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# Hippocampal Place Cells Show Increased Sensitivity to Changes in the Local Environment Following Prefrontal Cortex Lesions

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**It has been proposed that the prefrontal cortex modulates neural activity in posterior cortex via inhibitory mechanisms. As a result, damage to the former area may produce disinhibition in posterior regions and increase sensitivity to extraneous information. This hypothesis was investigated by examining how prefrontal cortex lesions affected the firing of hippocampal place cells in freely moving rats. In experiment 1, the positional firing of lesion-group cells was altered to a greater extent than that of control-group cells when objects were introduced into the recording environment. This suggested that place cell firing was overly influenced by local cues in the prefrontal-lesioned animals. In experiment 2 place cells were recorded while rats foraged on a circular track with access to both local and distal multimodal cues. Although the position of place fields in lesion-group cells was not excessively tied to local cues, a greater proportion of the fields lost their spatial selectivity following a rotation of these cues. The cue-related effects were associated with larger extracellular action-potential amplitudes and a greater incidence of burst-firing in lesion-group cells. This finding is consistent with the hypothesis that lesions of the prefrontal cortex result in a disinhibition of posterior cortex.**

**Keywords:** disinhibition, hippocampus, neural activity, place cells

## Introduction

It has previously been proposed that the prefrontal cortex has a role in complex behavioural and cognitive functions such as planning, attention and abstract thought (Milner, 1982; Shallice, 1982; Goldman-Rakic, 1987; Petrides, 1994; Fuster, 1995; Lee and Kesner, 2003). In humans, such higher order cognitive processes are often referred to as executive functions (Baddeley, 1986; Baddeley and Della Sala, 1996). It has been suggested that executive function may be mediated at the neural level by selection and filtering processes that occur at various stages of processing, with an important function of the prefrontal cortex being to inhibit the processing of extraneous incoming signals or noise in posterior cortex (Shimamura, 2000). This model predicts that an increase in the activity of prefrontal cortex should be paralleled with a decrease in posterior cortical activity and conversely that lesions of the prefrontal cortex should produce disinhibition in target regions. The results of several human studies are consistent with this prediction (Frith *et al.*, 1991). In particular, gross activity in posterior cortex (including temporal cortex) has been shown to increase after frontal cortex lesions (Knight and Grabowsky, 1995) and as a result of neuropathology linked to frontal lobe dysfunction (Meyer-Lindenberg *et al.*, 2001).

Two recent studies have investigated the neuronal-level effects of prefrontal cortex lesions on activity in the temporal cortex of rats. The findings of Zironi *et al.* (2001) are consistent with the hypothesis that prefrontal lesions altered the firing of the spatially selective neurons ('place cells'; O'Keefe and Dostrovsky, 1971; O'Keefe, 1976) of the hippocampus. A follow-up study which directly investigated the effect of prefrontal lesions on these latter neurons (Kyd and Bilkey, 2003) determined that the place cells of lesioned animals tended to shift firing location across multiple recording sessions compared with similar cells in control animals. One explanation of these results is that the place cells of animals with lesions may have been overly influenced by less stable, local environmental cues such as olfactory traces on the floor. This could occur if the hippocampal neurons in prefrontal-lesioned animals were disinhibited so that filtering processes were compromised. As a result, the tendency of many of these cells to respond to stable, distal stimuli (O'Keefe and Dostrovsky, 1971; Muller and Kubie, 1987; Hetherington and Shapiro, 1997) might have been altered. The purpose of the present study was to test this hypothesis.

In experiment 1 the effect of inserting a novel local cue (an object) into an otherwise stable testing environment was examined. In experiment 2, the position of local environmental cues was shifted with respect to stable distal cues. It was predicted that prefrontal lesions would result in a greater sensitivity of hippocampal neurons to changes in the arrangement of local cues in the environment. If this effect resulted from a decrease in the inhibition of hippocampal cells, then it could manifest as an increase in firing rate, an increase in action-potential burst firing episodes or an increase in spike amplitude in these cells.

## Materials and Methods

### *Subjects*

Sixteen male Sprague-Dawley rats were housed individually in translucent, plastic cages containing sawdust and shredded paper and maintained on a 12 h, light:dark cycle. The animals weighed between 347 and 540 g at the time of surgery. Food and water were available *ad libitum* both prior to and during the first 2 weeks after surgery.

### *Electrode implantation and lesions*

Surgery was performed under aseptic conditions. Rats were anaesthetized with sodium pentobarbitol (60 mg/kg; i.p.) and administered penicillin (0.15 ml i.m). They were placed in a stereotaxic frame (Kopf) where the head was held in the horizontal plane. An overhead heating lamp was used to maintain body temperature. Coordinates for prefrontal cortex lesions and hippocampal electrode implantation were derived from the rat brain atlas of Paxinos and Watson (1998).

A midline incision was made to expose the skull which was then scraped clean of connective tissue and dried so that bregma and the midline sagittal suture could clearly be seen. For prefrontal lesion animals, trephines were drilled on both sides of the skull at the coordinates 2.0, 3.0 and 4.5 mm anterior to bregma and 1.6 mm lateral to the midline. A monopolar lesioning electrode constructed from teflon-coated; stainless

steel wire (125 μm diam.) was lowered into each trephine at a 16° angle towards the midline at depths of 2.0 and 1.3mm at the first two anterior–posterior (AP) locations respectively from the cortical surface, and then 2.1 and 1.0 mm at the 4.5 mm location AP. Two milliamps of anoded direct current was then administered for 10 s to produce a lesion. Sham-control animals were operated in the same manner except that the lesioning electrode was not lowered into the brain.

A miniature, moveable microdrive (Bilkey and Muir, 1999) which contained a bundle of eight recording electrodes was implanted unilaterally (counterbalanced across hemispheres) immediately above the cell layer of the dorsal hippocampus (CA1) at 3.8 mm posterior and 2.5 mm medial to bregma, and 1.8 mm below the dural surface. The recording electrodes consisted of formvar-coated, nichrome wires (25 μm diameter) and the whole bundle was cut at a 45° angle just prior to implantation. The electrode assembly and a ground wire were connected to a headplug (McIntyre miniconnector) and anchored to the skull with dental acrylic and jewellers screws. After surgery the animals were administered analgesia (0.2 ml Temgesic; Reckitt and Colman) and left to recover. Two weeks after surgery the rats were placed on a food deprivation schedule during which their weight was reduced to, and maintained at, 85% of their free-feeding weight in readiness for the recording procedure.

### *Unit recording*

Extracellular spike activity was recorded in the hippocampus and buffered via a field effect transistor (FET) source-follower located in a head-stage mounted at the end of the recording cable. A 'quiet' electrode was used as an indifferent. The output signals were filtered at 300 Hz and 5 kHz, and amplified 10 000 times (Barc Neuro 8 Amplifier) before being digitized at 25 kHz by a Digidata 1200 series interface (Axon instruments) under the control of Axoscope (Axon instruments). Single unit signals were digitized when a spike on any channel exceeded a pre-determined threshold set above the background noise levels and were stored on a personal computer for off-line analysis.

The position of the rat's head was simultaneously monitored by a tracking system (Fast track) connected to the video camera located above the recording arena. This tracked the position of three infra-red light-emitting diodes (LEDs) mounted on the head stage. The LEDs were positioned in a triangular formation ~1 cm apart and centred on the crown of the head. Head position was sampled at 10 Hz (regardless of whether single unit activity was being recorded or not) and this information was made available to the Digidata acquisition system.

### *Identification of Place Cells*

Putative 'place cells' were classified as such if they had a spike width (peak-to-trough) of greater than 450 μs, and a signal-to-noise ratio of ~3:1 or greater. These cells were also characterized by the generation of complex spikes which were bursts of 2–5 action potentials that decremented in amplitude and which had an interspike interval of ~5 μs. Complex bursts were identified with an autocorrelation function (Matlab) that calculated the time between all spike pairs. The auto-correlation functions also allowed the experimenter to identify the post-spike refractory period, indicative of a well-isolated neuron, and to distinguish between place cell and theta cell (putative interneuron) firing patterns. Although all complex burst cells that were recorded generated place fields of some sort (regions of the environment where they fired most intensely), no attempt was made to classify cells on the basis of these place field properties during the recording session. Theta cells typically fired continuously while the animal was moving and were distinguished from complex burst spikes on the basis of their significantly smaller spike width (<450 μs) and lack of complex spike bursts. Any cells that exhibited the spike properties and firing characteristics that classified them as place cells or theta cells will be referred to as such for the remainder of this paper.

### *Procedure Experiment 1: Insertion of Novel Objects*

#### *Recording Apparatus and Environment*

Ten rats (six control, four lesion) were tested in a black, cylindrical plastic chamber (75 cm diameter, 56 cm deep) situated on the floor, in the middle of the recording room. A white, triangular cue card (23 cm each side) was attached to the inside wall beneath the rim of the chamber. A single lamp (60 W bulb), situated on a shelf next to the recording apparatus nearby the cylinder, provided indirect light. A video camera was mounted on the ceiling directly above the cylinder to record the animals' position, and a flexible cable connected to a commutator hung from the ceiling also, for unit recording. A speaker positioned above the cylinder emitted background masking noise. Other items in the room, such as a desk and chair, the recording apparatus and a radio, served as visual cues and were located ~1.5 m from the recording chamber. Visual stimuli were also located on the walls of the room. All cues were kept constant throughout the experiment as was the experimenter's position in the room.

#### *Habituation*

The rats were carried to the recording room in a high-wall, open-top box and connected to the recording apparatus, then placed into the cylindrical chamber for 15 min. Chocolate sprinkles were scattered evenly over the chamber floor at regular intervals to encourage the rats to move constantly across the surface of the environment as they foraged for this food. Concurrently, the electrodes were scanned for cellular activity. If no place cells were identified during this period the electrodes were advanced by 40 μm. This procedure was repeated for 3 days, or until the animals had learnt to forage and the first place cells were identified.

#### *Unit Recording Procedure and Insertion of Novel Objects*

The animals were brought to the testing room and connected to the recording apparatus as for the habituation procedure. During this procedure the rats were tested in an intermixed, pseudo-random order. They were run for two 10 min recording sessions separated by a delay of ~30 s. The first recording session (A) was always run in the standard 'empty' chamber where there were no objects (the baseline condition), but in the second session either a novel object was inserted into the chamber (B) or it remained empty (A′). These conditions were counterbalanced across two consecutive days so that for each cell the rat was tested in either the AA′ condition on the first day and AB on the second day, or vice versa. During the B condition the objects were placed into the cylinder in a pseudo-random position but always outside of the place field established during session A, and always such that the animals could explore fully around the object. The distance between the centre of the place field and the object ranged from 6 to 55 cm. The objects were always completely novel to ensure that in each trial they were the most salient cues in the animals' local environment. The objects (e.g. a glass coffee cup, a metal stapler, a plastic hole-punch, a square cardboard box and a circular tin can) varied in size (~60–1000 $cm^3$) and shape. The two 10 min sessions were run in succession although the rats were removed from the testing chamber between recordings for ~30 s and placed into the high-wall, open-top box which was situated beside the cylinder. The cylinder was not cleaned between sessions, hence all local odour cues were left undisturbed ensuring that the novel object was the only unstable local cue. Once a cell had been recorded for 2 days, the electrodes were advanced by 40 μm per day until another cell was isolated.

#### *Data Analysis*

Units were discriminated from noise and isolated from other cells with custom-built template-matching software utilized off-line (Placefielder). This software allowed the construction of a template that set boundaries at the upper and lower limits of the whole waveform. As each cell was recorded more than once, an identical template was used for each analysis. Cells were regarded as being stable across multiple sessions if their spike waveform fitted cleanly inside the template used to isolate the cell on the first recording session. That is, if waveform amplitude or shape changed across the sessions, then data from that cell would not be included in the full analysis procedure. If a cell became silent from one day to the next, it was assumed that the cell was lost. If a cell became silent within a session as a result of the experimental manipulation, we assumed that the cell had shut down its firing. The analysis software enabled spike amplitude and width (peak-to-trough) of cells to be measured as well as the interspike intervals (ISI) between all spike pairs. Only cells that generated >50 spikes in a 10 min recording session were included in the analysis.

Cell firing was mapped onto the animal's position within the experimental chamber. In this procedure maps were constructed by dividing the floor of the experimental chamber into a 20 × 20 pixel grid, where each pixel measured to 3.75 × 3.75 cm. For each pixel the number of spikes that occurred while the rat was within that pixel was divided by the total time spent in that pixel (dwell time), to generate the firing rate (FR). When an animal spent <500 μs in any pixel during the 10 min recording session, the data in that pixel was regarded as being undersampled. The values in these undersampled pixels were replaced with the average value of their neighbouring pixels. The mean FR was then determined by dividing the total number of spikes generated in the recording session by the total dwell time of the animal. A place field (PF) was regarded as a continuous region of the map where the FR of the unit was above the mean FR. Firing rate maps were used to calculate the place field size (the 'infield' region). Pixels not adjacent to at least two other 'infield' pixels were removed from the field.

To provide measures of spatial firing that do not require characterization of the place field, information content (Skaggs *et al.*, 1996), spatial coherence (Kubie *et al.*, 1990) and sparsity measures (Skaggs *et al.*, 1996) were calculated. The information content is a quantitative measure of the amount of information (in bits) about location provided by each spike that a cell generates. A value of 0 indicates that no spatial information is conveyed. In contrast, a typical place cell will normally generate around 1 or more bits of information per spike. The spatial coherence measure was used to establish the local smoothness of the place fields (Kubie *et al.*, 1990). This is an estimate of the strength of the spatial signal by means of a 2-D spatial autocorrelation. A positive value indicated the presence of a spatial determinant of firing. Coherence scores were normalized by computing *z*-scores before statistical analysis was performed (Fisher *r*-to-*Z* transform, $Z = 0.5 \times \log_e((1 + r)/(1 - r))$. The sparsity measure of spatial firing describes the relative proportion of the apparatus in which the cell fired (Skaggs *et al.*, 1996). A low value indicated that the cell was active in a small area of the environment, whereas a high value indicated more diffuse spatial firing.

In order to determine the distance that place fields shifted between multiple recording sessions (and also within a sub-period of the recording), the first order moment of the place field was calculated to determine its centre (analogous to a calculation of centre of mass; COM). The shift in the COM between recordings was determined by calculating the distance (cm) between the two COM values. The COM measure was utilized on the basis of findings by Fenton *et al.* (2000), who compared different methods of measuring how fields shift after a manipulation. The COM (described as 'centroid' in this article) was determined to be the best measure of this effect. The coordinates ($x$ and $y$) of the COM are defined by an equation where the mean $x$ and $y$ position of the pixels in the field are weighted by the firing rate in the pixel (Fenton *et al.*, 2000). In some cases (<10%) cell activity had disappeared on the second day of recording. This occurred equally for object and no-object conditions and for both lesion and control-group cells, and we attribute it to electrode movement. In order to be able to use the data from the first day of recording, the missing COM shift values from these latter sessions were replaced in the analysis using the Hot-deck imputation method. This technique is more accurate than simple missing data techniques such as mean substitution and list-wise deletion (Roth, 1994), as it has the advantages of preserving the distribution of item values. The main principle of the Hot-deck method is to use the current data (donors) to provide imputed values for records with missing values. For cells that acquired subfields the field with the highest mean firing rate was selected for the analysis of place fields (such as place field size and COM shift). The other measures of spatial firing (i.e. spatial coherence, sparsity and information content) were calculated from the entire firing rate distribution. The influence of novel objects on some of these firing properties was also assessed by calculating correlations (Pearson product moment coefficient, $r$) between the distance from the centre of the object to the COM of the place field and the firing rate of the cell, the place field size and the distance that the place field shifted after the object was introduced.

Finally, in order to ascertain whether any differences in the activity of place cells could be the result of behavioural differences between the groups, the rats' running speed was also calculated. This was assessed by measuring the change in position of the animal at each 100 ms timestamp over the ten minute recording session. Running speed was divided into 2 cm/s bins (with a maximum of 40 cm/s as there was minimal data generated above this speed) and the amount of time the animals spent moving at each speed was calculated. The average speed for each bin was then weighted by the time in that bin to determine the mean speed (cm/s) over the recording session. The data was collapsed across sessions and conditions in both experiments.

### *Procedure Experiment 2: Cue Rotation*

#### *Recording Apparatus and Environment*

Six rats (three control and three lesioned) were tested on a black, circular track (20 cm in width) constructed from a round, plastic, rimmed disk (75 cm diam. × 5 cm height) on which was centred a white, plastic, tapered cylinder (55 cm diam.). The track had minimal surface features except for a circular wooden plug (2.5 cm diameter) that was imbedded in the floor of the track. This, along with olfactory cues, served as the single major local cue. The track was elevated 80 cm above the floor on a table in the centre of the testing room. A video camera was mounted on the ceiling directly above the track to record the animal's position. A flexible cable connected to a commutator hung from the ceiling for unit recording. Light was provided from the monitor screens of two computers located ~1 m from the track, and these also served as prominent distal visual cues. Other items in the room, such as a chair, desk and shelves, as well as the recording apparatus, also served as visual cues. These were also located ~1 m from the track. All distal cues were maintained at a constant configuration during the entire experiment and the rats were able to view at least one distal cue from any position on the track.

#### *Habituation and Training Procedure*

The rats were trained to forage for chocolate sprinkles so that they ran continuously in a clockwise direction around the track. They were carried to the recording room in a high-wall, open-top box and connected to the recording apparatus. During the habituation phase, the rats were placed onto the track and left to forage freely for 15 min during which the chocolate was scattered randomly over the surface of the ring. This procedure was repeated for 3 days on average, depending on the individual animal's movement around the environment. Once the rats were foraging such that they were moving constantly around the apparatus, the training phase began. During the training procedure, food was placed in small caches 2–3 times per revolution, at arbitrary locations in the middle of the track to encourage constant movement in a clockwise direction. The experimenter administered the food while moving randomly around the apparatus. The rats underwent 5–16 training sessions (of 10 min duration, one per day) during which the electrodes were concurrently tested for complex burst spikes. If no complex spike cells were identified, the electrodes were advanced by 40 μm at the end of each session.

#### *Testing Procedure*

The testing procedure consisted of two phases. In the first phase, the track was positioned in the same orientation as utilized in the habituation and training procedures. In the second phase it was rotated 90° around its centre in either a clockwise or counterclockwise direction (counterbalanced across testing days for each rat). All other apparatus and cues remained stable within the room across the two phases. During this procedure the experimenter was blind to the group that the individual rats belonged to and hence they were treated as one intermixed group. In the first phase, the rats were brought into the testing room and connected to the recording apparatus, as for the habituation and training procedures. The rats were placed in the ring at the south-east location. Place cells were identified and after place field stability had been ascertained the recording session commenced, during which animals ran in a clockwise direction around the track for 10 min (they completed, on average, ~15 laps around the track during this time). They were then disconnected from the cable and placed into the holding box situated on the floor nearby while the track was rotated 90°. The surface of the track was not cleaned during this procedure, which took ~30 s. For the second phase, the rats were reconnected to the recording cable and placed back into the ring in the same (south-east)

location and the cell was recorded for ten min as for the first phase. If there were no other place cells to record, the electrodes were advanced by 40 μm at the conclusion of the recording session.

*Data Analysis*

The experimenter was blind to the groups that the rats belonged to until all of the data was collected and analysed for spike firing. From that point, the data analysis procedure was similar to experiment 2, except that several additional measures were used which were specific for the analysis of circular data. The strength and position of firing in the circular track were quantified by representing the mean firing as a vector. In this procedure the track was divided into 40 equally sized bins, and the mean firing rate (normalized for time in bin) was calculated for each bin. Circular statistics (Zar, 1996) were used to calculate a vector length (**r**) and a mean angle, which described the angular distribution of this firing activity relative to the centre of the track. The vector length described the concentration of the firing rate distribution around the circumference of the track. This measurement has no units, and ranges from 0 (where there is so much dispersion that a mean angle cannot be described) to 1.0 (when all the data are concentrated at the same direction). The vector length values were tested against a normal distribution curve to ensure normality. The Rayleigh test was used to determine whether the firing rate distributions for each of the sessions were significantly ($P < 0.05$) 'clustered' (directional) or if they were spread uniformly about the track.

As for experiment 1, cells were regarded as being stable across multiple sessions if their spike waveform fitted cleanly inside the template used to isolate the cell on the first recording session. That is, if waveform amplitude or shape changed across the sessions, then data from that cell would not be included in the full analysis procedure. If a cell became silent from one day to the next, it was assumed that the cell was lost. If a cell became silent within a session as a result of the experimental manipulation we assumed that the cell had shut down its firing.

*Histology*

Rats were deeply anaesthetized with Sodium Pentobarbitol (i.p.) and a 20 V DC current was administered for 10 s to each electrode to mark the final electrode tip positions in the brain. Rats were then perfused transcardially with saline (0.9%), followed by 10% formalin solution in 0.9% saline. The brains were removed and immersed in 10% formalin solution for 1 day, then switched to a 30% sucrose–formalin solution. Each brain was sectioned (60 μm) in the horizontal plane on a cryostat, then mounted on slides and stained with thionin. Recording electrode positions were determined as was the location and size of prefrontal cortex lesions.

## Results

### *Histology*

All recording electrodes passed through the CA1 layer of the hippocampus in both control and lesioned animals in both experiments. Rats in the lesion group had extensive bilateral damage to the anterior cingulate region (area Cg1; Paxinos and Watson, 1998; see Fig. 1). Lesions generally also extended into a small portion of the frontal association cortex (FrA) and motor cortex (M2) at their most anterior extent. They also encompassed the dorsal portion of the prelimbic area (PL), and for two animals with larger lesions the damage extended ventrally into the medial orbital cortex (MO). No other damage was evident in the orbital regions. In posterior sections lesions mainly encompassed the cingulate cortex, area 1 (Cg1) as well as M2 and, further laterally, part of M1. In three rats, lesions included a very small region of corpus callosum (fmi). The rat anterior cingulate and prelimbic region is thought to be homologous to the dorsolateral prefrontal cortex (DLPFC) in primates (Uylings and van Eden, 1990; Granon and Poucet, 2000; although see Preuss, 1995). The small variations in prefrontal damage did not correlate with any variations in the electrophysiological data and therefore all lesioned animals were treated as a homogeneous group.

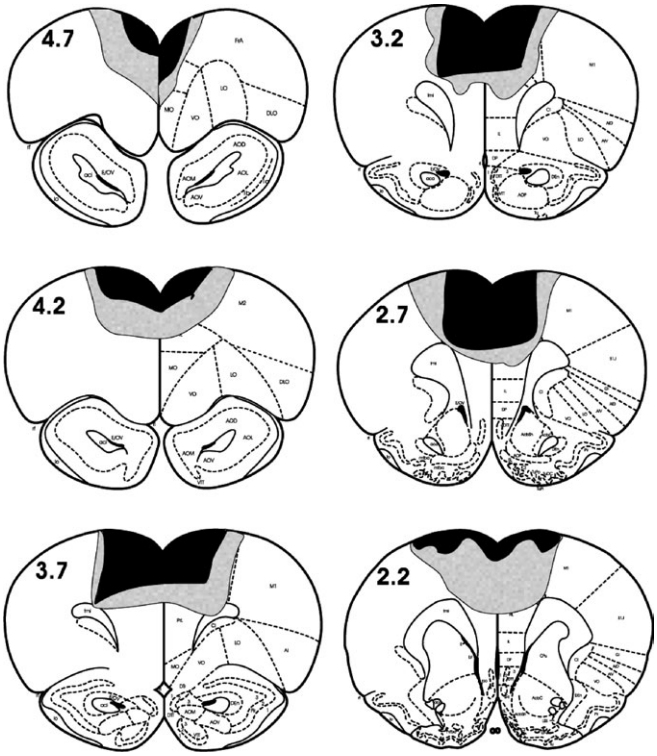


**Figure 1.** Coronal sections of the rat brain showing the location of prefrontal cortex lesions. Solid black regions represent the extent of the smallest lesions, and shaded regions show the extent of the largest lesions. Numbers indicate the distance (mm) of each section anterior to Bregma.

### *Experiment 1*

*Basic Firing Properties of Place Cells*

Fifty-nine place cells were recorded from control ($n = 25$) and lesioned ($n = 34$) animals. The cells were generally evenly distributed across the six control and four lesioned animals, although for three rats (two controls and 1 lesion) only one cell was recorded. The mean peak-to-trough spike amplitude and spike width was measured off-line during both A and B sessions of the novel object (AB) condition. A two-factor, repeated-measures analysis of variance (ANOVA) revealed a significant difference between groups for both of these measures. Lesion-group cells exhibited greater amplitudes than control-group cells in both the A and B sessions [see Table 1; $F(1,57) = 18.73$, $P < 0.0001$]. The amplitudes were also significantly larger in session B (when an object was placed in the environment) compared with session A (when no-objects were introduced) in both control- and lesion-group cells [$F(1,57) = 6.03$, $P < 0.05$]. See Table 1. Spike-width was also larger in lesion-group cells in both A and B sessions [$F(1,57) = 17.99$, $P < 0.0001$]; however, there was no significant change in spike-width when objects were introduced in either group. To assess the amount of spike bursting, interspike interval histograms were generated for each cell. The proportion of spikes occurring at intervals of 2–10 ms was calculated and compared between groups and sessions. The amount of spike bursting (proportion of spikes in the 2–10 ms

**Table 1**
A comparison of firing properties of cells across baseline and novel object conditions (mean ± SEM)

| | Control ($n$ = 25) | | Lesion ($n$ = 34) | |
|---|---|---|---|---|
| | Baseline (A) | Object (B) | Baseline (A) | Object (B) |
| Spike amplitude (μV) | 176 ± 14***† | 193 ± 22*** | 286 ± 24† | 295 ± 25 |
| Spike width (μs) | 482 ± 23*** | 458 ± 16*** | 527 ± 13 | 529 ± 12 |
| Spikes with 2–10 ms ISI (%) | 20 ± 2.3** | 20 ± 2.1** | 26 ± 2.3 | 29 ± 2.1 |
| Overall firing rate (Hz) | 2.50 ± 0.4 | 3.02 ± 0.4 | 3.07 ± 0.5 | 3.27 ± 0.4 |
| Field size ($cm^2$) | 811 ± 80*†† | 786 ± 97* | 684 ± 56†† | 559 ± 53 |
| Spatial coherence ($z$-score) | 0.74 ± 0.1 | 0.79 ± 0.1 | 0.72 ± 0.1 | 0.77 ± 01 |
| Sparsity | 0.36 ± 0.04 | 0.37 ± 0.04 | 0.33 ± 0.03 | 0.32 ± 0.04 |
| Information content (bits/spike) | 1.24 ± 0.2 | 1.26 ± 0.2 | 1.33 ± 0.2 | 1.52 ± 0.2 |

*$P$ < 0.05, **$P$ < 0.005, ***$P$ < 0.0001, significant difference between control- and lesion-group cells.
†$P$ < 0.05, ††$P$ < 0.005, significant difference between baseline and object condition.

bin) was significantly greater in lesion-group cells in both the A and B sessions [see Table 1; two-factor, repeated-measures ANOVA = $F(1,48) = 8.94$, $P < 0.005$]. A three-factor, repeated-measures ANOVA was used to compare the firing rate of control- and lesion-group cells between sessions (A and B, and also A and A′) as well as between conditions (AB and AA′). There were no significant differences between the groups, the sessions or the conditions.

*Spatial Firing Properties*

A three-factor, repeated-measures ANOVA revealed that the size of the place fields of lesion-group cells was significantly smaller than that of control-group cells (see Table 1) across all conditions [$F(1,57) = 6.86$, $P < 0.05$]. There was also a significant difference in the size of place fields between recording sessions; specifically, place fields were always smaller in the second recording session in both control and lesioned animals, regardless of whether the condition was AA′ or AB [$F(1,57) = 11.08$, $P < 0.005$]. There were no significant differences in any other measures of spatial firing, that is: spatial coherence, sparsity or information content (see table 1).

The stability of place fields was measured by comparing their location between the two recording sessions in the AA′ and AB conditions. Two-factor, repeated-measures ANOVAs revealed a significant difference in the distance that the centre of mass (COM) of place fields shifted between groups [$F(1,57) = 11.98$, $P < 0.001$] and between conditions [$F(1,57) = 7.50$, $P < 0.01$]. There was also a significant interaction between group and condition [$F(1,57) = 4.53$, $P < 0.05$; see Fig. 2]. A post-hoc Newman–Keuls analysis determined that the introduction of novel objects into the recording chamber (AB condition) altered the firing of lesion-group place cells significantly more than when the environment was unchanged between recordings (AA′ condition, $P < 0.01$). Furthermore, the effect that novel objects had on place cell firing in lesioned animals was significantly greater than the effect on control animals, which were not significantly affected by the insertion of objects. Figure 3 shows the distribution of the magnitude of place field shifts across the two groups. Figure 4 provides examples of the location of control and lesion-group place fields during the baseline and the object condition. In four cases, pairs of cells were recorded simultaneously in lesioned animals (no control-group cell pairs were recorded). The place fields of both cells in one pair remained stable when the object was introduced. In the other three pairs of cells, however, place fields were

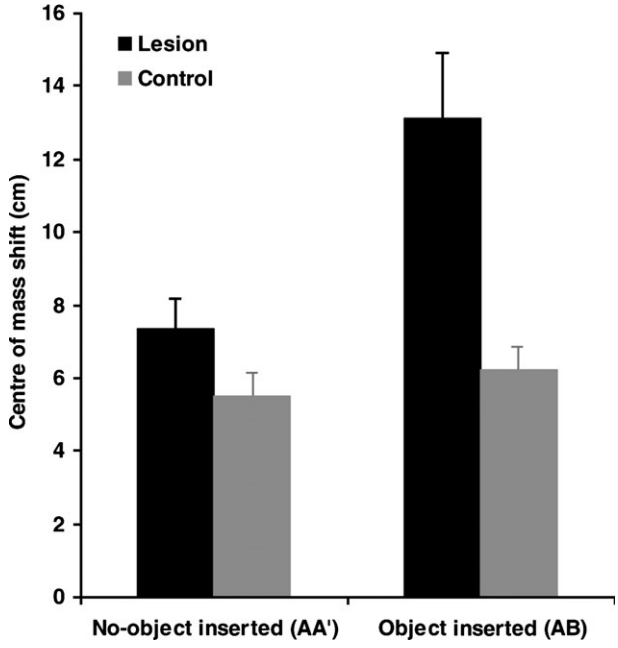


**Figure 2.** The shift in location of place fields of control and lesion-group cells in a control condition (AA′) and when a novel object was introduced into the recording environment (AB condition). Data shown are mean centre of mass shifts ± SEM.

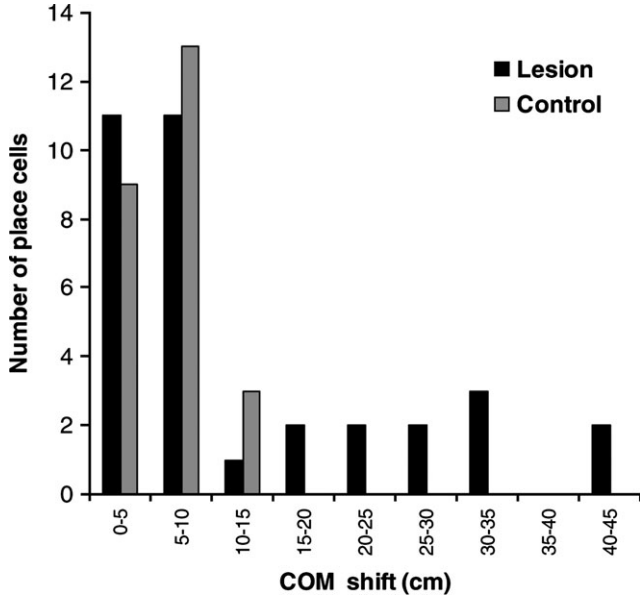


**Figure 3.** The distribution of field shifts in control and lesion-group place cells after novel objects were inserted into the recording environment.

differentially affected by the object. In these cases one field of the pair remained in the same location and the other remapped or disappeared. For several cells of both control and lesioned animals, subfields appeared in addition to the original place field after objects were inserted. Figure 4 provides an example of this. There were no significant differences between the two groups in terms of the percentage of cells in which this occurred.

To ensure that the COM shift effects were distributed across the groups of animals and not just across the groups of cells, a second analysis was conducted wherein the mean COM shift

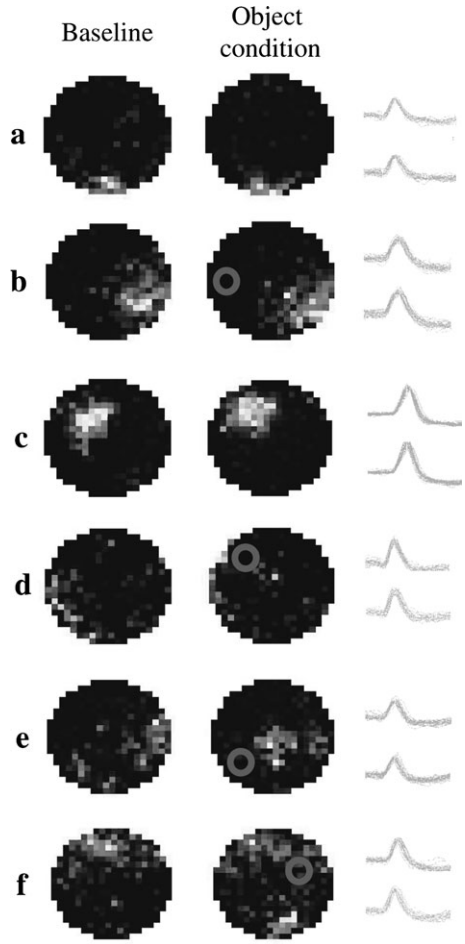


**Figure 4.** Examples of firing rate maps of two control (cells a and b) and four lesion-group place cells (c, d, e and f) during baseline recordings (left). The same cells were recorded immediately afterwards (middle) with an object placed into the recording apparatus at the location marked by the circle (*b*, *d*, *e*, *f*), or in a control condition where the environment was unchanged (*a*, *c*). The lighter coloured pixels correspond to regions where the cell fired at a higher rate. Typically, the cells of control animals fired in the same location during baseline and no-object (e.g. cell a), and object (e.g. cell b), conditions. Cells in lesioned-group animals were also relatively stable in the no-object condition (e.g. cell c). Place field shifts occurred, however, for many lesion-group cells when an object was introduced into the environment (e.g. cells d, e). In other cases new place fields developed (cell f). Examples of spike waveforms are shown for each cell (right) during the baseline (top waveform) and object manipulation conditions (bottom waveform).

value was calculated for each of the animals and then compared across the two groups. As for the original analysis, the COM shift in lesion-group cells was significantly greater when objects were inserted (14.6 ± 1.2 cm) compared with control-group cells (5.2 ± 0.4 cm; $t(8) = 6.74$, $P = 0001$). Furthermore, to investigate the possibility that the rats became used to the novel object insertions with successive trials we examined how the order that the cells were recorded in related to the corresponding COM shift scores. It was apparent that the effect of objects on place cell firing was consistent for the duration of the experiment, as large field shifts were just as likely to be observed in lesion-group cells recorded towards the end of the experiment as they were at the beginning.

To determine whether the place fields of lesion-group cells shifted between or within the recording sessions, a within-session analysis of field position was made by comparing the overall field shift with what had occurred by the first five min of the object condition. The results showed that the change in field position between the no-object recordings and first five minutes of the object session was of a similar magnitude to, and not significantly different from, the overall shift observed. This indicates that the place fields shifted rapidly when the object was introduced into the environment.

An analysis of the data from lesion-group cells was conducted to determine whether field shift was related to the cells' firing properties. There were, however, no significant differences in the firing rate properties (including spike amplitude and spike width) of lesion-group cells that had large place field shifts (>12 cm) compared with those that had small shifts (<12 cm). In addition, the effect of the object on place cell firing properties was examined, taking the distance between the novel object and the place field location into account. There was no correlation between distance and the subsequent firing rate, place field size or the magnitude of place field shift for cells of lesioned and control animals.

*Theta cells*

Fourteen theta cells were recorded from three control animals and sixteen cells were recorded from five lesioned rats during single 5 min sessions whilst the rats foraged in the cylinder. No objects were introduced during these sessions. Compared to the total number of hippocampal neurons recorded from control and lesioned rats, the percentage of theta cells was not significantly different between groups (36 and 31% control and lesion-group cells respectively; Yates corrected $\chi^2 = 0.025$, $P = 0.87$). The mean peak-to-trough spike amplitude of control- and lesion-group cells was not significantly different (220 and 240 μV respectively), and neither was the mean peak-to-trough spike width (318 and 340 μs). The overall mean firing rate was also not significantly different (22.8 and 22.3 Hz control/lesion-group cells respectively).

*Behavioural Correlates*

The running speed of the rats was categorized into four 10 cm/s bins. There was minimal data generated at >40 cm/s. A two-factor, repeated-measures ANOVA revealed that there were no differences between control and lesioned animals in the time spent moving at each speed, although there was a significant difference in the time spent across the bins within both groups [$F(3,162) = 2376$, $P < 0.0001$]. There was also no significant difference in mean speed between the two groups, or in the mean speed between the AA′ and AB conditions. The mean speed of control animals was 9.8 cm/s in the AA′ condition and 10.0 cm/s in the AB condition. Similarly, the mean speed of lesioned rats was 9.9 and 9.7 cm/s respectively.

***Experiment 2***

*Basic Firing Properties of Place Cells*

A total of 54 place cells were recorded, 27 cells were from control animals and 27 from lesioned animals. There were no less than three cells recorded from each of the three control and three lesioned rats. In this experiment, cells that generated <40 spikes were excluded from the data analysis. This value was lowered from the 50 spikes used in experiment 1 as otherwise too much data was lost due to reductions in the firing that occurred in some cells after track rotations. A two-factor, repeated-measures ANOVA revealed that there was no significant

difference in the mean peak-to-trough spike amplitude between the two groups, (see Table 2). There was, however, an effect of rotation [$F(1,52) = 8.42$, $P < 0.01$], whereby the spike amplitude of cells was reduced in recordings made after the track was rotated compared with recordings in the baseline condition. There was no group by rotation interaction, but some evidence to suggest that spike amplitudes were increased in the lesion-group cells that had disrupted spatial firing following the rotation (see below). There were no differences in the mean peak-to-trough spike width between groups or conditions. To assess complex spike bursting, interspike interval histograms were generated for each cell in order to ascertain the proportion of spikes occurring at intervals of 2–10 ms. A two-factor, repeated-measures ANOVA showed a significant difference in cell bursting between track conditions in both control- and lesion-group cells, indicating that cell bursting was lower after the track was rotated [$F(1,52) = 5.21$, $P < 0.05$; see Table 2]. There was no effect of group and no interaction.

An analysis of the overall firing rate (FR; a two-factor, repeated-measures ANOVA), indicated that there was no main effect of group, or rotation but a significant interaction [$F(1,52) = 7.55$, $P < 0.005$; see Table 2]. A post-hoc Newman–Keuls analysis determined that the FR of control-group cells was significantly higher after the track was rotated ($P < 0.05$), and also significantly greater than lesion-group cells post-rotation.

*Spatial Firing Properties*

There were no significant differences between control and lesion-group cells or between baseline and track rotation conditions when place field sizes were compared (see Table 2). The spatial coherence of place fields was also not significantly different between the groups but was significantly different between rotation conditions [two-factor, repeated measures ANOVA = $F(1,52) = 6.90$, $P < 0.05$]. There was a significant group by rotation interaction [$F(1,52) = 6.34$, $P < 0.05$], and post-hoc Newman–Keuls analysis indicated a greater reduction in the coherence of lesion-group cells after the track was rotated ($P < 0.01$). The information content of spikes decreased after rotation of the track in cells of both groups also [$F(1,52) = 4.49$, $P < 0.05$]; however, there was no main effect of group and no interaction. There were no significant differences between groups or rotation conditions for sparsity (see Table 2).

A comparison of vector length (two-factor, repeated-measures ANOVA), revealed no main effect of group but a significant main effect of rotation [$F(1,52) = 5.23$, $P < 0.05$] and a significant group by rotation interaction [$F(1,52) = 4.81$, $P < 0.05$]. A post-hoc Newman–Keuls analysis revealed that the vector length was significantly lower in cells of lesioned animals compared with controls after the track was rotated 90° ($P < 0.05$; see Fig. 5). To ensure that the differences in vector length were distributed across the groups of animals and not just across the groups of cells, the data were reanalysed by calculating a mean change in vector for each rat and then comparing lesion and control groups. The results were consistent with the cell-level analysis in that the rotation-induced change in vector length was significantly greater for lesion-group animals ($U$-test, $z = 2.40$, $P = 0.01$).

In order to gauge whether this change in vector length occurred immediately following the rotation or at some time during the second recording session, the 10 min recording was separated into two 5 min halves and vector length was reanalysed. There was no significant difference in the vector length of lesion-group cells between the first and second 5 min of recordings post-rotation. Since the vector length in each of these sub-sessions was similar to the pre-rotation condition this suggests that for some cells a change in field angle may have occurred mid-session.

The Rayleigh test determined that the firing of all control-group cells (27/27) was non-randomly distributed (significantly clustered) around the track, during both the baseline and rotation conditions. Similarly, all cells (27/27) from lesioned animals displayed significant clustering in the baseline condition. In the rotation condition, however, 6/27 cells from lesioned animals (but no control cells) lost this clustering (Yates corrected $\chi^2 = 4.69$, $P < 0.05$).

A further analysis assessed the firing properties of the lesion-group cells that did not have significant spatially clustered firing in the post-rotation condition. The spike amplitude of these cells ($n = 6$) was compared with that of control-group ($n = 27$) and lesion-group ($n = 21$) cells that remained significantly

**Table 2**
A comparison of firing properties of cells across baseline and cue rotation conditions (mean ± SEM)

| | Control ($n$ = 27) | | Lesion ($n$ = 27) | |
|---|---|---|---|---|
| | Baseline | Rotation | Baseline | Rotation |
| Spike amplitude (μV) | 240 ± 22** | 235 ± 22 | 266 ± 22** | 248 ± 22 |
| Spike width (μs) | 593 ± 14 | 593 ± 11 | 587 ± 9 | 581 ± 15 |
| Spikes with 2–10 ms ISI (%) | 33.8 ± 4.3* | 29.6 ± 4.0 | 32.3 ± 4.0* | 24.0 ± 4.0 |
| Overall firing rate (Hz) | 1.34 ± 0.3*† | 1.74 ± 0.6† | 1.26 ± 0.21 | 0.97 ± 0.26 |
| Field size ($cm^2$) | 555 ± 53 | 593 ± 58 | 587 ± 51 | 557 ± 57 |
| Spatial coherence ($z$-score) | 0.89 ± 0.1 | 0.89 ± 0.1 | 1.02 ± 0.1** | 0.77 ± 0.1 |
| Sparsity | 0.19 ± 0.03 | 0.22 ± 0.03 | 0.22 ± 0.02 | 0.22 ± 0.03 |
| Information content (bits/spike) | 2.14 ± 0.2* | 1.96 ± 0.2 | 2.07 ± 0.16* | 1.98 ± 0.2 |

*$P < 0.05$, **$P < 0.01$, significant difference between baseline and rotation conditions.
†$P < 0.05$, significant difference between control- and lesion-group cells.

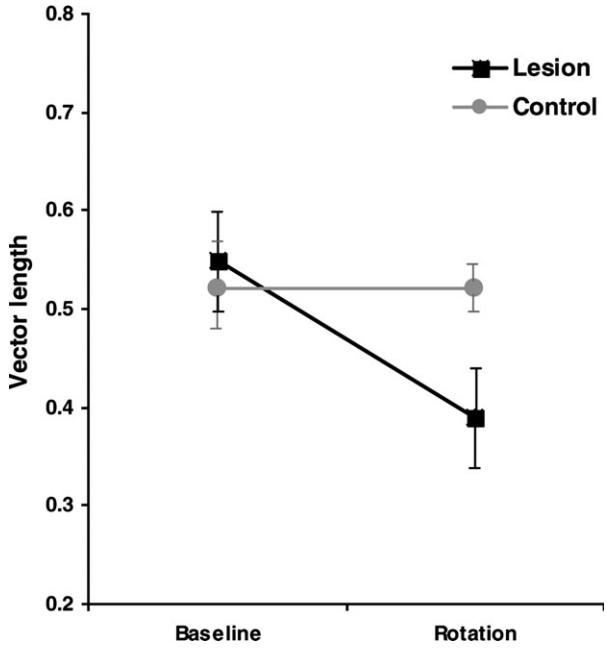


**Figure 5.** The mean length of the vector that describes the radial distribution of firing in the circular track during the baseline and track rotation conditions. The vector length of animals with prefrontal lesions is markedly decreased after the rotation, indicating that firing fields have become more dispersed.

clustered. A two-factor repeated-measures ANOVA revealed significant main effects of cell group [$F(2,78) = 4.14$, $P < 0.05$], rotation condition [$F(1,78) = 40.03$, $P < 0.0001$] and an interaction [$F(2,78) = 8.59$, $P < 0.0005$]. Post-hoc Newman–Keuls analysis indicated that the spike amplitude of non-clustered cells (319 ± 52 and 288 ± 58 μV baseline/rotation condition respectively) was significantly greater than that of both the clustered lesion group cells (251 ± 24 and 238 ± 23 μV; $P < 0.01$) and control-group cells (240 ± 22 and 235 ± 22 μV, $P < 0.01$) both pre- and post-rotation.

The amount of angular change in place field position was also compared between the baseline and rotation condition by calculating the absolute difference in the angular position of the fields in the two conditions. Both control and lesion-group place fields were rotated significantly [compared with zero, control: $t(26) = 4.69$, $P < 0.0001$; lesion: $t(26) = 5.89$, $P < 0.0001$] around the track following the rotation. There was, however, no significant difference between the two groups in the change in angular field position, although for lesion-group cells the change was greater (45.13 ± 9.6 and 53.20 ± 9.0° for control- and lesion-group cells respectively). A similar analysis of place field rotation that took into account the direction of rotation of the apparatus revealed that across the whole population of cells, place field rotations were close to zero (4.9 ± 13.0 and –1.21 ± 14.0° for control- and lesion-group cells respectively; $P > 0.05$). Figure 6 shows the distribution of absolute angular field changes after rotations for both groups of cells. In order to determine whether the reduction in vector length (indicating greater dispersion of firing) observed in lesion-group cells was a result of a rotation of the field during the post-rotation recording session, the angle of firing between the first and second half of the post-rotation recordings was compared. This was 36 ± 9° [$t(25) = 4.26$, $P < 0.0005$ compared with zero], indicating that a significant field shift occurred within this session. The fact that vector length was similar across the two halves of the session, however, indicates that some cells may have had field position shifts around the midpoint of the recording.

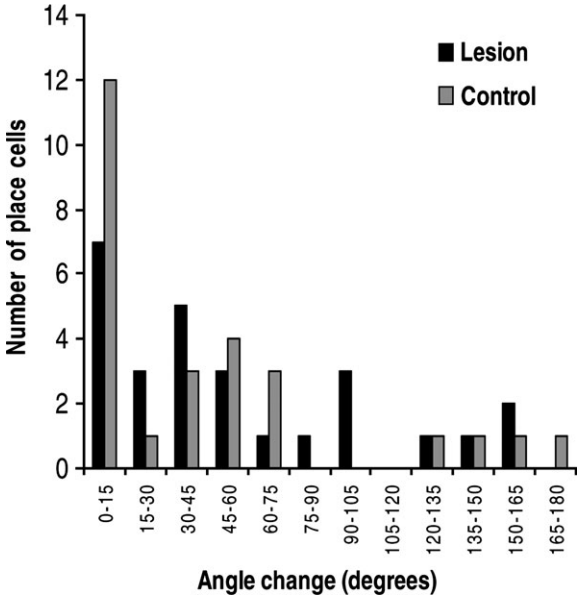


**Figure 6.** The distribution of absolute changes in angle of firing for control- and lesion-group cells after 90° rotations of the track.

The fields of three control-group cells acquired new fields after the rotation and the within-field firing of two other cells virtually disappeared. No new fields were acquired for lesion-group cells after the rotation, however, six fields disappeared. Figure 7 provides examples of place field distributions during the baseline condition and after the track was rotated 90°. In this experiment 15/27 lesion-group and 13/27 control-group cells were recorded simultaneously with at least one other cell. The fields of three pairs (and one triplet) of lesion- and one pair of control-group cells behaved similarly after rotations of the track (i.e. all fields remained stable or all changed their firing patterns) whereas the fields of three pairs of lesion- and four pairs (and one triplet) of control-group cells responded differentially after track rotations.

*Behavioural Correlates*

The running speed of the rats over the 10 min recording sessions was categorized into four 10 cm/s bins. A two-factor, repeated-measures ANOVA revealed that there were no differences between control and lesioned animals in the time spent moving at each speed, although for both groups, there was a significant difference in the time spent across the speed bins [$F(3,156) = 459$, $P < 0.0001$]. There was, however, a significant group by speed interaction [$F(3,156) = 3.15$, $P < 0.05$], which indicated that control animals spent less time than lesions

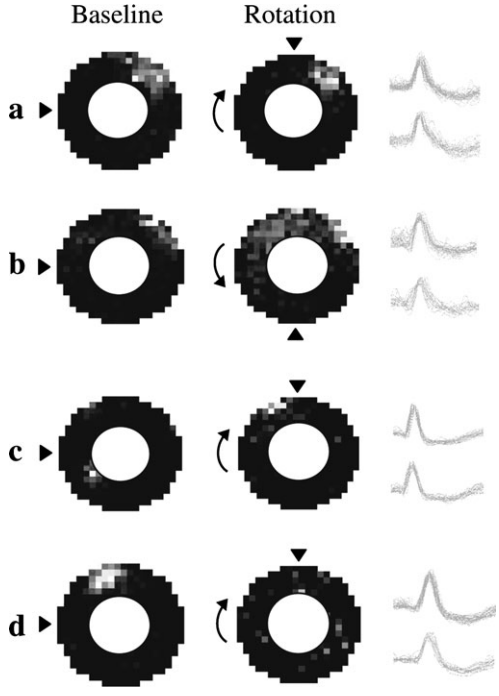


**Figure 7.** An example of firing rate maps from one control (*a*) and three lesion (*b–d*) group cells. Maps show the location of place field distributions during baseline and rotation conditions in the circular track. The lighter coloured pixels correspond to regions where the cell fired at a higher rate. The triangles mark a reference point on the track relative to the room and the arrows mark the direction of rotation. Typically cells of control animals fired at the same location in both conditions (e.g. cell a) as did many lesion-group cells. In other lesion-group cells the FR distributions became more dispersed after the track was rotated (e.g. cell b), rotated with the track (e.g. cell c) or disappeared as the cells became silent (e.g. cell d). Examples of the spike waveforms are provided for each cell in the baseline (top) and rotation (bottom) condition. Note that cell d virtually shut down after the rotation and as a result few spikes were available for display. The spikes shown in this example may, therefore, have come from another cell.

moving at the lowest (0–10 cm/s) speed. Statistical analyses indicated that the mean running speed of control and lesioned rats was not significantly different, but there was a significant main effect of rotation. A two-factor, repeated-measures ANOVA indicated that for both groups, animals' speed increased after the track was rotated [$F(1,52) = 22.86$, $P < 0.0001$]. However, there was also a significant group by rotation interaction [$F(1,52) = 4.22$, $P < 0.05$], which indicated that the mean speed of control animals increased more than that of lesioned animals after the track was rotated.

## Discussion

The present study tested the hypothesis that prefrontal damage produces an alteration of neural processing within the posterior cortex such that there is a failure to suppress responses to information that may be spurious to the task at hand. Experiment 1 examined the effects of inserting a novel object into an otherwise stable testing environment on the activity of hippocampal place cells in control and prefrontal-lesioned animals. It was shown that the presence of the object caused the location of place fields to shift position by a greater amount in cells recorded from the lesioned animals compared with control-group cells. This finding is consistent with the hypothesis that the firing of lesion-group cells is overly influenced by changes in local environmental cues (Kyd and Bilkey, 2003). The finding that the place fields of lesion group cells were significantly smaller than those of controls is also consistent with this latter hypothesis, on the basis that local cues are likely to provide the animals with better information about their location as a result of their immediate and discrete nature.

Previous studies have shown that in normal animals, stable, distal visual cues predominantly control the response of place cell activity (e.g. O'Keefe and Dostrovsky, 1971; O'Keefe, 1976; O'Keefe and Conway, 1978; Muller and Kubie, 1987). For example, place cells have been shown to fire in the same location relative to distal room cues when the recording apparatus is rotated. Furthermore, rotation of distal cues is accompanied by concurrent rotation of place cells' fields (O'Keefe and Conway; 1978; Kubie and Ranck, 1983; Muller and Kubie, 1987; O'Keefe and Speakman, 1987). Experiment 2 was designed to explicitly test whether, in prefrontal lesioned-animals, familiar, local environmental cues had increased control over place cell firing. This was examined by rotating a circular track containing local surface cues within a stable distal environment.

The results of experiment 2 were consistent with the findings of experiment 1 and showed that the firing distributions of lesion-group cells were more likely to become dispersed compared with baseline recordings following a manipulation of the environment that involved a ninety-degree rotation of the track. This was evident as a reduction in the length of the vector that described the spatial localization of firing, a loss of spatial clustering and a reduction of spatial coherence. Data from within-session comparisons indicated that one explanation of these effects is that lesion-group place fields changed position sometime around the midpoint of the recording. Since the mean angular field change between the baseline and rotation conditions was close to zero degrees for both groups, however, it appears that overall neither lesion nor control-group cells were exclusively controlled by the local cues (where concurrent 90° place field rotations would be expected if this were the case). Rather, in both groups some cells may have been responding to either local or distal cues or combinations of these, as has been reported previously (Young *et al.*, 1994; Knierim *et al.*, 1995; O'Keefe and Burgess, 1996; Shapiro *et al.*, 1997; Tanila and Shapiro, 1997; Fenton *et al.*, 2000; Knierim and McNaughton, 2001; Knierim, 2002).

One plausible explanation for the disruption of firing in lesion-group cells is that these cells were more likely to encode the relationship between local cues and distal stimuli than were control cells. It has previously been suggested that hippocampal neurons code for conjunctions or associations of features (e.g. Rudy and Sutherland, 1989; Sutherland *et al.*, 1989; Eichenbaum, 2000), and studies have shown that some cells in control animals encode configurations of distal stimuli (e.g. O'Keefe and Nadel, 1978; O'Keefe, 1979; O'Keefe and Speakman, 1987; Muller and Kubie, 1987; Hetherington and Shapiro, 1997). In experiment 2, a local–distal cue relationship would have been disrupted by rotation of the track (thus affecting the response of cells in lesioned animals) whereas a distal–distal configuration would not (resulting in control-group cells being unaffected). Alternatively, the place cells of prefrontal lesioned animals may have been more responsive to local cues and also have been slow to respond to the change in environment induced by the rotation such that fields shifted during the recording session and became 'smeared' across time. A further possibility is that prefrontal-lesioned animals might have difficulties recognizing the environment as being the same in the pre and post-object/rotation conditions. This might produce a remapping of place cells as observed in normal animals when the shape of the apparatus in which they are tested is changed (Muller and Kubie, 1987; Quirk *et al.*, 1992), causing place fields to shift to novel locations in the apparatus.

It is unlikely that the alteration of location-related firing in lesion-group cells is the result of behavioural differences between lesioned and control rats. In experiment 2 the experimenter was blind to the rats' lesion-status and was unable to distinguish between the groups on the basis of their behaviour in the apparatus. Furthermore, no between-group difference in running speed was observed in experiment 1, even though increased exploratory activity is a previously reported symptom of prefrontal lesions (Lacroix *et al.*, 1998; Braun *et al.*, 1993). Finally, although the speed of control animals was significantly greater than that of lesioned animals after (but not before) track rotations in experiment 2, the magnitude of this difference was small (1.29 cm/s).

In previous studies it has been shown that damage to brain regions outside of prefrontal cortex also alters the firing properties of hippocampal place cells. For example, separate lesions of both the perirhinal and entorhinal cortices have been shown to cause major disruptions to place cell activity (e.g. Miller and Best, 1980; Muir and Bilkey, 2001). Although this might suggest that damage to *any* region that contributes inputs to the hippocampus will produce such effects, it should be emphasized that in each of these studies the exact nature of the firing disruption was different. In particular, in neither of these previous studies was action potential amplitude altered by the lesion. This suggests that the present effect resulted from changes to different controlling mechanisms than were affected in previous studies.

As predicted by theories in which prefrontal cortex has inhibitory control over posterior cortex (Shimamura, 2000), the results of the current experiments indicate that the lesion-induced changes in hippocampal spatial firing may be the consequence of disinhibition. In experiment 1, spike amplitudes

were significantly greater in lesion-group cells compared with controls. In experiment 2, spike amplitudes were significantly greater in the lesion-group cells that lost their spatial selectivity after the rotation compared with control and lesion-group cells that maintained spatially-selective firing. It is assumed that the former cells are those most affected by the prefrontal lesions, as evidenced by their change in spatial responses. This suggests that there may have been greater variability in cell-level responses to the lesion in experiment 2 compared with experiment 1. Previous evidence suggests that spike amplitude, as measured during extracellular recording, may partially depend on the efficiency with which somatic action potentials back-propagate into the dentritic arbor (Buzsaki *et al.*, 1996; Quirk *et al.*, 2001). Action potential backpropagation (and hence, spike amplitude) can be increased by a reduction in the strength of inhibitory input onto the cell, provided for example by feedback inhibition (Tsubokawa and Ross, 1996). The increased burst-firing in lesion-group cells is also consistent with a disinhibition model as previous studies have shown that increased bursting occurs in the hippocampus when GABAergic inhibition is antagonized (Malouf *et al.*, 1990).

The significance of the spike amplitude results in the current study is that they demonstrate that the prefrontal lesions have a direct effect at the level of the hippocampal place cells, rather than the effect being due to changes in upstream processing. This does not necessarily imply a direct connection between prefrontal cortex and the hippocampus. Rather, there are a number of polysynaptic mechanisms via which a prefrontal lesion could result in a reduction in hippocampal inhibition. A reduction in the firing rate of inhibitory interneurons (Wilson and McNaughton, 1993), a reduction in the number of active interneurons *per se* (Quirk *et al.*, 2001) or a change in the effective coupling between pyramidal cells and interneurons (Csicsvari *et al.*, 1998) could all be implicated. The finding that the proportion of theta cells (putative interneurons) to place cells and the overall firing rate of theta cells were not significantly different between the lesion and control groups suggests otherwise, however (at least for this type of interneuron). Further work will be required to determine what mechanisms are involved, but possibilities include the prefrontal pyramidal cells that regulate the activity of dopaminergic neurons in the ventral tegmental area (VTA; Sesack *et al.*, 1989; Sesack and Pickel, 1992; Taber *et al.*, 1995). It has been shown that prefrontal stimulation increases burst firing of dopamine neurons (Gariano and Groves, 1988; Murase *et al.*, 1993; Tong *et al.*, 1996) and that inactivation of the prefrontal cortex produces the opposite effect (Svensson and Tung, 1989; Murase *et al.*, 1993; Carr and Sesack, 2000). Since the VTA projects to the CA1 layer of the hippocampus (Gasbarri *et al.*, 1994), where dopaminergic neurotransmission is thought to have a role in suppressing hippocampal excitability (Suppes *et al.*, 1985; Gasbarri *et al.*, 1997), a lesion of prefrontal cortex would reduce activity in this inhibitory input. Alternatively, the prefrontal cortex has projections to parahippocampal cortices such as the perirhinal and entorhinal cortices (Groenewegen and Uylings, 2000), and input from these regions reaches the hippocampus via the perforant path (Liu and Bilkey, 1999, Naber *et al.*, 1999; Witter *et al.*, 2000). Since there is some evidence to suggest that a portion of the perirhinal and entorhinal input to CA1 is directly onto inhibitory interneurons (Empson and Heinemann 1995), lesion-induced effects on inhibitory activity could be mediated via this route.

The current findings have significance for our understanding of the effects of frontal lobe damage. For example, humans with frontal lobe damage sometimes exhibit perseveration and an exaggerated dependency on environmental cues in guiding their behaviour (Lhermitte, 1983). We may, therefore, be observing a neural correlate of this effect. The results may also have relevance to several other forms of human pathology that are associated with fronto-temporal lobe dysfunction (e.g. Weinberger, 1999; Heckers, 2001). For example, in individuals with schizophrenia, reduced activation in the dorsolateral prefrontal cortex has been reported and associated with greater activity in the inferior temporal lobe, hippocampus and cerebellum (Meyer-Lindenberg *et al.*, 2001; Weiss *et al.*, 2003).

Shimamura (2000) suggested that an important function of the prefrontal cortex is to inhibit extraneous incoming signals, or noise in other sensory-association areas such as posterior cortex (Frith *et al.*, 1991; Knight and Grabowsky, 1995; Meyer-Lindenberg *et al.*, 2001). This may extend to mediation of the salience of perceptual signals in the hippocampus. According to this model, damage to the prefrontal cortex would cause 'disinhibition' in posterior cortex resulting in a failure of regions like the hippocampus to suppress responses to spurious information. The present study demonstrates that lesions of the prefrontal cortex alter the firing properties of hippocampal place cells in a way that is consistent with this hypothesis.

## Notes

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