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Long-term potentiation and the ageing brain

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Ageing is associated with learning and memory impairments. Data are reviewed that suggest that age-related impairments of hippocampal-dependent forms of memory, may be caused, in part, by altered synaptic plasticity mechanisms in the hippocampus, including long-term potentiation (LTP). To the extent that the mechanisms responsible for LTP can be understood, it may be possible to develop therapeutic approaches to alleviate memory decline in normal ageing.

Keywords: ageing; long-term potentiation; hippocampus; learning; memory

A testimonial to the importance of a scientific observation is when many investigators 'remember when and where' they first heard about it. The discovery of LTP is among the shortlist of such empirical breakthroughs in neuroscience, and it is fitting that, at the thirtieth anniversary of the publication of the first full manuscript written about it, many will wish to reveal the impact this finding had on their individual scientific development. Several conceptual and empirical breakthroughs occurred during the early 1970s that gave rise to an optimistic feeling that understanding the neural mechanisms of memory might be a tractable problem. These included previews of a promising manuscript by O'Keefe & Nadel (1978), Marr's then recent papers on how memories could be stored in networks that resembled the architecture of the hippocampus (Marr 1970, 1971), and, of course, the landmark publications on LTP that were published in 1973 (Bliss & Lømo 1973). The *zeitgeist* was thereby primed for raising questions about how the ageing process might impact the way in which memories are laid down or retrieved.

I was at Carleton University in Ottawa, Canada, in 1973 when I first heard about LTP. Afterwards I shifted the direction of my dissertation to focus on the relationship between LTP and learning across the lifespan. If the process that Lømo, Bliss and Gardner-Medwin described *did* reflect a mechanism used by the hippocampus to store information, then the ability to modify synaptic weights should be correlated with how well hippocampal-dependent behavioural tasks are learned and remembered. Although there was a small literature on age-related memory impairments in humans in 1973, there were very few experiments that had addressed memory impairments in aged animals to investigate the underlying mechanisms. The review of the hippocampal lesion literature that O'Keefe and Nadel had outlined in an early version of their manuscript suggested that a comparison of spatial memory and hippocampal plasticity over the lifespan would be a productive experimental approach. To evaluate the persistence of memories in relation to synaptic change, it would be necessary to use relevant behavioural experiments and an electrophysiological preparation that could be monitored over days or weeks. The latter methods were in use by Graham Goddard's group in Halifax (Douglas & Goddard 1975). The issue of what behavioural task to use remained. The first experiments conducted on memory, LTP and ageing were performed in Goddard's laboratory.

1. CORRELATING ELECTROPHYSIOLOGICAL CHANGES WITH BEHAVIOUR

The behavioural tasks that were in standard use at the time, and known to be hippocampal dependent, required the use of food restriction or shock. Because old rats were likely to be more frail than the young rats typically used in behavioural experiments, it was important to design any test of spatial memory, and specifically navigational accuracy, that stressed old animals minimally. A circular platform task was therefore developed, in which rats were required to learn which of 18 holes at the perimeter of a 1.2 m circular platform leads to a dark escape box. Rats naturally approach dark areas and avoid open, brightly illuminated spaces. Accordingly, when placed in the middle of the open platform, the rats would go to the edge to look for escape routes and eventually find the one hole under which the dark escape box was placed (Barnes 1979; figure 1). The apparatus was housed in a large open area (a television studio), and equipped for online manual video tracking, so that path-length could be monitored as the rats ran about the platform. Path-length is a measure independent of running speed, which changes over the lifespan. Latency and number of errors (nose pokes into holes not over the escape box) were also measured. Pilot studies with young rats showed that path-lengths, errors and latency measures all declined over trials and days, indicating an improvement in navigation to the correct location, despite the fact that olfactory cues were scrambled by randomly moving the surface of the platform from trial to trial. For the ageing experiment 32 young (*ca.* 14 months) and 32 old (*ca.* 32 months) male Long–

One contribution of 30 to a Theme Issue 'Long-term potentiation: enhancing neuroscience for 30 years'.

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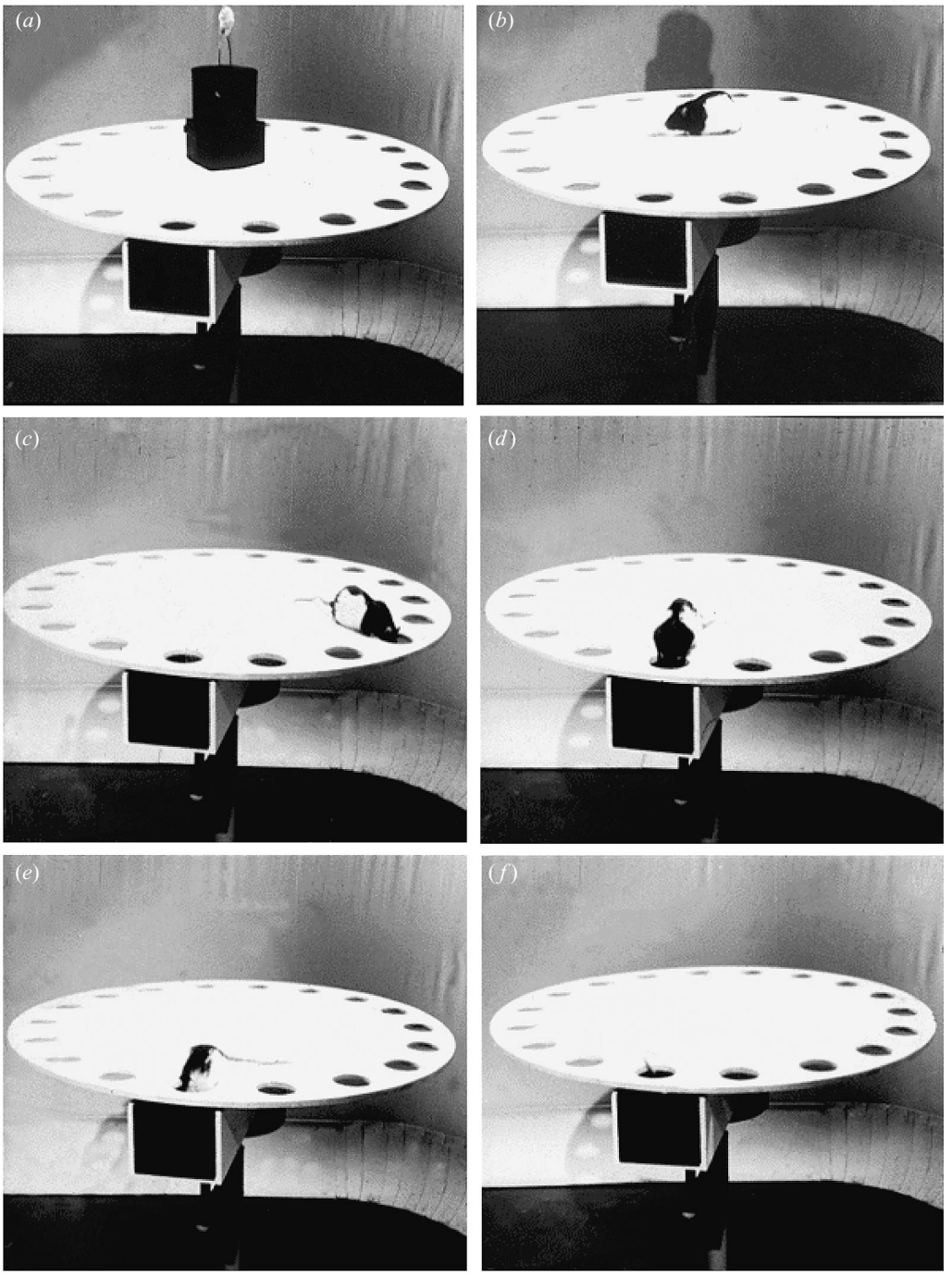

Figure 1. Circular platform apparatus. (*a*) Initially, the rat is placed in a start 'bucket' in the centre of the platform. (*b*) When the start bucket is raised, the rat is free to move and the trial begins. (*c*) The rats explore the surface of the platform searching for the escape box, and make errors, as illustrated here. (*d*) When the rat finds the escape box (*e*) he descends into it (*f*) and is allowed to remain there for 30–60 s.

Evans rats were given two trials per day for 6 days, and then a change in escape location was implemented for a further 5 days. The use of relatively many animals per group afforded the possibility of examining correlations between behaviour and electrophysiology with confidence.

After behavioural testing, all animals underwent surgery for the chronic bilateral implantation of electrodes used to record evoked extracellular field potentials. Recording electrodes were placed in the hilus of the fascia dentata and stimulating electrodes in the angular bundle, where the axons from the entorhinal cortex (the perforant pathway) converge. After behavioural testing, LTP was induced bilaterally using the robust stimulation parameters that had been developed by Douglas & Goddard (1975) to induce reliable enhancement of synaptic efficacy (20 ms bursts of 400 Hz stimuli, supra-threshold for population spikes, delivered at an overall rate of 0.2 Hz, repeated 15 times). First, one such high-frequency session was given (120 total stimulus pulses), and the resulting enhancement was monitored for 7 days. After this, high-frequency stimulation was delivered once every 24 h for 3 consecutive days, after which the synaptic responses were tested for two additional weeks. The slope of the average synaptic response was measured, and the fractional

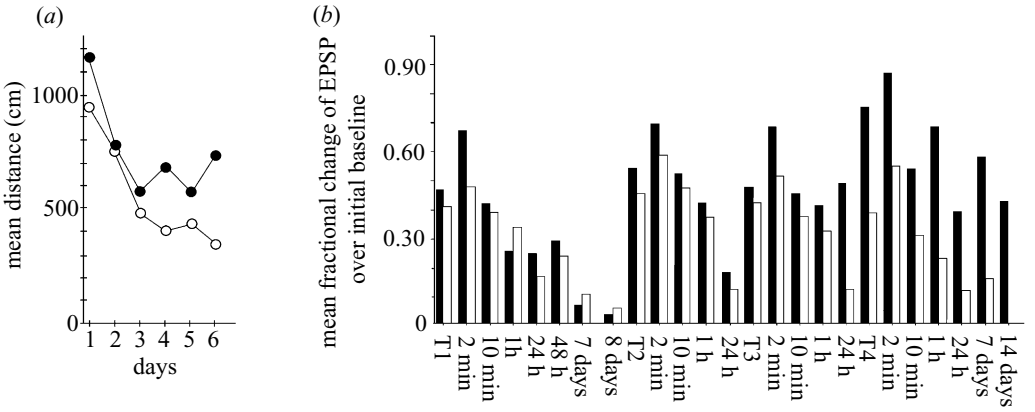

Figure 2. (*a*) Behavioural performance on the circular platform task over 6 days of training (two trials per day). Shown is the mean distance traversed before finding the escape box. The old rats (filled circles) showed poorer acquisition scores than did young rats (open circles). (*b*) LTP-inducing stimulation was given four times during this experiment (T1, T2, T3 and T4). Shown is the mean fractional change of the field EPSP for the young (filled bars) and old rats (open bars). Although the old rats did not show LTP induction or decay differences following a single high-frequency stimulation session (T1), after three consecutive daily high-frequency sessions (T4), the old rats showed significantly less LTP than did the young rats (adapted from Barnes 1979).

change of the evoked response, was calculated. Although other electrophysiological and behavioural measures were collected in this experiment, the main findings of interest for this review include observations of spatial acquisition on the circular platform, the induction of LTP of the synaptic potentials and decay of this LTP over time.

The data over the first 6 days of acquisition (two trials per day) are shown in figure 2*a*. Old rats exhibited longer path-lengths to the escape box (and more total errors and longer latencies) than did the young rats. From this first experiment with the circular platform, and others conducted later in ageing rats, the consistent finding has been that old rats are impaired in learning the location of the escape box (Barnes 1979; Barnes & McNaughton 1980*a*, 1985; Markowska *et al.* 1989), in retaining the memory of that location (Barnes & McNaughton 1980*a*) and in learning a reversal or change of location of the escape box (Barnes 1979). More recently, Bach *et al.* (1999) have found a similar pattern of spatial learning impairment in aged mice by using a modified version of the circular platform. In Bach's experiment, a visual discrimination problem was also administered, and revealed no impairment in the acquisition of a cued version of the task in the old, spatial memory-impaired, mice.

With the stimulation protocol used, there was no difference in the magnitude of LTP induced either after a single high-frequency session as a function of the age of the animals, nor after the first or second of the three consecutive daily high-frequency treatments. There was also no difference in LTP decay following a single LTP-inducing session, as measured over a one week period (figure 1*b*). The striking difference between age groups emerged in the persistence of LTP after three LTP-inducing sessions. It appeared that the good 'retention' of LTP observed in the young rats required repeated high-frequency input. This effect of repetition on persistence was not observed in the old animals. The finding in young animals was reminiscent of an observation made by Bliss & Gardner-Medwin (1973). The one rabbit that received repeated LTP-inducing sessions in their study showed more enduring LTP than did other rabbits with single sessions. In the present study, repeated stimulation extended the decay time-constant of LTP for the young adult, but not for the old rats. Finally, there was a statistically significant correlation between accuracy of performance on the circular platform task on the final day of acquisition and the amount of LTP after the third induction session. This correlation was statistically reliable in each age group alone, as well as across groups. The relationship indicated that the rats with the most durable LTP in a given age group tended to show the best spatial learning. These data provided the first support for the hypothesis that LTP at hippocampal synapses and spatial learning may depend on similar mechanistic processes.

Several questions remained outstanding: do the old rats simply require more repetition than do young rats to reach the same levels of LTP? With more repetitions, could the LTP decay time constant be extended equivalently? An additional study was designed specifically to examine these issues (Barnes & McNaughton 1980*a*). In this experiment, LTP-inducing stimuli were administered at 24 h intervals for 12 consecutive days to attempt to 'saturate' the LTP-induction process in both groups and perhaps allow sufficient repetitions for the old rats to show more durable LTP. The result of 12 daily LTP-inducing stimulation sessions was monitored for several weeks thereafter. Figure 3*a* shows the fractional change in the slope of the field EPSP at 24 h intervals following each daily LTP treatment (left of dotted line), and the magnitude of LTP after the cessation of high-frequency stimulation over several weeks (right of dotted line). The rate of growth of the decay time-constant for LTP was a decreasing function of the number of LTP-inducing sessions given (figure 3*b*). The young rats reached the maximum value on trial 5, whereas the old rats reached their maximum on trial 10. Even though the same absolute magnitude of LTP was reached in both age groups by the end of the 12 high-frequency sessions, the LTP decay time-constant was only 17 days for the old rats compared with 37 days in their young counterparts.

The faster decay of LTP in the older rats suggested that behavioural forgetting in young and old animals might

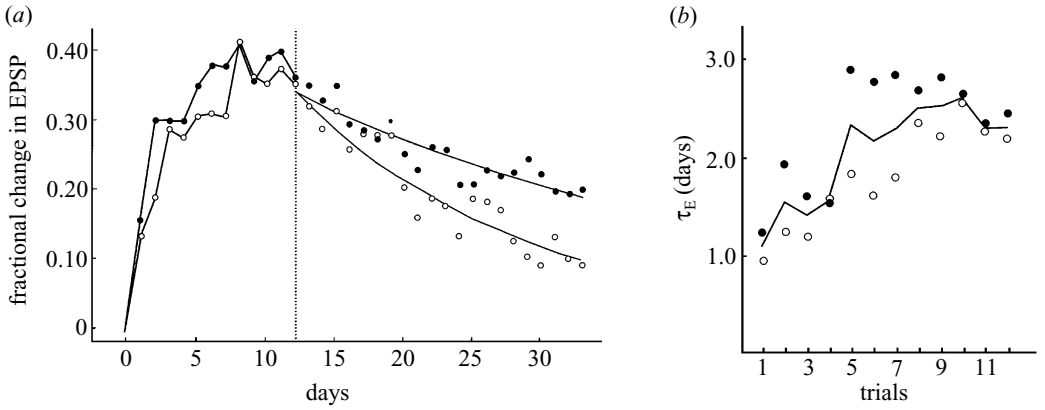

Figure 3. (*a*) Mean fractional change in the field EPSP in the young (filled circles) and old (open circles) groups of rats. To the left of the dashed line are the data 24 h after high-frequency stimulation (12 in total), and to the right of the dashed line are the data that follow the end of LTP-inducing sessions, also obtained at 24 h intervals. Note that by the end of the high-frequency stimulation sessions, LTP in the young and old rats was equivalent; however, the old rats showed faster decay of LTP over the ensuing days. (*b*) Mean time-constant of LTP for each 24 h period after the 12 daily LTP-inducing sessions for the young (filled circles) and old (open circles) rats shown in (*a*). The solid line is the mean for both groups combined. The young group reached their maximum value earlier than did the old group (adapted from Barnes & McNaughton 1980*a*).

share similar kinetics. Specifically, if the decay of hippocampal LTP and behavioural forgetting of a spatial problem shared common mechanisms, the old rats should show similarly accelerated rates of decline in both processes. By using 90 rats, with separate groups of rats for each retention time-point measured (10, 20, 30, 45 and 60 days), the animals were first trained on the circular platform, one trial per day for 16 days. The old rats, indeed, forgot the location of the escape box on the circular platform about twice as fast as did the young rats (Barnes & McNaughton 1985). In fact, when the ratios of behavioural forgetting were compared with the ratios of decay of LTP between groups, there was only a 1% difference—in other words, old rats show rates of forgetting and LTP decay that are about twice as fast as those of young rats. This lent additional support to the idea that the maintenance of LTP may play an important role in sustaining a robust memory. At approximately the same time, de Toledo-Morrell & Morrell (1985) found a significant relationship between the durability of LTP over days at the perforant path—granule cell synapse and behavioural performance on the radial 8-arm maze (another task that had been shown to be dependent on an intact hippocampus). More recent experiments have examined the relationship between LTP at the Schaffer collateral–CA1 synapse, and spatial performance on the circular platform. Bach *et al.* (1999) uncovered aged-related LTP maintenance deficits in CA1 of old mice after 3 h using the *in vitro* slice preparation. These decay rates were correlated, across age groups, with spatial performance on the circular platform task.

2. MECHANISMS UNDERLYING AGE-RELATED CHANGES IN MEMORY

LTP is often divided into phases—induction, expression and maintenance. It is appropriate to ask whether ageing affects any of the processes separately. The first reports indicated intact hippocampal LTP induction at the Schaffer collateral–CA1 synapse (Landfield & Lynch 1977; Landfield *et al.* 1978) and at the perforant path–granule cell synapse (Barnes 1979) in old rats. With few exceptions, this lack of an age-related LTP induction deficit has been repeatedly observed in CA1 and in the fascia dentata, when robust, high-intensity stimulation protocols are used. Experiments from two groups, however, in the early 1990s, helped to place the findings of experiments using robust stimulation parameters into the proper perspective. When fewer stimulus pulses and lower amplitude stimulus currents are used to induce LTP ('peri-threshold protocols'), old rats do show LTP induction deficits in the Schaffer collateral–CA1 synapse compared with their younger counterparts (Deupree *et al.* 1993; Moore *et al.* 1993). Furthermore, at the perforant path–granule cell synapse, Barnes *et al.* (2000*a*) have shown that a larger amplitude current injection is necessary for LTP to be induced in old rats when weak presynaptic stimulation is paired with direct depolarization of the postsynaptic granule cell. This points to a change in the induction threshold at this synapse as well. Taken together, these results show that LTP *can* be more difficult to induce in old rats.

What contributes to these changes in LTP characteristics in old rats relative to what is observed in younger animals? First, several anatomical and electrophysiological properties can be eliminated. There is no loss of hippocampal granule or CA1 pyramidal cells in old rats (Rapp & Gallagher 1996; Rasmussen *et al.* 1996), most biophysical properties of old pyramidal or granule cells do not differ from those in young cells (review in Barnes 1994), and there is no change in spontaneous firing rates of single cells in the hippocampus of freely behaving old rats compared with young rats (e.g. Shen *et al.* 1997). Second, there are certain changes observed during ageing that may contribute to the LTP deficits. For example, there is a reduction in the actual number of perforant-path synaptic contacts on granule cells (Geinisman *et al.* 1992) and a corresponding reduced amplitude of the presynaptic fibre potential and field EPSP elicited by perforant path stimulation (Barnes & McNaughton 1980*b*; Foster *et al.* 1991). In CA1, the field EPSP elicited by Schaffer collateral stimulation is also reduced, but the presynaptic-fibre-potential response is not (Kerr *et al.* 1991; Barnes *et al.*

1992; Potier *et al.* 2000). These two observations have also been confirmed *in vivo* (Barnes *et al.* 2000*b*), consistent with the hypothesis that there is a loss of functional synaptic contacts in CA1, although not of afferents *per se*. Such decreases in network connectivity certainly could contribute to plasticity changes during advanced age.

Third, Landfield and his colleagues have found deficits in several aspects of calcium regulation during ageing, including frequency potentiation (Landfield & Lynch 1977), an increased calcium-mediated inward potassium current in old rats (Landfield & Pitler 1984), and an increased density of L-type calcium channels in old rats (Thibault & Landfield 1996). These changes may also contribute to the altered plasticity characteristics of the ageing hippocampus. Consistent with this idea, a form of LTP that is NMDA-independent has been described (Grover & Teyler 1990), and can be induced if very high intensity stimuli are applied. This form of LTP appears to be mediated by calcium influx through vdcc. Shankar *et al.* (1998) observed that, if measured in isolation, vdccLTP in CA1 is increased in old rats. On the other hand, if NMDA-LTP was measured in isolation (vdccLTP blocked), an age-related LTP deficit was unmasked. These authors suggest that, in CA1, the observation of no age-related changes in LTP induction with robust stimulation parameters has arisen because of a shift in the balance between these two types of LTP in old rats. Furthermore, LTD and depotentiation are easier to induce in hippocampal slices from old rats than from adult rats (Norris *et al.* 1996). This may also be a result of alterations in calcium-mediated cascades in older animals, and certainly could contribute to the observed changes in decay rates of LTP in old rats.

3. SYNAPTIC PLASTICITY AND THE STABILIZATION OF HIPPOCAMPAL MAPS

If it is more difficult to induce LTP but easier to induce LTD, what impact might this have on the overall network properties of the ageing hippocampus? Although the correlations between artificially induced LTP and behaviour are consistent with the hypothesis that LTP-like processes may underlie learning, stronger support for this idea would be provided if LTP could be directly measured during some behavioural experience. Single-cell activity in the hippocampus of freely behaving rats shows striking modulation of firing rates of complex-spike cells, dependent on the location of an animal in a given environment. John O'Keefe first called these hippocampal cells 'place cells' because of this correlate (O'Keefe & Dostrovsky 1971). The region of the environment over which the cell responds is called its 'place field', and the distribution of these fields in a given environment is referred to as a hippocampal place field 'map'. With recent advances in multiple single-cell recording methods, it has become possible to record many hippocampal cells simultaneously (e.g. Wilson & McNaughton 1993). Because cell firing occurs in response to the animal's behaviour and sensory input, rather than because of artificial stimulation, the activity of hippocampal ensembles potentially provides a complementary window for viewing experience-dependent changes in brain function. In fact, Wilson & McNaughton (1993) demonstrated that it is possible to reconstruct a rat's location in an environment, simply from monitoring the activity of a large group of hippocampal cells. With repeated exposure to an environment, it has been suggested that hippocampal maps become stabilized as a consequence of LTP at the synapses carrying external and internal information to the hippocampus. Because LTP is compromised in old rats, this stabilization process may also be affected by the ageing process.

Can synaptic modification be inferred from the network dynamics of groups of hippocampal cells? Going back to Hebb's ideas on phase sequences or linked cell assemblies, several modern theoretical considerations of route learning predict that the pattern of place cell discharge should change as a consequence of repeated traversals of a route. Because of the temporal asymmetry of LTP (Levy & Steward 1983), repeated traversals of a route should eventually cause cells at a given location to activate subsequent cells in the sequence, before the rat actually reaches the original firing location. Just as predicted by theories of sequence learning (Levy 1989; Blum & Abbot 1996; figure 4*a*), when young rats traverse linear tracks, place fields do expand in the direction opposite to the direction of motion of the rat, and firing rates increase over the first few traversals of the track on a given day (Mehta *et al.* 1997). In addition to possibly encoding the sequences in which places have been visited, this experience-dependent place field expansion might cause an increase in the spatial information contained in the hippocampal map, producing more overlap in cell firing activity in an environment, potentially leading to greater map stabilization.

Although place field expansion was a theoretical prediction of route learning models, what other evidence suggests that it may be a behaviourally driven LTP-like process? Ekstrom *et al.* (2001) compared place field expansion characteristics in young rats given saline or the NMDA antagonist CPP while repeatedly traversing a rectangular track. If experience-dependent expansion of place fields shared common mechanisms with LTP, then a manipulation of the glutamate receptor that affects LTP, should correspondingly affect expansion of the place fields in these behavioural conditions. Experience-dependent place field expansion was, in fact, blocked by the NMDA receptor antagonist CPP, in similar doses to those that block LTP induction (Ekstrom *et al.* 2001). Because LTP mechanisms are disrupted in old rats, it was also reasoned that there should be a difference in place field expansion characteristics in old, spatial memory-deficient rats. Consistent with the hypothesis that LTP and the place field expansion effect share common mechanisms, Shen *et al.* (1997) confirmed that the expansion effect is much less robust in old, memory-impaired rats, than in young rats (figure 4*b*).

Recent studies have indicated that hippocampal cell-firing patterns during periods of quiet rest or sleep ('off-line' periods), reflect the patterns that were expressed during the immediately preceding behavioural experience (Wilson & McNaughton 1994). Moreover, the sequential order of neuronal firing, as reflected by asymmetry in neuronal cross-correlations, is significantly preserved (Skaggs & McNaughton 1996), suggesting that event sequences are reactivated during such periods. The deficit in experience-dependent place field expansion in old animals suggests that sequence encoding may be compro-

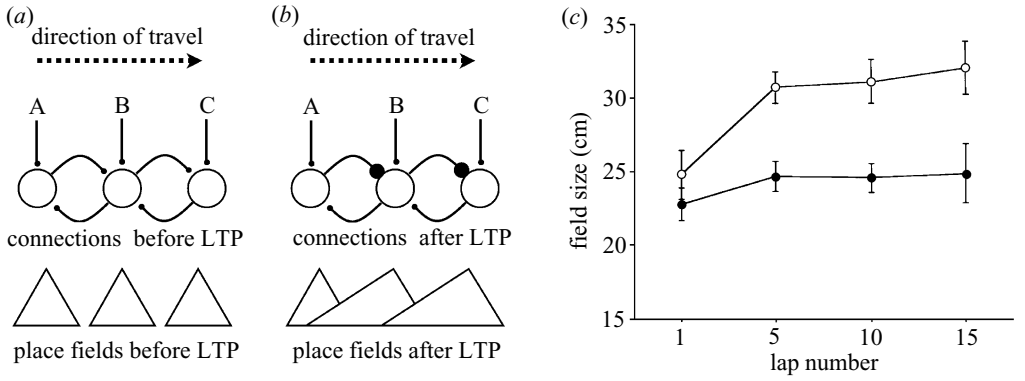

Figure 4. (*a*) Diagram of the theoretical basis for sequence learning and the experience-dependent place field expansion effect. (*b*) Repeated activation of a sequence (ABC) of cells causes an LTP-like asymmetric strengthening of the forward connections. This causes a given cell to begin to fire in response to the activity of cells earlier in the sequence with repetitions of that sequence. Hence, the place fields expand in a direction opposite to the motion of the rat. (*c*) The effect of age on experience-dependent place field expansion as young rats (open circles) and old (filled circles) rats traverse a rectangular track. Shown here are mean, and standard error of the mean, place field sizes for laps 1, 5, 10 and 15. The place field sizes expanded significantly from lap 1 to lap 5 for the young rats, but the old rats did not exhibit this expansion. The lack of place field expansion in the old rats provides indirect evidence for a failure of asymmetric LTP-like processes in the hippocampus during ageing (adapted from Shen *et al.* 1997).

mised, and this would be expected to affect the degree to which the sequential order of experiences is preserved during off-line reactivation in old animals. This expectation was recently confirmed by Gerrard *et al.* (2002). Moreover, preservation of sequence reactivation was positively correlated with spatial accuracy on the Morris swim task, in both age groups. This provides a further, albeit indirect, link between behaviourally observed memory performance and LTP-like processes in the hippocampus.

Another prediction of the hypothesis that LTP-like mechanisms may play a role in stabilizing hippocampal maps is that old rats should show less effective map retrieval. It has been shown that NMDA receptor blockade does not prevent the formation of coherent place fields in a novel environment, but this treatment does prevent hippocampal map stabilization and retrieval in young rats (Kentros *et al.* 1998). Barnes *et al.* (1997) found that when old rats are brought into a familiar environment, they occasionally retrieve a completely different hippocampal map than was retrieved in the same environment earlier in the day. On these occasions some fields changed location, some cells no longer fired in the environment and some previously silent cells began to fire. However, once a map had been retrieved by an old animal, it was stable throughout the entire session (as long as the rat was not taken out of the room), just as animals with NMDA receptor blockade show well-formed hippocampal maps when introduced into an environment. Again, analogous to young animals with reduced LTP mechanisms (NMDA receptor antagonism), old rats can show instability of the map retrieval process.

Another change in place-field dynamics observed in old rats is a delayed realignment in the hippocampal map when visual cues and self-motion information are mismatched (Rosenzweig *et al.* 2002). When rats are trained to run back and forth along a track with a journey origin that changes from trial to trial, in the journeys from the start box toward the end of the track, self-motion cues tend to provide information about the rat's position relative to the start box, while external visual cues provide independent information about the rat's position relative to the end of the track (Gothard *et al.* 1996; Redish *et al.* 2000). The start box in this task was moved from trial to trial, forcing a mismatch in the position estimates from the two forms of information. Under these conditions, place fields near the start box tend to be aligned to the start box, and place fields near the end of the track tend to be aligned to the room, indicating that the hippocampal map realigns during the course of each journey. In old rats, the map realignment from motion to room coordinates is delayed (Rosenzweig *et al.* 2002). That is, aged rats are closer to the end of the track when the hippocampal map changes from a self-motion-based alignment to a visual-cue-based alignment. Some models of hippocampal function (e.g. Samsonovich & McNaughton 1997; Redish 1999) suggest that cues and landmarks are bound to the map secondarily through an LTP-like process. The observed delay in map realignment in old rats is consistent with the idea that old rats possess a naturally occurring LTP deficit, and that weaker cue binding forces the hippocampal representation to depend more on self-motion information in old rats. Another hypothesis, tested in this same experiment, was that spatial localization accuracy should require a hippocampal map that is room aligned to facilitate finding a spatial goal. In fact, the position at which a given rat's map alignment switched from start-box coordinates (variable) to room coordinates (fixed), was significantly correlated with how well a given rat learned the location of a hidden reward zone at a fixed location in room coordinates (Rosenzweig *et al.* 2002), regardless of age group. That is, the further along the track map alignment occurred in individual rats, the less accurate was that rat's spatial performance.

As mentioned above, old rats can show map retrieval errors ('re-map') when the environment is unchanged (Barnes *et al.* 1997). Other observations, however, suggest that under different circumstances, old rats fail to re-map when the local cues in the environment are intentionally changed (Tanila *et al.* 1997; Oler & Markus 2000). These seemingly incompatible results can be conceptualized as

indicative of age-related impairments in two opposing functions of the hippocampal network. Redish *et al.* (1998) have suggested that inappropriate re-mapping may reflect defects in pattern completion in the CA3 component of the hippocampal network, whereas the failure to re-map appropriately may reflect defects in pattern separation or the orthogonalization process, attributed to the fascia dentata (Marr 1971; McNaughton & Morris 1987; Redish 1999). That is, impaired pattern completion in aged rats might cause the occasional retrieval of an incorrect map upon entry to a familiar environment, whereas impaired pattern separation in aged rats might prevent the formation of a new map in response to environmental changes. Either way, if an inappropriate map is retrieved, or if an inappropriate map is maintained, the final result will be profound changes in spatial cognition.

4. CONCLUSION

It is plausible to propose that, at the core of most of the age-related changes discussed above, there is a fundamental defect in the basic mechanisms by which the hippocampus stores and retrieves information. It is more difficult to store and stabilize memory traces as we age, easier for these traces to decay, and consequentially harder for them to be retrieved. Changes in the plasticity characteristics of hippocampal circuits contribute to major alterations in network dynamics observed in older rats, and may explain the more general observation that older organisms have a greater tendency to become lost.

This leaves us with the fascinating issue of whether, having secured this basic understanding of what happens within the hippocampus over the lifespan, it will be possible to develop therapeutic treatments to alleviate memory decline in normal ageing. Some of the most promising approaches to this problem include alterations of glutamatergic receptors at hippocampal synapses (e.g. 'ampakines'; Staubli *et al.* (1994)), positioned strategically to affect LTP; however, many other avenues are being pursued to modify transmission through the synapses that are involved in memory formation and retrieval. Fortunately, most of us will not succumb to dementing illnesses that tend to occur at older ages. Nevertheless, memory decline does, indeed, appear to be a natural consequence of the ageing process. Ensuring the fidelity of memories from the past, as well as the laying down of future memories, would certainly contribute to life quality for those in their sixth decade and beyond. It is not unreasonable to suppose that, largely because of the past 30 years of work on LTP, a 'fountain of youth', at least where memory is concerned, may well be discovered.

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GLOSSARY

CPP: 3-((I)-2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid
EPSP: excitatory postsynaptic potential
LTD: long-term depression
LTP: long-term potentiation
NMDA: *N*-methyl-D-aspartate
vdcc: voltage-dependent L-type calcium channels