figure 5 Impaired allocentric learning, overnight performance and accelerated forgetting with prolonged training. (Ai) Group mean escape latencies across 50 training trials revealed improvement for both groups. Group (n = 2) × Trials (n = 50) ANOVA on escape latencies; Group, F(1, 35) = 10.25, P < 0.01; Trial, F(49,1715) = 47.64, P < 0.01; Interaction, F(49, 1715) = 2.08, P < 0.01. Simple main effects revealed controls had shorter latencies than kainate animals in Trials 5, 6, 8, 10, 13, 17 and 25, F(1,1750) = 5.98, P < 0.05. Error bars for controls (n = 19) and kainite animals (n = 18) are mean ± 1 SE. (Aii) Group escape latencies meaned across all training trials. Main effect of Group across all training trials revealed escape latencies for controls were shorter than for kainate animals, F(1, 35) = 10.25, P < 0.01. (Bi and Bii) Group mean escape latencies in Trial 4 and Trial 1 of following day suggest there is little drop in performance overnight for controls, but there is for kainate animals between several training days. Group (n = 2) × Trial (n = 2) × Day (n = 12) ANOVA on escape latencies; 3-way interaction, F(11, 385) = 2.01, P < 0.05. Simple main effects revealed shorter latencies in Trial 4 than in Trial 1 of the following day for Days 1 and 2, 3 and 4, 6 and 7, and Days 7 and 8, F(1, 420) > 4.62, P < 0.05. (C) Group mean time in platform area in probe Trials 1 and 2. Kainate animals spent less time in the platform area than controls only during probe Trial 2. Group (n = 2) × Probe (n = 2) ANOVA on time in platform area; Group, F(1,33) = 3.35, P > 0.05; Probe F(1, 33) = 11.79, P < 0.05; interaction, F(1, 33) = 4.47, P < 0.05. Simple main effects revealed an effect of group on Probe 2, F(1, 33) = 7.79, P < 0.01 but not on Probe 1, F < 1. Kainate animals were also found to spend less time in the platform area in Probe 2 than Probe 1, F(1, 33) = 15.39, P < 0.01. This was not true for controls, F < 1. KA = kainate animals.

suggesting that fluoxetine had restored performance in the kainite-treated group.

However, comparison of the last learning trial on one day and the first trial of the next (Fig. 9Bi–iii) revealed poor overnight retention in both the kainate and kainate + fluoxetine treated groups, compared with the control animals; Group × Trial × Day interaction, F(6, 69) = 2.64 P < 0.05. Simple main effects revealed that for both kainate and kainate + fluoxetine groups there was a significant decrement between days [F(1,92) > 4.06, P < 0.05] suggesting fluoxetine had not improved overnight retention.

During Probe 1, controls and kainate + fluoxetine treated animals spent more time in the platform area than the kainate animals (Fig. 9C), again suggesting fluoxetine has improved spatial learning. During Probe 2, both kainate + fluoxetine and kainate animals perform worse than the control animals; Group × Probe interaction, F(2,23) = 5.45, P < 0.05. Simple main effects revealed that there was an effect of group in Probes 1 and 2.
[F(2, 46) > 3.22, P < 0.05]. Dunnett post hoc testing showed in Probe 1 only kainate animals were impaired compared to controls whereas in Probe 2 both kainate + fluoxetine and kainate animals were impaired.

The training and probe data together suggest that fluoxetine improved learning performance over the course of a day compared to the kainate group. However, fluoxetine did not improve the impairment in the overnight decrement or the accelerated forgetting.

**Discussion**

We have demonstrated impairments in the acquisition of an allocentric spatial task in patients with unilateral hippocampal sclerosis. We also show that patients have accelerated forgetting of the learned spatial task and that this is associated with damage to the non-dominant hippocampal formation. We go on to show a very similar chronic pattern of allocentric learning and accelerated forgetting in a status epilepticus model of mesial temporal lobe epilepsy in rats, which is associated with reduced and abnormal hippocampal neurogenesis. Finally, we show that reversal of the neurogenic deficit using fluoxetine is associated with reversal of the learning deficit but not the accelerated forgetting, pointing to a possible dissociation in the underlying mechanisms, as well as a potential therapeutic strategy for improving hippocampal dependent learning in patients with mesial temporal lobe epilepsy.

As we did not monitor seizure activity in our animals, we cannot definitively exclude an influence of ongoing seizures on learning and memory, but we did not observe any clinical seizures in
animals during behavioural training and testing. Likewise, we cannot be certain that our model mimics severe ongoing poorly controlled epilepsy, in addition to being a model largely of the consequences of status epilepticus. However, there is strong clinical evidence that cognitive deficit in human mesial temporal lobe epilepsy is related to the degree of initial insult and not to the rate of spontaneous seizures (Helmstaedter and Elger, 2009). This is supported by longitudinal volumetric MRI studies, showing that brain volume reduction in temporal lobe epilepsy is the cumulative effect of an initial precipitating injury and age-related cerebral

Figure 8 Fluoxetine (FLX) reverses the neurogenic deficit after kainate. (A) Oral fluoxetine given for 5 weeks prior to sacrifice restores the number of newly born doublecortin-positive cells to normal in kainate-treated animals. One-way ANOVA revealed a significant effect of Group \( F(2, 18) = 11.68 \). Post hoc Dunnett tests revealed that controls had significantly more doublecortin-positive cells per dentate gyrus than the kainate \((P < 0.05)\). There was no significant difference between fluoxetine-treated kainate animals and controls. (B) Fluoxetine restores the average length of the dendritic tree of doublecortin-positive neurons. A one-way ANOVA on the average total dendritic tree length shows that the main effect of Group was significant, \( F(2, 16) = 5.00, P < 0.05 \). Post hoc Dunnett \( t \)-test revealed that the length of the dendritic tree of doublecortin-positive neurons for kainate animals was significantly lower than for controls \((P < 0.05)\), but there was no significant difference between fluoxetine-treated kainate animals and controls. (C) Fluoxetine restores the angle of the main dendritic process of doublecortin-positive cells to normal after kainate. One-way ANOVA on mean angle of deviation of the main dendrite for the three groups shows a significant main effect of Group, \( F(2, 14) = 5.16, P < 0.05 \). Post hoc Dunnett \( t \)-test revealed that the angle of deviation for kainate animals was significantly more than for controls \((P < 0.05)\), but there was no significant difference between fluoxetine-treated kainate animals and controls. (D) Fluoxetine significantly increases the number of BrdU positive cells. One-way ANOVA on BrdU + cells per dentate shows that the main effect of Group is significant, \( F(2, 26) = 5.02, P < 0.05 \). Post hoc Dunnett’s tests comparing the control to experimental groups revealed that the mean for the fluoxetine-treated kainate animals was greater than that for controls \((P < 0.05)\). (E) Schematic showing the timings of fluoxetine, BrdU, behavioural training, probe trials and sacrifice. Two months after kainate-induced status epilepticus (SE) animals were given 20 mg/kg fluoxetine in their drinking water. Twice daily intraperitoneal BrdU injections were given 14–16 days later. At 3 months post kainate-induced status epilepticus, 11 days of Morris water maze training was commenced followed by probe Trial 1 on Day 11 and probe Trial 2 on Day 20 after which the animals were sacrificed. KA = kainate-treated animals; KA&FLX = kainate animals treated with 7 weeks of oral fluoxetine (20 mg/kg).
atrophy and is not related to seizure burden (Liu et al., 2005). We also noted no difference in the pattern of cognitive deficits seen between our patients with hippocampal sclerosis and those after selective hippocampal resections, even though the former were seizure-free and the latter had drug refractory epilepsy. There is compelling evidence that ongoing neuroinflammation initiated by status epilepticus is likely to be the underlying pathophysiological mechanism giving rise to both recurrent seizures (Balosso et al., 2008), and altered neurogenesis and cognitive dysfunction (Coras et al., 2010).

DEFICIT IN AllocENTRIC LEARNING

Consistent with previous research (Abrahams et al., 1997, 1999; Astur et al., 2002; Incisa della Rocchetta et al., 2004; Glikmann-Johnston et al., 2008), we have shown that patients with hippocampal sclerosis or resection are significantly less efficient than controls in learning allocentric spatial tasks. There was no lateralizing effect during learning, but there was during delayed recall in the patients with right-sided hippocampal sclerosis, possibly due to dual encoding. Findings are consistent

**Figure 9** Fluoxetine (FLX) reverses the learning deficit but not the overnight decrement or accelerated forgetting after kainate. (Ai) Group mean escape latencies across initial 18 training trials revealed improvement for all three groups. Group \((n = 3) \times \) Trials \((n = 18)\) ANOVA on escape latencies; Group, \(F(2, 23) = 5.58, P < 0.05\); Trial, \(F(17, 391) = 11.46, P < 0.01\); Interaction was not significant, \(F(34,391) = 1.26, P > 0.05\). Three additional trials, following probe Trial 1, revealed the probe trial had little effect on training performance. Group \((n = 3) \times \) Trial \((n = 3)\) ANOVA; Group, \(F < 1\); Trial, \(F(2, 46) = 2.38, P > 0.05\); Interaction, \(<1\). Error bars for controls \((n = 9)\), kainate \((n = 9)\) and kainate + fluoxetine animals \((n = 8)\) are mean \(\pm 1\) SE. (Aii) Group escape latencies meaned across initial 18 training trials. Dunnett post hoc testing of the significant main effect of Group revealed kainate animals had longer mean latencies than controls \((P < 0.05)\). (Bi, ii and iii) Group mean escape latencies in Trial 4 and Trial 1 of following day suggest there is little drop in performance overnight for controls, but there is for kainate and kainate + fluoxetine animals across several training days. Group \((n = 3) \times \) Trial \((n = 2) \times \) Day \((n = 4)\) ANOVA on escape latencies; three-way interaction, \(F(6, 69) = 2.64, P < 0.05\). Simple main effects revealed shorter latencies in Trial 4 than Trial 1 of the following day across Days 3 and 4, and 4 and 5, for kainate animals and across Days 2 and 3, 3 and 4 and 4 and 5 for kainate + fluoxetine animals, \(F(1, 92) > 4.06, P < 0.05\). (C) Group mean time in platform area in probe Trials 1 and 2. Controls and kainate + fluoxetine animals spent more time in the platform area than kainate animals during probe Trial 1. In probe Trial 2, controls spent more time in this area than both kainate and kainate + fluoxetine animals. Group \((n = 3) \times \) Probe \((n = 2)\) ANOVA on time in platform area; Group, \(F(2, 23) = 4.05, P < 0.05\); Probe, \(F(1, 23) = 58.04, P < 0.01\); Interaction, \(F(2, 23) = 5.45, P < 0.05\). Simple main effects revealed a significant effect of Group on Probes 1 and 2, \(F(2, 46) > 3.22, P < 0.05\). Dunnett post hoc testing showed that in Probe 1 kainate animals spent less time than controls in the platform area \((P < 0.05)\). In Probe 2, kainate and kainate + fluoxetine animals spent less time in this area than controls, \(P < 0.05\). KA = kainate animals; KA + FLX = kainate + fluoxetine treated animals.
with Maguire et al. (1998), who showed that both hippocampi are active on PET imaging during virtual navigation, but only right hippocampal activation predicted navigation accuracy. They are also in agreement with Astur et al. (2002) who found no lateralizing effect of mesial temporal resections on allocentric learning.

In our animal studies, a lesional status epilepticus model of mesial temporal lobe epilepsy, we found a similar deficit in allocentric learning. Performances across the trials of each session, however, suggested two separate causes for the deficit. Kainate animals had longer latencies than controls in Trials 1–3 on Days 2–4 of training. The poorer performance in the first trial of a session compared to last trial of the previous session seems likely to be due to an overnight decrement in long-term memory. The poorer performances in Trials 2 and 3 could be due to a deficit in working memory.

Impaired acquisition has been reported using the Morris water maze task in adult rats treated with kainate 20 and 60 days prior to training (Stafstrom et al., 1993). However, Stafstrom et al. (1993) reported averaged performance across six training trials per day. Increasing the number of trials per session reduces the influence of an overnight decrement and thus suggests a deficit in working memory. However, poorer performance in a Morris water maze task after an overnight period has been noted previously in juvenile (post-natal Day 40) animals subjected to post-natal flurothyl-induced seizures from post-natal Day 0 to post-natal Day 25 (Karnam et al., 2009). Our study significantly extends these to chronic findings in adult animals using a status epilepticus model of mesial temporal lobe epilepsy and highlights separate deficits in learning and memory across the training period.

We found that the working memory deficit was restricted to Days 2–4, whilst the overnight decrement, seen in Trial 1, persisted until Day 8, suggesting that there are different biological mechanisms underlying working and long-term memory. Our experimental paradigm did not allow us to distinguish between a deficit in overnight consolidation and retrieval as a mechanism for the overnight decrement. However, given that performance improved to control levels by Trial 2 in the later overtraining sessions, it might be suggested that consolidation had occurred, but a reinforced trial was necessary for retrieval.

Our hypothesis of a defect in working memory to explain the poorer within day performances of the kainate group is speculative, but consistent with defects in working memory previously reported using the kainate model of chronic epilepsy (Sayin et al., 2004). Interestingly, Karnam et al. (2009) found a defect in working memory on a radial-arm task in juvenile rats given 100 flurothyl-induced seizures between post-natal Day 15–37 and tested between post-natal Day 60–80. Earlier Morris water maze task training (post-natal Day 42) in these animals also showed poorer performance in the first trial of the day, although this was not discussed in this article.

The cellular mechanisms underlying spatial working memory are incompletely understood. The dentate gyrus has long been hypothesized to function as a pattern separator, which by differentially encoding small changes from similar or interfering inputs, increases the accuracy of memory encoding (Marr, 1971). The dentate gyrus is unique as an area of ongoing neurogenesis throughout adult life, which supports pattern separation (Clelland et al., 2009) and is necessary for complex relational spatial learning (Dupret et al., 2008). Given that neurogenesis is adversely affected in both quantity and quality in chronic temporal lobe epilepsy in both animal models (Hattiangady et al., 2004; Jessberger et al., 2007a, b) and in human hippocampal sclerosis and mesial temporal lobe epilepsy (Paradisi et al., 2010), and that memory function appears to be inversely correlated with the levels of neurogenesis seen in the resected dentate gyrus of patients undergoing epilepsy surgery (Coras et al., 2010), then it is a reasonable conjecture that the less efficient spatial learning seen in our Morris water maze task experiments in the kainate-treated animals might be partly due to inefficient spatial working memory/pattern separation secondary to the reduced and altered neurogenesis they exhibited. We did not examine the specific contribution of abnormal pattern separation to spatial learning in our experiments but this will be the subject of future work.

**Accelerated forgetting**

Accelerated forgetting has previously been demonstrated for verbal memory tasks (Blake et al., 2000) and may in part explain the discrepancy between patient’s reports of significant memory dysfunction and that measured on formal testing, where long-term recall is assessed after only 30 min (Corcoran and Thompson, 1992; Gleissner et al., 1998b; Blake et al., 2000; Butler and Zeman, 2008).

Herein, we show that patients with hippocampal sclerosis or selective hippocampal formation resection also exhibit accelerated forgetting for an allocentrically learned spatial task. Why we saw a lateralizing effect on delayed recall but not in allocentric acquisition is unclear, but might be a consequence of dual encoding, with a concomitant failure of verbalizable cues to rescue the retrieval of the spatial memory or a more rapid accelerated forgetting of these verbal components (Blake et al., 2000). These findings are consistent with Butler et al.’s (2008) report of accelerated forgetting of declarative memories in a patient with transient epileptic amnesia and left hippocampal sclerosis (Butler et al., 2008). Although a morphometric study has not shown any significant association between accelerated forgetting and hippocampal volume changes (Butler et al., 2009), seizure focus was not lateralized and the average volume reduction was small (8%), raising the possibility that averaging across pathological and non-pathological hippocampi attenuated pathological volume differences.

Similar to the patient cohorts, we found evidence of accelerated forgetting in the chronic phase of an animal model of mesial temporal lobe epilepsy 3 months after kainite-induced status epilepticus. However, in contrast with the working memory deficit, accelerated forgetting was not compensated for by extended training, again indicating a possible dissociation in the underlying mechanisms subserving these processes. A mechanistic dissociation between working and long-term memory has been hypothesized (e.g. Groves and Thompson, 1970; Barker et al., 2006), and is supported by recent studies (Sanderson et al., 2009; Rust et al., 2010; for review see Baneraman and Sprengel, 2010).

Although the roles of the dentate gyrus and neurogenesis in memory consolidation and retrieval need further exploration (Aimone et al., 2010; Alme et al., 2010), accelerated forgetting...
might implicate additional downstream hippocampal pathology, as hippocampal place cells are reactivated in spatial memory recall (Dupret et al., 2010) in addition to sparsely encoding newly born neurons (Tashiro et al., 2007). Indeed, CA1 and CA3 damage are features of hippocampal sclerosis and its kainate model (Nadler et al., 1978), and our findings do not rule out subtle cell loss (<20%) or synaptic reorganization.

Indeed, the mechanism of accelerated forgetting may well be similar to that of the overnight decrement seen during allocentric learning. Recent theories underpinning the neurobiology of memory emphasize the iterative nature of the learning process, updating of previous memory schemas with novel information through bidirectional communication between hippocampus and cortex (Redondo and Morris, 2011). Interestingly, and in support of our conjecture that the overnight decrement observed in training is due to accelerated forgetting, Butler et al. (2008) have described accelerated forgetting after delays as short as 24 h after exposure to the initial learning event in a patient with mesial temporal lobe epilepsy.

An alternative explanation of the overnight decrement in kainate animals may be increased stress on the first trial of a session. However, there was no evidence of increased thigmotaxis or vocal activity, associated with higher levels of stress, on the first trial of a day in the kainate animals compared to controls.

Effects of fluoxetine

The antidepressant fluoxetine has been reported to improve working memory in patients after chemotherapy and to reverse methotrexate-induced spatial working memory deficits in rats (Lyons et al., 2011a, b). Although the mechanisms of this effect are unknown, there is evidence that this may be due to its effect of increasing hippocampal neurogenesis (Elbeltagy et al., 2010; Lyons et al., 2011a). Fluoxetine is also a powerful anti-neuroinflammatory agent (Chung et al., 2011) and this action may affect neural function directly, as neuroinflammation is a prominent process in the initiation and maintenance of hippocampal sclerosis (Vezzani et al., 2008), the most common cause of mesial temporal lobe epilepsy. These effects may be overlapping as neuroinflammation is detrimental to hippocampal neurogenesis (Ekdahl et al., 2003; Monje et al., 2003). A further possibility is that an anticonvulsant effect of fluoxetine may mediate its behavioural effects, although we feel this is unlikely given that fluoxetine restores both neurogenesis and working memory after methotrexate (Lyons et al., 2011a, b) and in a mouse model of Huntington’s disease (Grote et al., 2005), paradigms where seizures are not present.

We therefore used fluoxetine to see if we could reverse some or all of the deficits in our rodent kainate model. That fluoxetine restored neurogenesis is supported by the significantly increased numbers of BrdU-labelled cells, as well as the increased number of cells staining for doublecortin. Doublecortin is a well-validated marker for generally assessing dentate neurogenesis (Brown et al., 2003; Rao and Shetty, 2004) and immunohistochemically detectable cell staining in tissue sections reliably identifies bone fide neurons or precursors restricted to the neuronal lineage (Walker et al., 2007) and not uncommitted or primitive stem cells (Lugert et al., 2010). However, the maturity and functional quality of the neurogenic response to fluoxetine remains to be demonstrated, e.g. using Neu-N immunostaining as well as functional recordings.

Given that dentate neurogenesis appears to be necessary for complex allocentric spatial learning (Dupret et al., 2008; Zhang et al., 2008; Clelland et al., 2009), its restoration (in number and connectivity) by fluoxetine may account for the normalization of allocentric learning in the kainate rats. However, whether this functional improvement is due to the restored neurogenesis remains to be proven. Interestingly, oral fluoxetine had no effect on accelerated forgetting, again indicating that these phenomena have different underlying mechanisms (vide supra). In further support of our hypothesis, early attenuation of status epilepticus in animals with valproic acid prevented the development of chronic aberrant neurogenesis and hippocampal learning deficits (Jessenberger et al., 2007a).

Given the identified role of hippocampal neurogenesis in long-term spatial memory retention (Imayoshi et al., 2008; Deng et al., 2009) and retrieval (Trouche et al., 2009), the failure of fluoxetine to improve accelerated forgetting is unexpected. However, our behavioural studies may have been too early to see an improvement in retrieval after restoration of neurogenesis. Also, kainate damage to the CA3 and CA1 components of the tri-synaptic pathway (necessary for pattern completion based memory recall (Nakashiba et al., 2008)), may confound the effect of rescuing the upstream neurogenic component.

Relevance to patients with mesial temporal lobe epilepsy

Fluoxetine has been reported to improve memory in patients with impaired cognition in depression (Levkovitz et al., 2002; Gallassi et al., 2006) and mild cognitive impairment (Mowla et al., 2007). Based on our findings, there may be translational potential in treating patients with mesial temporal lobe epilepsy with mild hippocampal sclerosis and a history of status epilepticus, with fluoxetine in order to improve spatial and perhaps verbal learning, since the pattern of spatial learning and memory deficits was very similar in patients and animals. Whether or not, the beneficial effect of fluoxetine is mediated through its neurogenic, neurotrophic, anti-inflammatory or possible anticonvulsant actions, remains to be definitively determined.

The persistence of accelerated forgetting might be interpreted as a confounder of restored learning; however, the restoration of learning is a requisite for subsequent behavioural and or pharmacological efforts to overcome accelerated forgetting. Overtraining may not be a realistic strategy in patients where ‘training’ is often a single exposure to an event that is required to be remembered later, and a well tolerated pharmacological therapy that restores learning to normal could be of great clinical benefit.

Although severe damage to the hippocampus may confound all attempts at successfully manipulating neurogenesis to effect cognitive improvement, many patients with learning and memory problems and mesial temporal lobe epilepsy have milder forms of hippocampal damage and these patients may present a fruitful
cohort for restoring learning and memory function. Finally, the possibility that separate mechanisms underlying working memory impairment and accelerated forgetting in mesial temporal lobe epilepsy suggested by this work, will inform further studies of this clinically important, but investigationally neglected, aspect of cognitive impairment in mesial temporal lobe epilepsy.

**Funding**

This study was supported by grant P0603 from Epilepsy Research UK (ERUK) to WPG.

**Supplementary material**

Supplementary material is available at *Brain* online.

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