

alfalfa fields on five dates in May, June and August 1996, and dissected a total of 643 aphids for larval *A. ervi*. Data were analysed with χ^2 test, blocked by field and date.

Susceptibility of colour morphs to *C. septempunctata* on plants. We measured the susceptibility of the two aphid colour morphs to predation by allowing a single adult *C. septempunctata* to forage on caged alfalfa plants with 15 adults of each morph for 4 h; the experiment was replicated 27 times. After removing the predator from each plant, the number of remaining aphids of each morph was recorded and subtracted from 15 to determine the number consumed. The data were analysed with a 2-tailed, paired *t*-test.

Use of colour cues by *C. septempunctata*. We investigated the use of colour cues by *C. septempunctata* by allowing single adult beetles to forage for aphids of both colour morphs in red, green and white containers. To maximize our ability to detect differences in predation rates between morphs, we designed the experiment as a split-plot, with background as the whole plot and aphid colour morph as the split plots. Each arena had a single background colour and 5 similar-sized (third or fourth instar) aphids of each colour morph. Predators foraged for 30 min, and at the end of the experiment the number of remaining aphids of each colour morph was recorded and subtracted from 5 to determine the number consumed. All predators foraged actively and consumed at least one aphid. Each treatment was replicated 20 times. Data were analysed as a split-plot analysis of variance.

Comparison of reproductive rate of the colour morphs. The reproductive rates of the aphid colour morphs were compared by pairing 10 of each morph on individual caged alfalfa plants and allowing them to reproduce for 14 days. At the end of the experiment, all aphids of each morph was recorded. The experiment was started with 14 plants, but 2 plants were severely wilted after two weeks so these were excluded from the analysis. Data were analysed with a 2-tailed paired *t*-test.

Received 24 February; accepted 6 May 1997.

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Acknowledgements. We thank D. Hogg, R. French-Constant, T. Garland, M. Strand, M. Hamill, J. Foufopoulos, E. Klopfer and J. Klug for comments on earlier versions of the manuscript. This work was supported by a grant from the US Department of Agriculture to A.R.I.

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Multistability of cognitive maps in the hippocampus of old rats

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Hippocampal neurons provide a population code for location¹. In young rats, environments are reliably 'mapped' by groups of neurons that have firing locations ('place fields'²) that can be stable for several months³. Old animals exhibit deficits in spatial memory, raising the question of whether the quality or stability of their hippocampal 'cognitive maps'⁴ is altered. By recording from large groups of neurons, we observed the hippocampal spatial code to be multistable. In young rats, the place field maps were reliable both within and between episodes in a familiar environment. In old rats, place field maps were accurate and stable during an episode, but frequently exhibited complete rearrangements between episodes. In a spatial memory task, both young and old rats exhibited bimodal performance, consistent with map multistability early in training. However, the performance of young rats became almost unimodal with further training, whereas that of old rats remained markedly bimodal. The multistability of the hippocampal map provides an insight into the dynamics of neural coding in high-level cortical structures and their changes during ageing, and may provide an explanation for the frequent failure of place recognition in elderly humans.

Spatial memory is deficient in healthy elderly humans⁵, non-human primates⁶ and rodents⁷. The hippocampus is important for spatial learning⁴, and exhibits complex, region-selective changes in its anatomical connectivity, synaptic physiology and neurochemical organization during ageing^{8–10}, including a decline in its ability to maintain synaptic long-term potentiation (LTP)^{7–11}. Paradoxically, however, there are only small changes in the spatial information conveyed by hippocampal pyramidal neurons in aged animals^{12–14}.

How is this apparent preservation of spatial signalling, despite substantial alterations in cellular physiology and behaviour, to be explained? Place fields can appear in complete darkness during the first trial in an environment and remain unchanged in subsequent illumination¹⁵, suggesting that place-field interrelationships can be prespecified in the synaptic matrix¹⁶, rather than learned or imposed by external stimuli, as earlier theories had suggested^{17–20}. Current evidence indicates that self-motion signals, rather than relationships among landmarks *per se*, are used to specify relative position on a place-field map^{4,16,21}. However, landmark information seems to become bound to map locations through associative learning, and can subsequently provide position fixes that correct for the inevitable drift error in such a self-motion-based navigational system^{21,22}. Associative binding of landmark information to preconfigured maps would also enable the recall of a consistent map for a previously visited environment¹⁶. If place-field maps depend primarily on pre-existing weights within the network but landmark binding depends on LTP of external inputs, then the LTP deficit that occurs in old rats^{7,10,11} might result in the failure to select a consistent map for a given environment, even though the place fields themselves would appear relatively normal.

Multiple CA1 pyramidal cells were monitored simultaneously (number of cells per session (mean \pm s.e.m.): young, 34 ± 13 ; old, 37 ± 16) during the course of two consecutive episodes of running

on an elevated track 'maze' that were separated by ~ 25 min to 1 h, and also during sleep periods before and after this behaviour (see Methods). Only those cells that exhibited spike amplitude stability were included. The between-episode correlations in spike amplitudes were high and identical in the two age groups (young, $r = 0.959$; old, $r = 0.959$). The spike amplitudes and firing rates during the maze episodes were: old, $144 \pm 6 \mu\text{V}$, 0.91 ± 0.08 Hz; young, $143 \pm 5 \mu\text{V}$, 0.97 ± 0.10 Hz.

To determine the consistency of place fields, smoothed firing-rate maps²³ (bin size, 1.7×1.7 cm) were constructed for each cell for the first and second maze episodes, and the spatial correlations of these distributions were computed. These correlation coefficients were then averaged across all simultaneously recorded cells to provide an 'ensemble' estimate of the map consistency between episodes. There was a significant difference in mean correlations over trials between age groups (Figs 1 and 2). In young rats, the place-field maps were highly correlated between the first and second maze episodes. In about 70% of sessions, the ensemble correlations

for old rats were also highly correlated; in the remaining sessions, however, there was complete rearrangement of the place fields. The distribution of correlation scores was unimodal in young rats (Fig. 2b) and bimodal in old rats (Fig. 2a), indicating that the rearrangement reflects an all-or-none process ($\chi^2 = 8.69$, $P < 0.03$). Within each maze episode, however, the place fields of old rats were as stable as those of young rats (Fig. 2c,d). This was determined by dividing each of the two maze episodes into halves, and computing the within-episode correlations. These were uniformly high in both age groups (r_{young} , 0.79 ± 0.05 ; r_{old} , 0.77 ± 0.08 ; $\chi^2 = 3.56$, $P > 0.32$). This within-episode stability implies that the unreliability in the old rats is in the selection of the correct cognitive map for a given environment, not in maintaining the map once it is selected.

The old rats sometimes succeed in retrieving the correct map but sometimes do not, suggesting that there may be a bimodality in their performance on spatial tasks. Data with which to explore this question were available from 98 young and 93 old rats (including

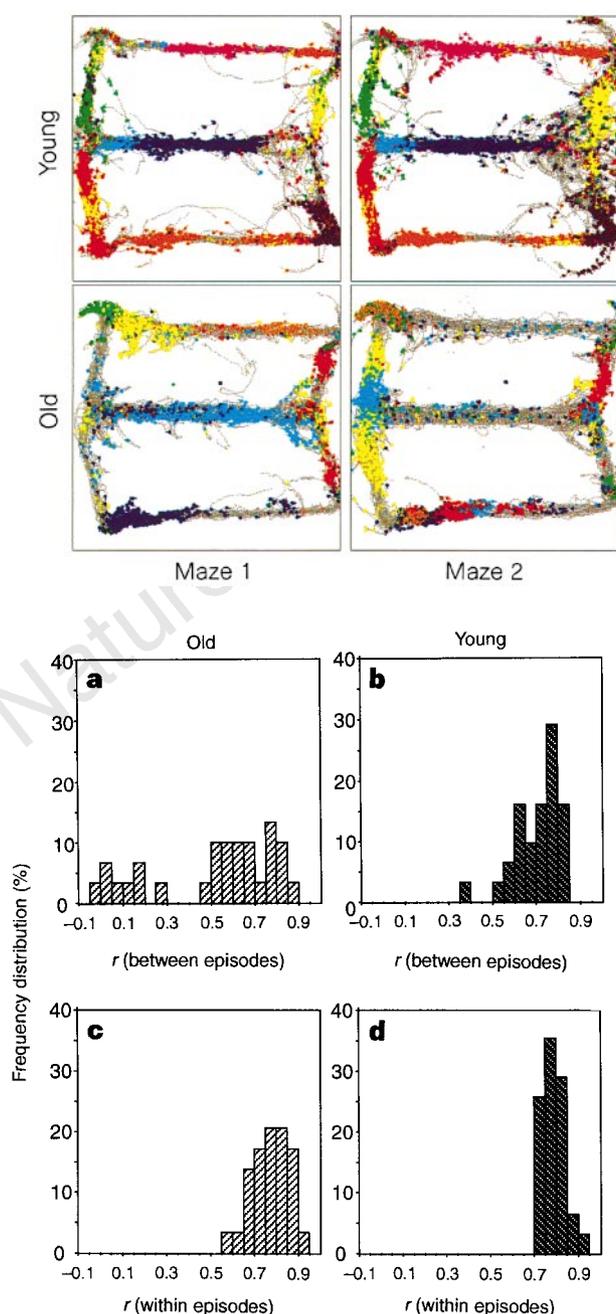


Figure 1 Place-field distributions from one young and one old rat recorded on two consecutive episodes of running on a rectangular figure-8 maze. Between episodes (Maze 1, Maze 2), the rats were removed from the room. The locations at which spikes were emitted are represented as coloured dots, with a different colour for each neuron. The colour scheme is consistent between episodes for each rat. Only a representative subset of the simultaneously recorded cells is illustrated. The grey lines indicate the trajectories of the rats. The spatial clustering of spikes from a given cell defines its place field. The distribution of place fields is referred to as a place-field map. Overlapping sets of place cells are known to participate in different mappings in different environments, but the relationships among place fields in two maps are essentially uncorrelated³⁰. Place-field maps of young animals were typically highly correlated between the two maze episodes on a given day. In old rats the maps were often uncorrelated, even though the abundant visual, auditory, tactile and olfactory cues in the environment were not altered in any way.

Figure 2 a, b, Frequency distributions of average place-field correlations between maze episodes in the (*r* (between episodes)) for all recording sessions in all rats. Each observation represents a single recording session. For young animals the distribution was unimodal, reflecting a high degree of consistency of the place-field map between episodes. In old animals the distribution was bimodal, with one peak ($\sim 70\%$ of trials) near that of the young animals, and another peak ($\sim 30\%$ of trials) near zero. Taking r (between episodes) = 0.5 as an arbitrary cut-off, the distribution of remappings within the two age groups was as follows (the numerator and denominator indicate the number of remappings and recording sessions, respectively, with the value for old rats followed by that for young rats: pair 1, 1/2, 0/3; pair 2, 3/4, 0/5; pair 3, 3/6, 0/6; pair 4, 1/6, 0/6; pair 5, 1/6, 0/6; and pair 6, 1/6, 1/6. The mean between-episode correlations for each rat were as follows, with the value for old rats followed by that for young rats: pair 1, 0.36, 0.70; pair 2, 0.18, 0.65; pair 3, 0.44, 0.70; pair 4, 0.62, 0.75; pair 5, 0.61, 0.73; pair 6, 0.69, 0.70. The age differences in mean correlation were statistically significant ($F_{1,10} = 7.67$, $P < 0.02$). **c, d**, Within episodes, place-field distributions were highly correlated in both age groups. Thus, without removal from the environment, place fields in old rats were just as stable as in young rats.

the 12 rats in the present study), which were subjects in different experiments, but which were all pretested on the same apparatus using identical procedures (Fig. 3a). Both groups initially exhibited a pronounced bimodality in their performance score distributions (Fig. 3c,e), sometimes exhibiting short swim paths and sometimes long ones. By the last day of training, however, the young rats exhibited only a small proportion of long swim paths, whereas the old rats, although showing some improvement, exhibited about equal proportions of short and long paths. If this bimodality resulted from variation between animals, rather than variation within animals across trials, then the distribution of mean performances within the population of old rats should also be bimodal. The mean path lengths for individual old rats were therefore averaged over the six trials on the last day of testing, when the group behaviour was nearing asymptote. The distributions of mean within-animal performance for old rats was broad, but exhibited no evidence of bimodality (Fig. 3b). Thus old rats as a group continued to exhibit strong bimodality on the last day of training. Performance was also strongly bimodal in young animals earlier in training,

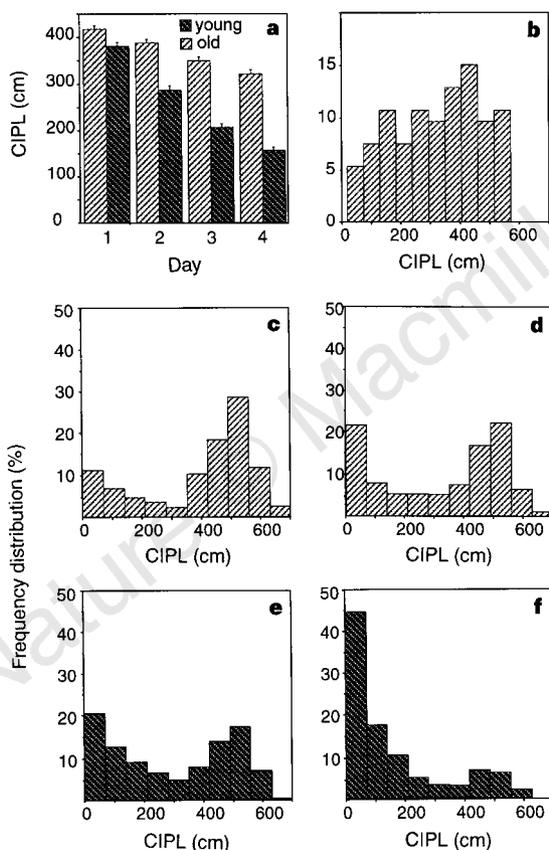


Figure 3 a, Mean performance scores (CIPL; see Methods) versus trial number for 98 young and 93 old rats on the Morris water task. Old rats were significantly impaired at finding the hidden platform in relation to external spatial landmarks. b, Frequency distribution of mean performance scores for old rats during the last six trials (day 4), when performance was nearing asymptote. Although mean performance was variable across rats, there is no evidence that the population of old rats segregates into distinct groups. The bimodal performance illustrated in c-f is thus due to variation within rats, not between rats. c-f, Frequency distributions of performance on individual trials were strongly bimodal in both young and old rats early in training (day 2). By day 4 the performance of young rats was almost unimodal, whereas old rats exhibited about equal proportions of short and long swim paths. The bimodality in path length was not an artefact of the 60-s trial limit used. Removal of the relatively few time-out trials did not appreciably affect the distribution shapes. c, Old rats, day 2; d, old rats, day 4; e, young rats, day 2; f, young rats, day 4.

suggesting that young rats with less experience may exhibit a higher incidence of place-field rearrangements. In a preliminary study¹⁶, a higher incidence was observed in young rats with less total experience in the recording apparatus than in the present study; however, the studies are not quantitatively comparable because of other important procedural differences.

These findings can be understood within a theoretical framework¹⁶ in which the hippocampus contains, within its synaptic matrix, a set of predetermined distributions of place fields ready to be used as spatial coordinate systems for different environments, but not initially bound to particular landmarks or events. The number of available coordinate systems is potentially quite large (about 0.04 times the number of neurons²⁴). During initial exploration, a coordinate system may be selected, and external stimuli may become associated with coordinates through hebbian synaptic strengthening (such as LTP). This could provide a mechanism both for establishing spatial relationships among arbitrary features and events in an environment, and for selecting the correct map upon entry into a familiar environment. According to this theory, disruption of LTP during ageing^{7,10,11} would result in failures of both functions, even though the place cell activity itself would seem normal.

When different maps are selected, is the selection random or restricted to only a few maps for the same environment? The latter case might lead to slower learning, but ultimately would result in the same asymptotic performance. At present, the data are insufficient to allow a definitive to answer this question, although several studies suggest that the asymptotic performances of young and old rats on spatial tasks do not converge²⁵. To the extent that animals improve their performance, one or a small number of maps gradually wins out, as seems to be the case in young rats.

One alternative to the defective-LTP hypothesis is that the quality of sensory information reaching the hippocampus is insufficient for accurate map retrieval. Old rats exhibit visual impairment²⁶, as well as changes in other sensory modalities, although the old rats in this and other studies were relatively normal on visual association tasks, despite being impaired on spatial tasks. Moreover, the environment used was highly structured and rich in spatial cues of all sensory modalities, and the sensory information received by the old rats was sufficient to enable retrieval of the correct map on most trials and to maintain that map once selected. Finally, both young and old rats exhibit bistable behaviour at some point in training, indicating that explanations invoking learning, rather than sensory impairments, are the more plausible.

In summary, old rats fail to retrieve the same map for a given environment more often than do young rats with equivalent experience. This effect may explain why, in an earlier study²⁷ in which the rats were removed from the apparatus between trials, place fields of old rats were less reliable over trials, and also less spatially specific on average across trials. In the present study, the place fields of old rats were at least as reliable and specific as those of young rats, as long as they remained in the environment. Both young and old rats also exhibited bimodal performance in a place-finding task early in training, but the incidence of 'lost' behaviour declined more rapidly with experience in young than in old rats. Whether the behavioural and neurophysiological phenomena are linked remains to be determined. Nevertheless, the data suggest that old animals have intact frameworks for representing spatial relationships, but cannot recall them in a consistent manner, possibly because of a problem in binding information about the external world to locations in these frameworks. This deficit in the ability to recall correctly the spatial context²⁸ in which an event occurred could contribute to the general decline in episodic memory observed during old age. □

Methods

Behavioural testing. Six pairs of one young (12 months old) and one old (28

months old) F-344 rats were first tested on the Morris swim task (six trials per day for four days), which requires that the rat learns the location of a submerged escape platform in a pool of water, on the basis of external landmarks. The performance measure, corrected integrated path length (CIPL)²⁵, is the sum of the distances from the target minus the shortest possible sum if the rat had swum directly to the platform at its mean speed. As reported previously²⁵, the old rats were impaired on this task (mean CIPL \pm s.e.m. on day 4: young, 1.81 ± 0.61 m; old, 2.76 ± 0.39 m; $F_{1,10} = 4.99$, $P < 0.05$), but they were unimpaired when the platform was not submerged and a distinct visual cue was suspended above it (on final trial: young, 0.15 ± 0.07 m; old, 0.16 ± 0.10 m; $F_{1,10} = 0.90$, $P > 0.36$). Thus the old rats were deficient in spatial memory, a characteristic of hippocampal dysfunction, but exhibited normal visual association memory, which does not depend on an intact hippocampus²⁹.

Neurophysiological recording. The rats subsequently underwent the surgical implantation of a micromanipulator array that carried 12 tetrode recording probes, for parallel recording of groups of hippocampal neurons^{1,21}. The rats were trained using a food reward to traverse a track 6 cm wide in the shape of a rectangular figure 8 (Fig. 1a), located in a moderately illuminated room with prominent visual landmarks and numerous tactile, auditory and olfactory spatial cues. Initially, the rats were confined to the north half of the apparatus by a removable partition that prevented access to or view of the other portion. The rats thus ran repeatedly (15–20 laps per episode) around a rectangular course. Three different manipulations were carried out to investigate the consistency of place-field maps on repeated visits to a fixed environment. The first was to allow the rats to spend ~25 min exploring the unfamiliar (south) portion of the track before returning to the familiar portion. This was carried out twice for each rat. In subsequent manipulations, rats were removed from the recording room for 1 h. In half of these sessions, they were returned to their home room; in the other half, they were allowed free exploration in each of six different rooms, for 10 min each, before returning to the recording apparatus. For five young and four old rats, the recording apparatus for the latter manipulations consisted of the north half of the figure 8. For two old rats and one young rat, the full apparatus (with no partition) was used as the test environment, instead of just the north half. (The details of the behavioural experience sequences are available as Supplementary Information.)

Each recording session thus consisted of 5 phases. Sleep 1, a period of ~30 min as the rat sat quietly and/or slept in a small 'nest'; Maze 1, in which the rat made multiple traversals of the track, always running in the same direction; Treatment, in which the rat was either transferred to the novel portion of the track or was removed from the room; Maze 2, in which the rat was returned to the track in its Maze 1 configuration; and Sleep 2, in which the rat was returned to the 'nest'. For four young–old rat pairs, data were available for two sessions in each of the three recording conditions. For technical and logistical reasons, the number of usable data sets was reduced for two rat pairs (Fig. 2).

Received 10 December 1996; accepted 25 April 1997.

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Supplementary information is available in Nature's World-Wide Web site (<http://www.nature.com>) or as paper copy from Mary Sheehan at the London editorial office of Nature.

Acknowledgements. We thank R. D'Monte, J. L. Gerrard, W. E. Skaggs, K. Stengel, J. Wang and K. L. Weaver for assistance with data acquisition and analysis; P. J. Best, D. Chialvo, L. Nadel, W. E. Skaggs and F. A. Wilson for comments on the manuscript, and D. Clayman for instigating the NIA extramural program through which this work was supported. This work was supported by NIA and NIMH.

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cAMP-induced switching in turning direction of nerve growth cones

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Development of the nervous system depends on the correct pathfinding and target recognition by the growing tip of an axon, the growth cone^{1–3}. Diffusible or substrate-bound molecules present in the environment may serve as either attractants or repellents to influence the direction of growth-cone extension^{4–11}. Here we report that differences in cyclic-AMP-dependent activity in a neuron may result in opposite turning of the growth cone in response to the same guidance cue. A gradient of brain-derived neurotrophic factor normally triggers an attractive turning response of the growth cone of *Xenopus* spinal neurons in culture, but the same gradient induces repulsive turning of these growth cones in the presence of a competitive analogue of cAMP or of a specific inhibitor of protein kinase A. This cAMP-dependent switch of the turning response was also found for turning induced by acetylcholine, but not for the turning induced by neurotrophin-3 (NT-3). Thus, in the presence of other factors that modulate neuronal cAMP-dependent activity, the same guidance cue may trigger opposite turning behaviours of the growth cone during its pathfinding in the nervous system.

Isolated spinal neurons in 14–20 h *Xenopus* cultures were used for these experiments. A microscopic gradient of brain-derived neurotrophic factor (BDNF) was created near the growth cone by pulsatile application of picolitres of BDNF-containing saline with a micropipette^{12,13}. The tip of the micropipette was positioned