Prefrontal Cortex Lesions Augment the Location-related Firing Properties of Area TE/Perirhinal Cortex Neurons in a Working Memory Task

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It has previously been proposed that prefrontal cortex may have some role in keeping temporal cortex-based representations 'on-line' during a working memory task. To test this hypothesis, the effects of electrolytic prefrontal cortex lesions on the firing of area TE and perirhinal cortex (PRC) neurons were examined while rats performed a delayed non-match to position task in the T-maze. The behavioural performance of control ($n = 4$) and lesioned ($n = 4$) animals were similar during this task, and many neurons displayed a statistically significant location-related variation in firing rate during the sample (44/56 neurons) and test (39/56 neurons) phases. Units from prefrontal-lesioned animals (82%) were more likely to display a significant variation in firing across the maze compared to controls (50%; $P < 0.01$), and to have more discrete location-related properties (50% of neurons) compared to the control (5%) group ($P < 0.0005$). This finding suggests that prefrontal cortex normally modulates the transmission and/or processing of spatial information in area TE/PRC during a working memory task. Modulation could be mediated through direct connections between the structures or via prefrontal control of subcortical structures. This finding has implications for our understanding of prefrontal-temporal involvement in memory and cognitive disorders.

Introduction

Inferotemporal cortex regions such as area TE and the perirhinal cortex (PRC) appear to be located at an interface between perceptual and memorial processing (Nakamura and Kubota, 1996). Neurons in these areas respond selectively when monkeys are presented with specific objects such as hands and faces (Gross, 1992) and stimulus-specific responses have also been observed in neurons recorded from homologous regions of the rat (Zhu and Brown, 1995; Young *et al.*, 1997). These findings suggest that neurons in area TE and PRC are part of an object recognition network. Neurons in these regions also display object-specific activity during the delay period of a memory task (Desimone, 1996) and respond to the relative familiarity of a stimulus (Brown and Xiang, 1998), indicating that they may also participate in memorial processes. This latter proposal is supported by findings that lesions to the PRC and neighboring regions such as entorhinal cortex and hippocampus produce deficits in declarative memory processing (the ability to store new facts and events) in both rats and primates (Squire, 1992; Meunier *et al.*, 1993; Eichenbaum *et al.*, 1994; Jarrard, 1995; Wiig and Bilkey, 1995; Murray, 1996; Corkin *et al*, 1997; Ennaucer and Aggleton, 1997; Liu and Bilkey, 1998; Kornecook *et al.*, 1999).

The prefrontal cortex region also appears to play a crucial role in many memorial processes (Goldman-Rakic, 1995; Shimamura, 1995). Lesions of prefrontal cortex produce working memory deficits in both primates and rats (Goldman and Rosvold, 1970; Shaw and Aggleton, 1993; Granon *et al.*, 1994; Shimamura, 1995; Bilkey and Liu, 2000), and it has been shown that neurons in prefrontal cortex are active during working memory processing (Goldman-Rakic, 1995; Miller *et al.*, 1996; Funahashi *et al.*, 1997). It has been proposed that one function of this region may be to activate object representations during the performance of a working memory task (Baddeley, 1986). Since object representations may be stored in inferotemporal cortex regions such as area TE and PRC, it follows that prefrontal cortex may perform this function via the reciprocal connectivity between these structures (Guldin and Markowitsch 1983; Markowitsch and Guldin, 1983; Sesack *et al.*, 1989; Takagishi and Chiba, 1991; Burwell *et al.*, 1995; McIntyre *et al.*, 1996; Rempel-Clower and Barbas, 2000). One prediction of this model is that lesions of prefrontal cortex should alter the firing behaviour of neurons in area TE and PRC while an animal is involved in a working memory task. The aim of the present study is to explicitly test this hypothesis.

Materials and Methods

Subjects

Nine male Sprague–Dawley rats, weighing between 300 and 500 g at the time of surgery, were individually housed in wire mesh cages and maintained on a 12 h light–dark cycle. Subjects had free access to water and food pre-surgery and for 2 weeks post-surgery, but were food-deprived to 85% of their free-feeding body weight during the experimental period. After the surgery the rats were returned to their home cages to recover for 10 days or more prior to the start of the training protocol. Surgical and behavioral procedures were conducted during the light cycle. The rats were examined daily for their state of health and adequate measures were taken to minimize pain and discomfort where necessary. The research was approved by the University of Otago Animal Ethics Committee and used procedures in accordance with guidelines laid down by the NIH in the US regarding the care and use of animals for experimental procedures.

Electrode Implantation and Lesions

The rats were deeply anaesthetized with sodium pentobarbital (50 mg/kg, i.p.) and placed in a stereotaxic apparatus where body temperature was maintained at 37°C. A midline incision was made, the scalp retracted to expose the skull and trephines were drilled at the coordinates 5.5 mm posterior to Bregma and 5.5 mm lateral to the midline. One miniature moveable Scribe microdrive (Bilkey and Muir, 1999) was chronically implanted into the temporal cortex. The electrode tips were initially located in area TE, above the PRC [4 mm ($n = 8$) or 4.5 ($n = 1$) deep measured from the dural surface] and oriented laterally at 10° from the vertical. In four rats electrolytic prefrontal cortex lesions were made at the coordinates 2.0, 3.0, 3.0 and 4.5 mm anterior to Bregma and 1.6 mm lateral to the midline. The monopolar lesioning electrodes, which were constructed of 125 μm diameter Teflon-coated wire, were lowered to a depth of 2.0, 2.1, 1.3 and 1.0 mm respectively from the cortical surface with a medial orientation of 16° from the vertical. The lesions were created by passing DC current at 2 mA through these electrodes for 8–10 s at each anterior–posterior position. Five sham rats were operated in the same manner as for experimental groups except that lesioning electrodes were not lowered into the brain. Several anchor screws were implanted in the skull, one of which was used as a ground lead. The electrode implants were encased in dental acrylic.

Unit Recording

The recording electrodes consisted of a bundle of eight Formvar-insulated 25 μm diameter nichrome wires twisted together and threaded inside a 30 gauge guide tube (hypodermic needle) mounted on the microdrive. The electrode tips were cut obliquely just prior to the surgery so that ~3 mm extended from the cannula. Extracellular spikes were recorded via a Field effect transistor (FET) source-follower head-stage mounted on the animal's head with a quiet electrode used as an indifferent. The output signals were filtered between 300 Hz and 5 kHz, amplified 10 000 times, digitized at 28 kHz by a DigiData 1200 series interface (Axon instruments) under the control of AxoScope (Axon instruments) and stored on a personal computer for off-line analysis. The animal's location was monitored by a video camera mounted on the ceiling of the recording room. This was connected to a computerized tracking system that monitored the position of two infra-red light-emitting diodes (LEDs), mounted on the head-stage 12 cm apart and parallel to the longitudinal body axis, at a 25 Hz sampling rate. This positional information was made available to the DigiData acquisition system, which simultaneously acquired any activity from the unit electrodes that passed a user-specified voltage threshold. The experimenter manipulated pushbuttons connected to the data acquisition system to indicate whether a particular trial was the sample or test phase of the procedure. The start of each phase was designated to begin 2 s before the onset of the trial and to finish 2 s after the animal reached the end point of the arm. The signal generated by these button presses was stored simultaneously with the electrophysiological and tracking data.

Data Analysis

Single units were discriminated from noise during off-line analysis that utilized custom-built template-matching software. Unit firing was mapped onto the animal's position within the environment and normalized for time-in-location (dwell time). Place fields were represented as firing rate maps where the mean firing rates calculated over 10 trials were condensed into square 3 × 3 pixel maps such that the interior of the T-maze was subdivided into five pixels (three along the top and two down the stem). Any pixel that was undersampled (dwell time of <200 ms) during a trial was marked as a missing value for subsequent analysis. In order to determine whether a unit's firing rate varied according to the animal's location in the apparatus, frequency of firing was compared across each of the five subregions of the T-maze with a one-way, repeated-measures analysis of variance (ANOVA; Gbstat). Missing values were replaced with the average value of all other pixels during this procedure. When significant location-related firing was observed, a multiple comparisons test (Newman–Keuls) was then conducted in order to determinate within which subregions this occurred. Finally, a Student's *t*-test was utilized to determine whether there was a significant difference in the firing rate of each unit when firing was compared only at the distal end of the left and the right arm of the T-maze. The sample and test phases of the procedure were analysed separately. Where unit activity was also recorded in the open environment, firing rate maps were generated as above except that the environment was represented as a 10 × 10 pixel array.

Apparatus and procedures

During the T-maze procedure rats were tested in a black-painted wooden apparatus as utilized previously (Wiig and Bilkey, 1994; Liu and Bilkey, 1998). The floor of the maze was 12 cm wide, the sides were 10 cm high, the stem was 74 cm long, and the arms were 30 cm long. The starting area was separated from the rest of the maze by a guillotine door that was located 36 cm from the beginning of the stem. Wooden sliding doors were positioned at the entrance to each arm and there was a recessed food well at the end of each arm into which chocolate reward could be placed. The maze was elevated ~1 m above the floor. Room cues were stable throughout the procedure. The rats were transported from the home cage to the recording room in a black box, which was placed next to the behavioural apparatus and used to hold the animals between each trial.

For the open-field procedures three rats were also recorded while moving freely in a grey-painted chamber (60 × 57 cm), the sides of which were 34 cm high. Three sides were wooden and grey-painted and one was constructed of Plexiglas. The animals foraged freely for food (chocolate hail) in this open field. The open field was located in the same position in the room as the T-maze. Background masking noise was provided by a speaker located on the ceiling of the recording room during both open field and T-maze procedures.

Training Procedures

Shaping

For the first 2 days of training, pieces of reinforcer (small pieces of chocolate) were scattered throughout the entire maze while electrolytic lesioned and sham controls were allowed to explore the environment for 10 min each. On day 3, 10 trials were conducted during which the rats were trained to enter an open arm (the other arm was closed with the sliding door). These trials were initiated by placing each rat into the start box and then immediately opening the guillotine door. Reinforcement was provided only when the rat had reached the end of the open arm. The rat was removed from the maze after eating. The location of the open arm was varied between trials according to a pseudorandom schedule.

Training

Each training trial consisted of a sample phase and a test phase. This procedure was initiated by placing the animal in the start box with the door raised and waiting until it entered the maze stem. During the sample phase, the rat was forced to enter one arm of the T by closing the door to the other side. The location of the open arm was varied between trials according to a pseudorandom schedule. The rat was then removed and placed in the start box with the sliding door closed. The junction point of the maze was wiped with a damp rag during this delay period in order to remove olfactory cues. After a delay period of either 0 s in early trials and then 15 s for later sessions the start box door and the two sliding doors were opened, which permitted the rat access to either arm. The rat was rewarded for entering the arm that it had not visited during the sample phase. It was then removed from the maze and returned to the holding box to await the next trial. Ten trials were run per day until rats reached criterion performance (80% or better correct over 30 trials) with a 15 s delay period inserted between the sample phase and test phase.

Data recording

Each electrode was checked once per day for unit activity by recording from the animal while it moved freely about in the open field. When a unit with a signal-to-noise ratio of at least 3:1 was evident the rat was run for 10 trials (5 left, 5 right) in the T-maze while electrophysiological data were recorded. In one case recording was repeated on the following day without intervening electrode movement with the T-maze rotated around its central axis so as to be positioned 90° clockwise and then 90° counterclockwise relative to its normal location in the recording room. Three of the animals (two lesion, one control) were also recorded for a further 10 min as they roamed freely in the open field, foraging for chocolate pieces scattered randomly around the environment. At the end of each recording session, the electrode was advanced a minimum of 40 μm. The electrode was allowed to settle for at least 24 h before further recordings were made. In the few cases were a neuron was recorded on the same wire before and after a 40 μm electrode shift, careful analysis of waveshape, firing rate and behaviour was made in order to prevent resampling of the same unit.

Histological Procedure

On completion of the recording and behavioral experiments, the electrode tip locations were marked by passing DC current at 2 mA through the recording electrodes. The rats were then perfused through the heart with saline (0.9%), followed by a 10% formalin solution in 0.9% saline. The brains were removed and immersed in 10% formalin solution for 1 day or more and then switched to a 30% sucrose-formalin solution for 3–5 days. Each brain was sectioned (60 μm) in the coronal plane on a cryostat, mounted on slides, and stained with thionin. Coronal sections were selected from each rat at locations 4.5–6.5 mm posterior to Bregma to determinate the track of the electrode and 1.0–5.5 mm anterior to Bregma to determinate the location and size of the prefrontal cortex lesions.

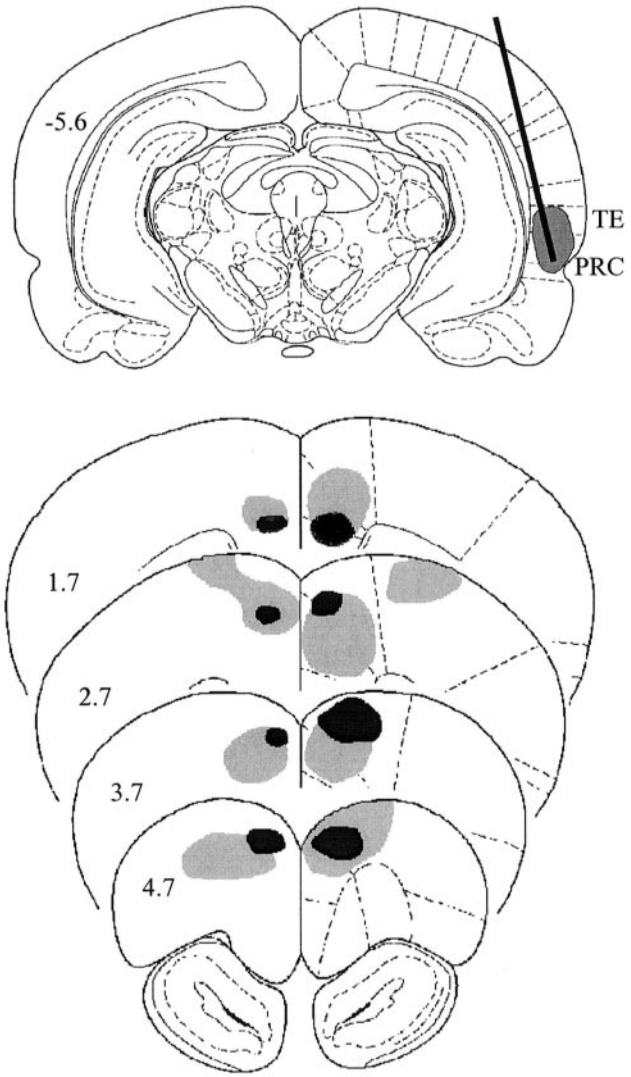

Figure 1. (Top) A coronal section through temporal cortex showing a typical electrode tract (dark line) and the region of area TE and PRC from which single units were recorded (shaded area) as the electrodes were moved through this tissue. (Bottom) Diagrams of coronal sections through the anterior regions of the rat brain with the solid area illustrating the smallest, and shaded area illustrating the largest, extent of the prefrontal lesions. Numbers represent the anterior–posterior distance from bregma of each section. Based on the Paxinos–Watson atlas (Paxinos and Watson, 1998).

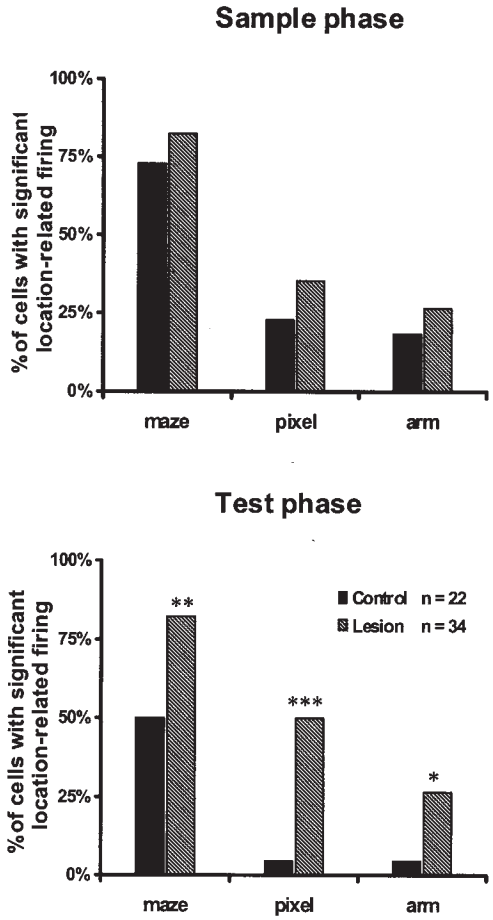

Figure 2. The percentage of neurons recorded from area TE and PRC that displayed statistically significant location-related changes in firing rate during the DNMP procedure. Data from the sample and test phase of the procedure are presented separately, as are the results for three different measures of spatial resolution. The left columns represent cells that had significant location-related firing at some position or positions within the t-maze. The middle columns represent the subset of these cells where location-related firing was specific to one pixel of the maze. The right columns illustrate a comparison of firing in the left and right arms of the maze. Key: $*P < 0.05$; $**P < 0.01$; $***P < 0.0005$ compared to controls.

Results

Histological Results and Electrode Location

Lesion sites and electrode tracks were examined under a light microscope in order to determine their extent and position respectively. In eight of the nine animals the recording electrode track could be seen to have passed through area TE and in three lesion and two control animals, into the PRC (Fig. 1). In the ninth (control) animal the guide tube was misaligned (due to an error in stereotaxic placement) and the electrode tip was identified as being in the most lateral extent of the hippocampus. Data from this animal was removed from further analysis. Our previous experience in the temporal cortex region indicated that when recording electrodes are too dorsal, units respond to auditory stimulation (as a result of being in auditory cortex). No examples of this type of response were noted in the present case, which provides a functional measure of the dorsal limits of electrode placement.The extent of the prefrontal lesions (Fig. 1) was similar, although less extensive than that described by Bilkey and Liu (Bilkey and Liu, 2000). All rats in the lesion group had bilateral damage to FR2 as described by Zilles (Zilles, 1990). One animal also had bilateral involvement of FR1 and two had lesions that extended into the dorsal portion of cingulate area CG1.

Behavior in the T-maze

Recording sessions were initiated once animals achieved the criterion of 80% correct on the delayed non-match to position (DNMP) task. During subsequent recording their performance averaged 83.5% correct for control animals and 84.6% correct for the lesioned group. These values were not significantly different from each other. There was also no significant between-group difference in terms of the mean amount of time that animals spent completing a trial.

Spatial Firing Characteristics in the T-maze

A total of 56 well-isolated units were recorded during the behavioural procedure. Twenty-two of these units were recorded from four sham control animals and 34 from the four lesioned animals. The mean firing rate calculated over all the units was 15.1 Hz and

Table 1
Firing characteristics of area TE/PRC neurons (mean ± SEM)

	n	Firing rate (Hz)			Spike width (μs)
		Overall	Test phase	Sample phase	
Control	22	14.4 ± 2.0	14.4 ± 2.0	14.4 ± 2.0	395 ± 24
Lesion	34	16.4 ± 1.7	16.8 ± 1.7	16.0 ± 1.6	383 ± 24

the mean spike width was 0.387 ms. There were no significant differences between the lesion and control groups in terms of these two parameters [firing rate, $t(51) = 0.34$, $P = 0.73$; spike width, $t(50) = 0.39$, $P = 0.69$]. These data are summarized in Table 1. All of the units fired across the full extent of the environment but for most (79%) units there were statistically significant ($P < 0.05$) variations in this firing rate (as determined by the ANOVA measure) that were related to the location of the animal within the apparatus.

Sample Phase of DNMP Procedure

Most units (44/56) displayed a statistically significant, location-related variation in firing rate across the T-maze during the sample phase of the procedure, as determined by ANOVA (Fig. 2). There was, however, no significant difference in the proportion of units that displayed location-related firing when the lesion (82%) and control (73%) groups were compared (Fisher's exact test, $P = 0.29$). As a measure of the specificity of this firing rate variation, a multiple-comparisons test revealed that in 35% of the units from lesion animals a significant change in firing rate occurred in only one subregion (pixel) of the maze. Slightly less specificity was observed in control rats, where 23% of units responded in this manner, although this between-group difference was not statistically significant (χ^2, $P = 0.32$). There was also no statistically significant difference between the proportion of lesion (27%) and control (18%) cells that had a difference ($\alpha = 0.05$) in firing rate in the left and right arm of the T-maze (Yates corrected χ^2, $P = 0.69$).

The variation in each unit's firing rate across the surface of the T-maze was also examined by determining the minimum and maximum firing rates observed across the maze for each unit and comparing these values across the two groups. A two-factor, repeated-measures ANOVA that compared minimum versus maximum rates in cells from control and lesioned rats revealed that there was no effect of group [$F(1,54) = 0.1$, NS]. There was, however, a significant rate effect [$F(1,54) = 61.1$, $P < 0.0001$] and, importantly, a significant group by rate interaction [$F(1,54) = 9.5$, $P < 0.005$]. This latter effect was a result of there being a markedly higher maximum firing rate in lesioned animals as compared to controls (Newman–Keuls test $P < 0.01$) whereas the difference in the minimum firing rate was not significantly different.

Test Phase of DNMP Procedure

Many units (39/56) displayed a statistically significant variation in firing rate across the T-maze during the test phase, as determined by a repeated-measures ANOVA (Fig. 3). Furthermore, units from lesioned animals (82%) were more likely to display a significant variation in firing across the maze as compared to units from control (50%; $\chi^2 = 6.6$, $P < 0.01$) rats (Fig. 2). As a measure of the specificity of this firing rate variation, a multiple-comparisons test revealed that in 50% of the units from lesion animals a significant change in firing rate occurred in only one subregion (pixel) of the maze. Significantly less specificity was observed in control rats, where only 5% of units responded with such specificity ($\chi^2 = 12.7$ $P < 0.0005$). There was also a significant difference in the proportion of lesion (27%) and control (5%) units that displayed a significant difference in firing rate in the left versus right arm or vice versa (Fisher's exact test; $P < 0.05$). It is of interest to note that in a survey of all units, significant variations in activity were observed to occur in all subregions of the maze except for in the pixel corresponding to the choice point, at the top of the stem, where no units changed their firing rate.

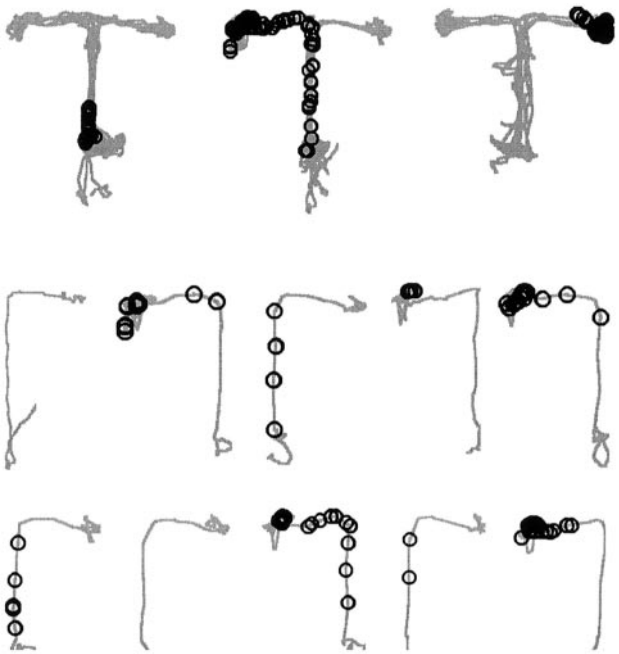

Figure 3. (Top) Examples of location-related firing in three different neurons (left to right) recorded from area TE and PRC of temporal cortex while a rat performed the test phase trials of a DNMP task in the T-maze. The grey lines represent the movements of the animal during a series of 10 trials directed to the left and right arm. The dark circles indicate the positions at which the neuron being recorded from fired at a rate that was above a preset threshold. Note that each neuron fires above this rate in only a subregion of the whole maze. (Middle and bottom) Data, presented as above, for one neuron recorded over 10 individual DNMP test trials with one trace per trial. Note that the neuron consistently fires at a higher rate in the stem and left arm of the T-maze.

The way in which a unit's firing rate varied across the surface of the T-maze was also examined by determining the minimum and maximum firing rate for each unit and comparing these values across groups. A two-factor, repeated-measures ANOVA that compared minimum versus maximum rates in cells from control and lesioned rats revealed that there was no effect of group [$F(1,54) = 0.1$, NS}, but an effect of rate [$F(1,54) = 59.6$, $P < 0.0001$], and most interestingly a significant group by rate interaction [$F(1,54) = 11.3$, $P < 0.005$]. This latter effect was a result of there being a markedly higher maximum firing rate in lesioned animals as compared to controls (Newman–Keuls test $P < 0.01$), whereas the difference in the minimum firing rate was not significantly different (Fig. 4).

Firing During Rotations and in the Open Field

One unit that was recorded from a lesioned animal and that had an increased firing rate in the stem and left arm of the T-maze was also recorded 24 h later with the maze rotated 90° clockwise and 90° counterclockwise about its central axis (Fig. 5). It appeared that the firing 'field' rotated with the maze during the initial counterclockwise rotation. With a subsequent clockwise

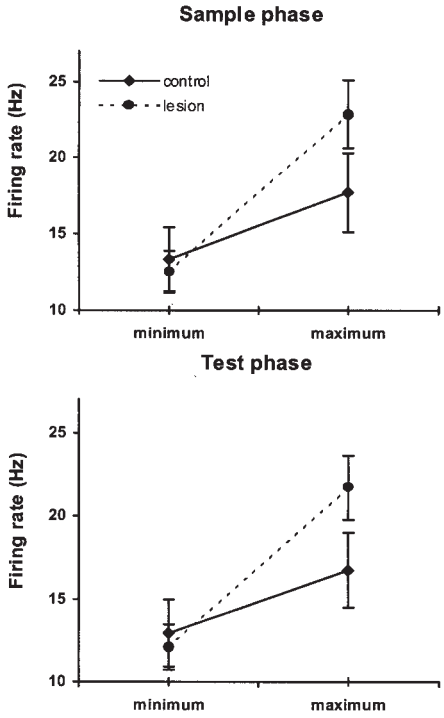

Figure 4. A graph illustrating the mean (± SEM) minimum and mean maximum firing rate recorded in the T-maze. Data from the test and sample phase of the DNMP procedure are represented separately. Note that neurons in prefrontal-lesioned rats have a higher maximum firing rate than neurons in control animals but that there was no between-group difference in the minimum firing rate recorded. As a result there was a significant group by rate interaction in both the sample [$F(1,54) = 9.5$, $P < 0.005$] and test phase [$F(1,54) = 11.3$, $P < 0.005$] of the procedure.

rotation, however, the field also included the right arm. When this cell was subsequently recorded in the open field it had a higher firing rate in the lower portion of the environment, i.e. the region of space that had originally contained the stem of the T-maze (Fig. 5). In total, 15 units from lesioned animals and 4 units from control animals were also recorded in the open field. In most of these neurons there seemed to be no systematic relationship between firing rate and location in this evironment. In particular, apart from the one example cited above, in 10 cells that had location-related firing in the T-maze, there was no evidence to suggest a corresponding location-related firing in the open field (Fig. 5).

Cell Firing Characteristics and Spatial Response

A comparison was made between the spike width of control units that did and did not display a significant variation in firing rate across the surface of the maze during the test phase in order to determine whether these might have represented different populations of cells. The results of a *t*-test revealed that there was no significant difference in this parameter.

Discussion

The results of the present study demonstrate that a large proportion (79%) of neurons recorded from area TE and PRC of rats display significant location-related firing when the animal is performing a DNMP procedure in the T-maze. This finding is consistent with the results of one previous study where location-related behaviour was observed in PRC neurons (Burwell *et al.*, 1998). The location-related behaviour observed in the present study is, however, unlike that observed in the 'place cells'

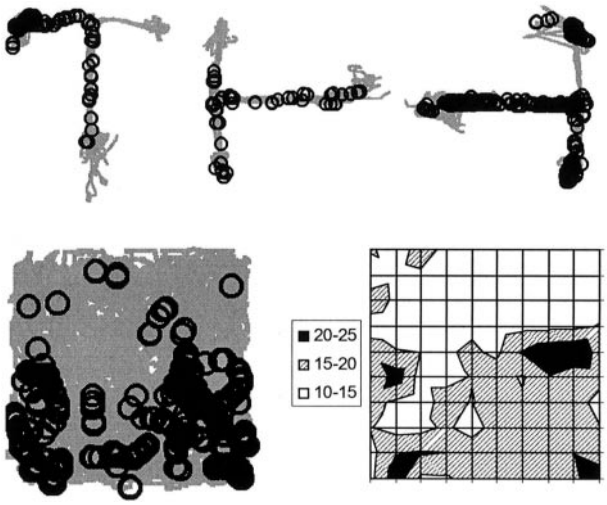

Figure 5. (Top) An example of location-related firing in an area TE neuron presented as for Figure 3. In separate recording sessions the maze was rotated 90° about its central axis. Note that the neuron appears to respond both to egocentric space (left arm of maze) and allocentric space (bottom region of space). (Bottom) After completion of the DNMP procedure this same neuron was recorded while the animal foraged freely in an open field environment located in the region of space that had previously held the T-maze. Note that this neuron fires at a greater rate in the 'south' region of the open field (these data are presented on the left in the same form as for previous figures and on the right as a topographic map of firing rates; note that shading key = firing rate in Hz).

(pyramidal cells) of the neighboring hippocampus, in that the firing rate of these latter neurons drops to near zero once the animal is outside the cell's 'place field' (O'Keefe and Dostrovsky, 1971). In contrast, in area TE/PRC neurons a relatively high firing rate of ~15 Hz is maintained across the full extent of the apparatus, with the location-related response occurring as a modulation on this background activity. This mean firing rate is similar to that previously described for visually responsive neurons recorded in area TE and PRC (Zhu and Brown, 1995) of anaesthetized rats but higher than that reported by Young *et al.* for PRC neurons recorded while awake animals performed an odor-guided task (Young *et al.*, 1997).

A primary question is whether or not the location-related responses evident in these data actually reflect the encoding of spatial information or whether the cells may have been responding to aspects of the behavioural task or environment that happen to occur at a particular location in space but that are actually non-spatial in nature. At the present time we cannot be sure of the answer to this question, and for this reason we will use the term 'location-related' rather than 'place' to describe this firing behaviour. It is of interest to note, however, that in 23% of the neurons recorded, significantly different rates of firing were observed between the left and right arms of the T-maze, where factors like reinforcement and behaviour should have been identical.

If location-related responses represent an encoding of the position of the animal within the environment, then the results of the open field and rotation manipulations suggested that some neurons may respond to a combination of both room-centered and maze-centered reference frames. For example, the one neuron tested with a rotation first appeared to shift position with the arm as the maze was rotated (maze-centered) and then appeared to respond to both the left arm (maze centered) and the 'south' region of space (room-centered) when the maze was rotated in the other direction. This neuron also responded to the 'south' when the animal was subsequently allowed to forage in

the open field. This finding aside, however, no other neurons which had a location-related response in the T-maze responded systematically to a particular location in space in the open field, suggesting that if this is 'spatial' firing then it may be task-dependent.

The major finding of the present study is that lesions of prefrontal cortex altered the location-related firing of area TE/PRC neurons. In particular, during the test phase of the procedure units from lesioned rats were more likely to display location-related firing compared to units from control animals. This finding is somewhat surprising, as one would expect that brain damage would degrade neural functioning and, therefore, reduce the information content of a representation (Fuster *et al.*, 1985). One possible explanation for the current findings, however, is that they resulted from a systematic variation in the recording sites in lesion and control animals. We believe that this is unlikely as we were able to determine that the electrode array had passed through area TE in all eight animals from which data were utilised and on into PRC in three of these lesion and two of these control animals. For the latter five animals there did not appear to be any major difference in the firing properties of neurons that could be explained merely by whether they had been recorded early (i.e. from area TE) or late (from PRC) during the procedure. Furthermore, when a comparison of control and lesion unit firing was made only between units that were recorded in similar areas, the basic effect was still evident. Interestingly, in the one animal with a hippocampal placement (data excluded from analysis), the mean firing rate was anomalous, being the lowest recorded from any animal, suggesting that the other units were selected from a relatively homogeneous population. A second possible explanation of the between-group difference in firing is that it resulted from a difference in the behavior of the two groups of animals. This is unlikely, however, since the overt behaviour of the animals appeared similar and the performance of the two groups in the DNMP task was virtually identical in terms of both the percentage correct measure and the mean time that it took to complete each trial.

With alternatives discounted, the most likely explanation of the current finding is, therefore, that the prefrontal cortex normally modulates the firing of activity in temporal cortex and that the removal of this modulation augments location-related firing. A simple explanation of this effect is that prefrontal lesions produced an increase in the signal-to-noise ratio (for location-related information) of area TE/PRC neurons by removing a 'noisy' input. If this were the case, however, then one would predict that the firing rates of lesion-group neurons would be lower than for the control group. This prediction was not supported by the data. An analysis of the pattern of firing behavior illustrated in Figure 4 points to a second explanation, however. These data indicate that, whereas the minimum firing rates of neurons recorded from lesioned and control animals are virtually identical, neurons from lesioned animals have a higher maximum firing rate. This suggests that the prefrontal cortex may normally inhibit the location-related firing of area TE/PRC neurons and, therefore, that a prefrontal lesion selectively disinhibits this activity. Interestingly, this type of inhibitory interaction has previously been proposed to exist between prefrontal and posterior cortex as a result of the analysis of imaging studies of normal and schizophrenic subjects (Frith *et al.*, 2000, 1995).

Frontal modulation of area TE/PRC activity could be mediated via the direct projections that have previously been described between these regions (Guldin and Markowitsch, 1983; Markowitsch and Guldin, 1983; Sesack *et al.*, 1989; Takagishi and Chiba, 1991; Burwell *et al.*, 1995; Rempel-Clower and Barbas, 2000). Modulation could also, however, be mediated indirectly via the disinhibition or increased activation of a region that provides area TE/PRC with spatial or sensory information, e.g. the entorhinal, postrhinal or parietal cortices or the hippocampus. Modulation could also be exercised via subcortical connections. The prefrontal cortex controls the activity of subcortical dopaminergic projection neurons via influences on structures such as the nucleus accumbens, the ventral tegmental area and the substantia nigra (Tong *et al.*, 1996; Gorelova and Yang, 1997). Since it has been shown that dopaminergic fibres from the ventral tegmental area and the substantia nigra innervate the hippocampus (Gasbarri *et al*, 1994, 1997), it is possible that these projections could modulate spatial processing in this latter region. Recent evidence has indicated that dopamine can inhibit responses in the major input pathway into the hippocampus [the perforant path (Otmakhova and Lisman, 1999)], and inhibit the excitatory *N*-methyl-D-aspartate receptor channel in hippocampal neurons (Castro *et al.*, 1999), providing a putative mechanism via which inhibition and disinhibition could occur. Alternatively, the recent finding that a portion of prefrontal cortex projections to the ventral tegmental area synapse specifically on GABAergic neurons (Carr and Sesack, 2000) suggests that disinhibition may also occur via a lesion induced reduction of ventral tegmental area inhibitory activity. Interestingly, preliminary data from our laboratory indicate that systemic administration of haloperidol, a D1/D2 dopaminergic antagonist, augments location-related neural activity in area TE/PRC (Zironi *et al.*, 2000) in much the same way as a prefrontal lesion. Further work will be required, however, in order to determine whether this effect is mediated via modulation of dopaminergic receptors in temporal cortex, or by a direct action in prefrontal cortex itself (Goldman-Rakic *et al.*, 2000).

It is of interest to consider why the prefrontal lesion, and subsequent change in temporal cortex activity, did not disrupt DNMP performance in this experiment. There are several possible explanations for this finding. One possibility is that the particular aspects of the environment being monitored by prefrontal and temporal cortex may not have been relevant to the performance of this particular task. For example, temporal cortex neurons may have been monitoring the environment for novel events (Brown and Xiang, 1998), and since these did not occur in the well-learned T-maze task, no critical output was required. It is of interest to note, however, that in a previous study utilizing the radial maze (Bilkey and Liu, 2000), deficits in spatial working memory tasks were observed with similar (although larger) lesions. The failure to observe a behavioral deficit in the current task may, therefore, have been a result of the smaller lesion. Alternatively, however, that fact that the delay utilized (15 s) was relatively short, that the animals were overtrained, or that the task did not place as many demands on prefrontal processing as did the radial maze may have been critical factors. Interestingly, a recent study (Delatour and Gisquet-Verrier, 2000) reported that prefrontal lesioned rats showed normal acquisition of a delayed non-matching to position task. Sanchez-Santed *et al.* have also reported that a prefrontal lesion-induced deficit in a delayed spatial alternation disappeared after repeated training (Sanchez-Santed *et al.*, 1997).

The present findings indicate that prefrontal cortex is able to modulate the activity of brain areas that have a role in object representation processes and object memory. This suggests that, as part of its putative role in executive function (Baddeley, 1986), prefrontal cortex could potentially influence the

selection of a representation from memory and the duration over which that representation is activated. The finding that this modulation is location-related suggests that prefrontal cortex may normally inhibit the degree to which either environmental context or particular cues in the environment influence the activation of a particular memory and/or behaviour. In this regard, it is of interest to note that one characteristic of frontal injury in humans is the appearance of what has been termed 'utilization behaviour' (Lhermitte, 1983), whereby patients with frontal damage demonstrate an exaggerated dependency on environmental cues in guiding their behaviour. It is possible that the augmentation of location-related firing that we see in the lesioned animals in the current study is a neural correlate of this type of response. If this modulation of spatial/contextual activity is shown to be dependent on dopaminergic systems, it may have important implications for our understanding of dopamine-related disorders of memory and cognition. For example, it has recently been shown that a dysfunction in prefrontal cortex (Weinberger and Berman, 1996; Frith *et al.*, 2000) may underlie the dopaminergic dysregulation in schizophrenia (Bertolino *et al.*, 1999; Byne and Davis, 1999). Since this could affect the way that prefrontal cortex controls temporal cortex responses (Frith *et al.*, 1995, 2000) it may provide a possible explanation for the alterations in response to environmental context that accompany this disorder (Manschreck *et al.*, 1997; Cohen *et al.*, 1999; Stratta *et al.*, 2000).

Notes

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