

(Fig. 1B), which indicates that an intact R1C may be necessary for FKBP-12 binding. We also tested FKBP-12Δ5 (a clone of FKBP-12 lacking the first five amino acids) for interaction with a panel of type I receptor molecules (Fig. 1D), all of which showed weakened interaction with FKBP-12Δ5. Thus, an intact NH₂-terminus of FKBP-12 is required for optimal interaction.

Co-immunoprecipitation was used to confirm the specific interaction between FKBP-12 and R4C in vitro. We used fusion proteins of LexA-R4C or LexA-R1C-JM (the juxtamembrane domain of the R1C) (Fig. 1C, lane 2) made in yeast and lysates of mink lung cells, which are a rich source of FKBP-12 as confirmed by protein immunoblotting (19). FKBP-12 was coprecipitated with LexA-R4C but not with LexA-R1C-JM (Fig. 2).

Two immunosuppressant drugs, FK506 and rapamycin, bind to the same site on FKBP-12 (22). We therefore investigated whether the type I receptors and the drugs share the same binding site on FKBP-12. If the binding sites are the same or partially overlap, drug binding to FKBP-12 would compete with the cytoplasmic domain of the type I receptors. This would result in a decrease of the β-galactosidase activity in the yeast transformants. We added FK506 to a liquid culture of the yeast transformants at two concentrations that did not affect yeast growth. FK506 effectively competed with R4C for FKBP-12 binding at a concentration of 1 μM (Fig. 3), but not at 100 nM. When cyclosporin was used at various concentrations in the same assay, no competition was observed. To further confirm that the type I receptors and the drugs share the same binding site on FKBP-12, we tested in the two-hybrid system a mutant FKBP-12 (D37G) (18), which was shown to be defective in binding to FK506 and rapamycin. It failed to interact with the type I receptors (19).

Our results suggest that FKBP-12 interacts with type I receptors in a specific manner. A K230R mutation on R4, which abolishes R4 signaling activity (12), decreased binding of R4C to FKBP-12, as did a D37G mutation on FKBP-12, which suggests that the interaction may be functionally important. In mammalian cells, ligand binding may promote the type I receptors to bind FKBP-12; alternatively, it may stabilize a preexisting type I receptor-FKBP-12 complex. Although the function of FKBP-12 in the type I receptor-mediated signaling pathway needs to be clarified in TGF-β-responsive cell lines, our data indicate that the binding sites on FKBP-12 for R4C and FK506 may be shared or overlap, which suggests that the type I receptor may be a natural ligand for FKBP-12. Because the competition of FK506 for R4C to bind FKBP-12 can be easily monitored, this yeast system provides a potential screen for other

candidate immunosuppressant drugs. If these interactions are confirmed to occur in mammalian cells, rapamycin and FK506 may prove useful in analyzing the downstream actions of TGF-β family ligands.

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17. R1C (residues 147 to 509) was amplified with the polymerase chain reaction (PCR) with Eco RI and Bam HI attached at the 5' and 3' ends, respectively, and subsequently inserted into the Eco RI and Bam HI sites of the multicloning region of PEG202 (14), with the LexA DNA binding domain fused 5' to R1C.
18. Abbreviations for the amino acid residues are: D, Asp; G, Gly; K, Lys; P, Pro; R, Arg; and S, Ser. Mutations are indicated as follows: Lys²³⁰ → Arg, K230R.

19. T. Wang, P. K. Donahoe, A. S. Zervos, unpublished results.
20. The entire R4C (residues 147 to 501) was amplified by PCR and then subcloned into the Eco RI and Xho I sites of PEG202.
21. The constructs were generated by PCR and subcloned as described for LexA-R1C (17), except for the LexA-aRIIC construct. DNA sequencing and protein immunoblotting confirmed the expression of the fusion proteins.
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24. The neonatal rat heart cDNA library was from A. Green (Beth Israel Hospital, Boston). An R4 K230R pCMV6 plasmid was provided by X.-F. Wang. The LexA-aRIIC construct was from R. Periman and R. A. Weinberg (Whitehead Institute). We thank T. Haqq for technical assistance; R. Brent for encouragement, support, and valuable suggestions; T. E. Starzl and W. W. He for helpful discussions; A. Green for the rat neonatal cDNA library; and X.-F. Wang, R. Periman, R. A. Weinberg, and B. Bierer for materials critical for this study. We particularly thank S. Schreiber for supplying FK506 and antibody to FKBP-12; B. Gladstone for the FKBP-12 mutant; R. Finley, P. Baciu, M. Kozlowski, A. Vincent, P. Busto, H. Y. Lin, and J. Schnitzer for technical advice; and R. Brent, P. Goetink, S. Schreiber, J. Avruch, L. Perkins, D. MacLaughlin, and J. Teixeira for comments on the manuscript. Supported by a National Institute of Child Health and Human Development (NICHD) Reproductive Sciences Training Grant (P-32 HD07396) (T.W.) and by grant CA17393 from the National Cancer Institute and by P30 Reproductive Sciences grant (P-30 HD28138) from NICHD (P.K.D.). A.S.Z. was funded under an agreement between Massachusetts General Hospital and Shiseido.

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Reactivation of Hippocampal Ensemble Memories During Sleep

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Simultaneous recordings were made from large ensembles of hippocampal "place cells" in three rats during spatial behavioral tasks and in slow-wave sleep preceding and following these behaviors. Cells that fired together when the animal occupied particular locations in the environment exhibited an increased tendency to fire together during subsequent sleep, in comparison to sleep episodes preceding the behavioral tasks. Cells that were inactive during behavior, or that were active but had non-overlapping spatial firing, did not show this increase. This effect, which declined gradually during each post-behavior sleep session, may result from synaptic modification during waking experience. Information acquired during active behavior is thus re-expressed in hippocampal circuits during sleep, as postulated by some theories of memory consolidation.

The selective strengthening of interactions among small sets of neurons engaged in the encoding of specific external events has been a foundation of modern theories of neural information storage. Yet, despite indirect evidence that changes in synaptic

efficacy may be the basis of learning within the hippocampus (1, 2), there has been no demonstration of changes in functional interaction among hippocampal cells specific to the representation of a given experience (3). Recent experiments with parallel recording methods, however, have revealed rapid changes in neuronal ensemble codes for space within the hippocampus during exposure to a novel environment (4). Also, Pavlides and Winson (5) previously demonstrated an increase in

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firing rate, during sleep, of those hippocampal cells that had been active during the prior waking period. Although this finding is suggestive of mnemonic operations, without knowledge of the distributed structure of the activity across the

neuronal population it cannot be determined whether this activity is organized into coherent representations of the preceding experience (memories).

Here we address the question of whether information acquired during periods of ac-

tive behavior results in the modification of neuronal circuits within the brain and whether the reactivation of such memory traces can be detected in the hippocampus during sleep. In principle, this question can be studied by the examination of statistical pair-wise interactions between neuronal spike trains. However, because the expected number of cells involved in encoding any particular event is small (4, 6), the probability of observing and quantifying such interactions in small samples of neurons is remote. To overcome this problem, we have studied the activity correlations among large sets of simultaneously recorded cells (4), because the number of possible interactions that can be observed increases as the square of the sample size.

Fig. 1. Spatial firing characteristics of populations of simultaneously recorded hippocampal pyramidal cells from three rats (rat 1: 49 cells; rat 2: 74 cells; rat 3: 69 cells). Each panel represents the average firing rate of a particular cell as a function of location in the recording apparatus. The colored areas represent visited regions in the apparatus, with red indicating high firing rate (~10 Hz) and blue indicating no firing. (Several of the silent cells from each rat are not shown, due to space constraints.)

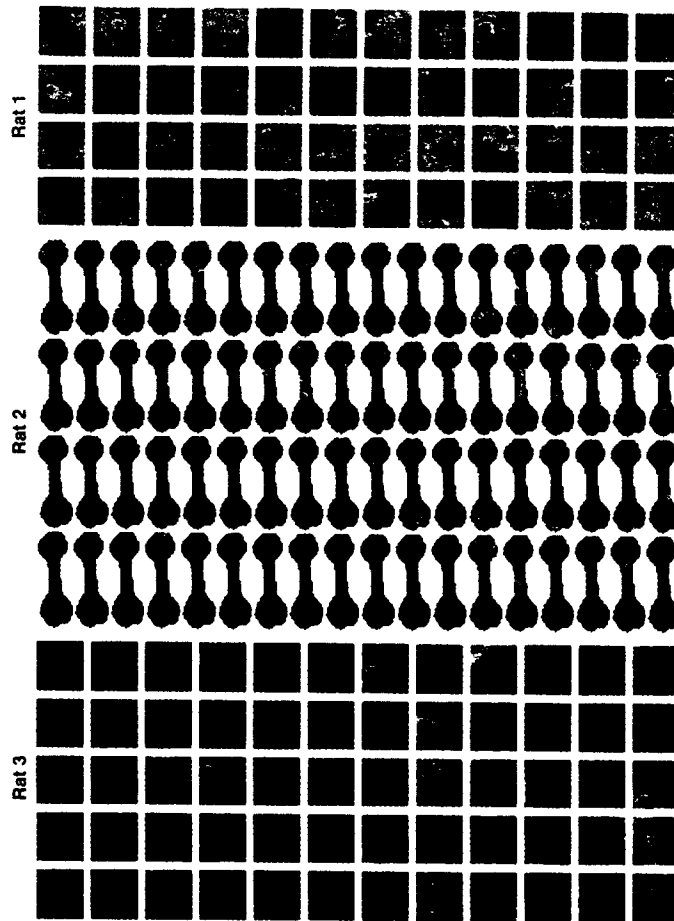


Fig. 2. Representative cross-correlation histograms from cell pairs with spatially overlapped (lower left) and non-overlapped (lower right) firing during the RUN phase (data from rat 2; color code as in Fig. 1). Periodicity during the RUN phase reflects theta rhythm modulation (9). This modulation is absent during the PRE and POST sleep periods. Comparison of the central peaks (100 ms) of the PRE and POST correlation histograms reveals an increase in coactivity for the cell pair (left column), which was coactive during running (center left histogram) because of spatially overlapped firing. This increase does not appear to cells that are active during running but are not coactive (right column). The y-axis gives correlation in terms of the number of spike pairs that occurred at the specified time lag. The bin size is 10 ms.

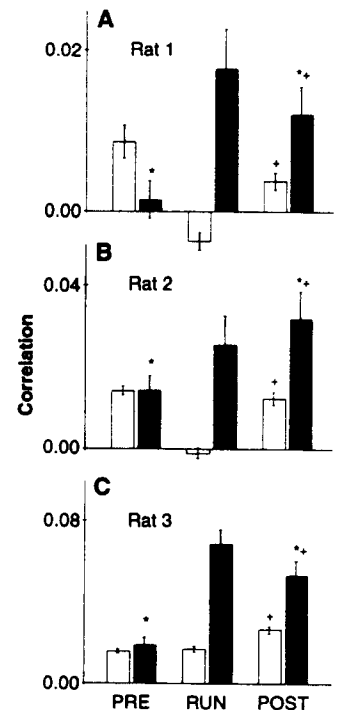
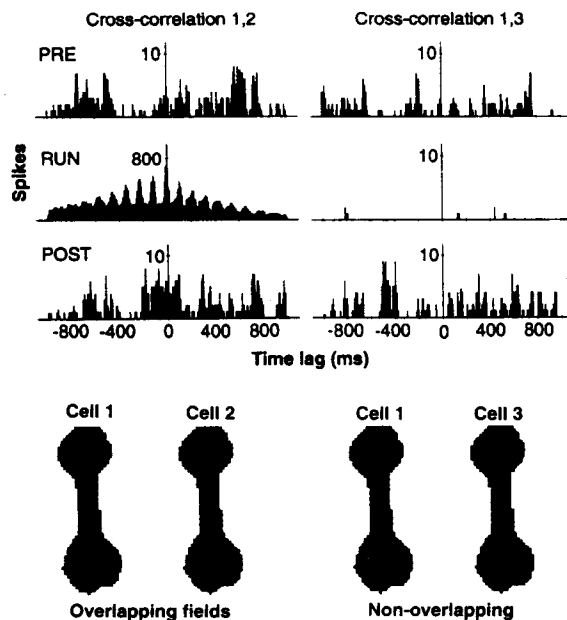


Fig. 3. Mean cross-correlations (± 100 ms) for cell pairs during PRE, RUN, and POST phases (Fig. 2). Only cells with significant spatial firing on the apparatus are included (10). Cell pairs were grouped on the basis of the amount of overlap between their spatial firing distributions. Cells that were correlated (OVR, solid bars) during the RUN phase exhibited a significant (analysis of variance, $P < 0.05$) increase in correlation during the post-run (POST) sleep relative to pre-run (PRE) sleep (*) or to cells that were non-overlapped (NON, hollow bars), and hence uncorrelated during running (plus signs). Correlations between cells that were active during sleep but inactive during RUN did not change between POST and PRE and were not different from the average PRE values of the cells active during RUN. The numbers of cell pairs contributing to each histogram were as follows: (A) Rat 1, NON 437 and OVR 60; (B) Rat 2, NON 719 and OVR 95; (C) Rat 3, NON 941 and OVR 147.

Rats were surgically implanted with microdrive arrays and then trained on one of two food-reinforced, spatial behavioral tasks (7). With the use of multielectrode recording techniques (4), the activity of 50 to 100 single cells in area CA1 of the hippocampus was monitored simultaneously during sleep periods before and after brief behavioral episodes (Fig. 1). Spike-train cross-correlations were computed for all pairs of principal cells during the pre-behavioral sleep (PRE), running (RUN), and post-behavioral sleep (POST) periods. For each cell pair, the short latency (± 100 ms) cross-correlation of spike trains was computed over each period (8); each period was approximately 20 min in duration (9). The correlation pairs were sorted by the amount of spatially overlapped activity between cells in the pair (10), as determined by the spatial firing characteristics ("place fields") of these cells during the running phase (RUN) (Fig. 2). During the RUN phase, as expected, cells with overlapping place fields exhibited highly positively correlated activity, whereas cell pairs with nonoverlapping fields did not exhibit such activity (Fig. 3). On the hypothesis that hippocampal activity during sleep reflects the reactivation of population events representing the experiences of the prior wak-

ing behavior, cell pairs that were coactive during the RUN phase (because of their place field overlap) were examined during the POST phase and compared with cell pairs that were active but not coactive during behavior (non-overlapping place fields) (Figs. 2 and 3). Cells that were coactive during behavior showed a significant increase in correlation from their PRE level compared to pairs in which both cells displayed spatial firing but not in the same region of space (11). This selective reactivation of correlated states declined during the POST phase with a time constant of approximately 12 min (12).

The increased correlation is consistent with an underlying associative synaptic modification at some stage in the system, although not necessarily in the hippocampus. Indeed, there is little direct connectivity among pyramidal cells within CA1, and, therefore, the emergence of experience-specific correlated states in this region is likely to arise from changes in common inputs, such as those from area CA3 (which has extensive intrinsic connectivity) or entorhinal cortex.

Changes in neocortical or subcortical pathways might underlie the increased correlations. However, on the basis of current understanding of the physiological dynamics of the hippocampus during slow-

wave sleep, it is possible to construct a plausible hypothesis for a hippocampal origin of the phenomenon. During behavioral inactivity and slow-wave sleep, the hippocampus displays a significant change in its electrical activity compared either to active waking behavior or to paradoxical rapid eye movement (REM) sleep. During slow-wave sleep, cells discharge in intermittent, synchronized bursts (ripples) (9), associated with electroencephalogram (EEG) sharp-wave (SPW) activity. It has been proposed that information transfer to neocortex occurs during sleep in general (5, 6) and particularly during the synchronized bursts (13). To investigate this hypothesis, correlation effects were examined both during ripples and during the intervals between them. Correlations were significantly larger during ripples than in the intervening intervals (14). This difference is consistent with previous theoretical models of autoassociative memory (6), in which recurrent excitation is used to reproduce a previously stored activity pattern, even when the input contains very little of the relevant information. In such networks, even random background noise can occasionally lead to the emergence of correlated states, manifested as population bursts (ripples), reflecting stored patterns. The self-terminating nature of these bursts (9) would then reset the network to its "ground state" and allow the process to start anew. Consistent with this notion, recent physiological studies (15) have shown that SPWs and ripples are initiated in CA3, and that the output layers of entorhinal cortex, but not the input layers, exhibit neuronal activity correlated with CA1 SPWs. This relation suggests that the induced correlations during SPWs arise from modifications within the hippocampus itself and are propagated to the output layers of entorhinal cortex.

The foregoing observations demonstrate that, during sleep, the activity of hippocampal cells engaged in place-specific activity during prior waking (5) retains the structure of distributed representations of the visited locations (Fig. 4). According to the proposed hypothesis, initial storage of event memory occurs through rapid synaptic modification, primarily within the hippocampus. During subsequent slow-wave sleep, synaptic modification within the hippocampus itself is suppressed (16) and the neuronal states encoded within the hippocampus are "played back" as part of a consolidation process by which hippocampal information is gradually transferred to the neocortex (6, 17).

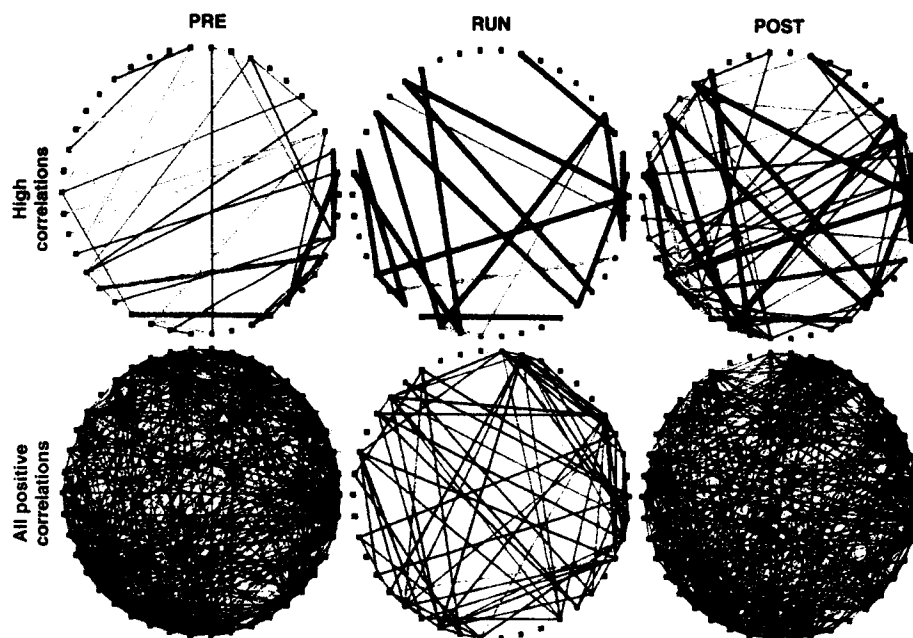


Fig. 4. Diagram of the effective connectivity matrix of a network of 42 cells (selected at random) from rat 2. Individual cells are represented as dots around the perimeter of a circle. Lines indicate a positive correlation between the pair, with color reflecting the magnitude of the correlation [red, high (0.2); blue, low (0.002)]. The lower three panels show all positive correlations for each of the PRE, RUN, and POST conditions and illustrate the dramatic contrast in overall correlation structure between slow-wave sleep and active behavior. The upper three panels show a subset of the same data having positive correlations above 0.05. Bold lines indicate cell pairs that were correlated during RUN and also correlated during either PRE or POST. These panels reveal that most of the highly correlated pairs that appear during the run phase also appear in the POST phase but are typically absent from the PRE phase.

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 - In one task, the rat searched steadily within an enclosed box (62 by 62 cm; rats 1 and 3) for a randomly scattered food reward. In the second (spatial working-memory) task, an elongated, X-shaped, four-arm track (167 by 25 cm; rat 2) was used with two adjacent arms designated as start and the opposite two arms designated as goals. The correct goal arm was a function of the randomly selected start arm. Animals were male Fisher 344 rats, approximately 300 g and 9 months of age. All surgical procedures were carried out according to NIH guidelines.
 - Both principal cells (excitatory pyramidal cells) and inhibitory interneurons were recorded during these sessions. Interneurons, identified on the basis of wave shape, firing rate, and spike interval characteristics, were not included in the study. Cross-correlations were normalized by spike counts [D. H. Perkel, G. L. Gerstein, G. P. Moore, *Biophys. J.* 7, 419 (1967); G. L. Gerstein and D. H. Perkel, *Science* 164, 828 (1969)].
 - Hippocampal EEGs from eight of the unit recording sites were continuously monitored. Sleep phases were predominantly characterized by intermittent SPW and ripple activity [J. B. Ranck Jr., *Exp. Neurol.* 41, 461 (1973); J. O'Keefe and L. Nadel, *The Hippocampus as a Cognitive Map* (Oxford Univ. Press, Oxford, 1978), pp. 150-153; G. Buzsáki, *Brain Res.* 398, 242 (1986)] with population bursts of variable duration (100- to 300-Hz band EEG, mean duration 74 m, mean inter-burst interval 1.7 s) with little or no REM sleep. The behavioral phase was dominated by theta activity (6- to 9-Hz modulation of EEG and unit discharge), which has been correlated with locomotion [C. H. Vanderwolf, *Electroencephalogr. Clin. Neurophysiol.* 26, 407 (1969)].
 - Hippocampal neurons exhibit robust selectivity for spatial location. The preferred location for a given cell is called its "place field" [J. O'Keefe and J. Dostrovsky, *Brain Res.* 34, 171 (1971)]. For each cell pair in which both members exhibited significant spatially related firing in the apparatus, the distance between the locations of their peak firing was used as a measure of overlap (Fig. 1). The criterion for overlap was a distance between peaks of <16 cm

(approximately the diameter of an average place field). To eliminate any possibility of spurious overlap due to incomplete isolation of single units on a given probe, cell pairs taken from the same probe were eliminated from the analysis. The mean firing rates of cells in coactive cell pairs were the same as those for non-coactive pairs. Thus, the increased correlations were not due to firing rates per se.

- Figure 2 reveals a tendency for pairs that were negatively correlated (not overlapping) during behavior (see animals 1 and 2 in Fig. 3) to result in reduced correlation during the POST phase. This effect was small and statistically significant only for rat 1.
- The time constant for decay of correlation was estimated by dividing the initial 10 min of the POST sleep phase into two 5-min periods and computing the mean correlation for overlapping cell pairs in each period. A third point obtained from the mean correlation of the PRE phase was assumed to be the asymptotic base line for the decay. The mean time constant was determined by the fitting of a single exponential to these three points. Rat 1 latency to sleep onset was 20 min, sleep duration was 18 min, and the time constant estimate was 15 min. Rat 2 latency was 10 min, duration was 20 min, and the time constant was 9 min. Rat 3 latency was 8 min, duration was 10 min, and the time constant was 13 min.
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Dependence on REM Sleep of Overnight Improvement of a Perceptual Skill

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Several paradigms of perceptual learning suggest that practice can trigger long-term, experience-dependent changes in the adult visual system of humans. As shown here, performance of a basic visual discrimination task improved after a normal night's sleep. Selective disruption of rapid eye movement (REM) sleep resulted in no performance gain during a comparable sleep interval, although non-REM slow-wave sleep disruption did not affect improvement. On the other hand, deprivation of REM sleep had no detrimental effects on the performance of a similar, but previously learned, task. These results indicate that a process of human memory consolidation, active during sleep, is strongly dependent on REM sleep.

Perceptual learning—the improvement of perceptual skills through practice—is a type of human learning that may serve as a paradigm for the acquisition and retention of procedural knowledge, "habits," or "how to" memories (1). Recent results suggest that when observers practice a simple texture discrimination task the large and consistent improvements that occur over the course of several consecutive daily sessions

are subserved by discrete changes dependent on retinal input and within an early stage in the stream of visual processing (2). Psychophysical data implicate neuronal mechanisms of figure-ground segmentation at a stage in the processing pathway as early as the primary visual cortex in mediating (by becoming more efficient and faster) the learning of this basic visual skill (2, 3). These results, as well as results from several other perceptual learning paradigms (4), suggest that different levels of visual processing may, under specific retinal input and task-defined conditions, undergo long-term, experience-dependent changes (functional plasticity) (5).

Recently, we and others have found that an improvement in perceptual performance occurs neither during nor immediately after practice but rather 8 to 10 hours after a training session has ended, suggesting a slow, latent process of learning (6). As the improved visual skills were not forgotten even

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