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Hippocampal growth and attrition in birds affected by experience

(passerines/memory/hippocampus/apoptosis/food-storing)

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ABSTRACT **Hand-raised marsh tits (*Parus palustris*) were exposed to experience of storing and retrieving food at three different ages (35–59, 60–83, 115–138 days posthatch). At equivalent ages, control birds were given identical experience except for storing and retrieving food. Volumetric analysis was carried out to measure the hippocampal region, ectostriatum, and telencephalon of experienced and control birds. Individuals with experience of storing and retrieving food had a larger hippocampal region relative to the rest of the telencephalon than did controls, independent of age. The hippocampal region of experienced birds also contained more neurons and fewer apoptotic cells than that of controls. No volumetric differences were observed in ectostriatum, which served as a control brain region. The results suggest that some aspect of food-storing and retrieval directly influences growth and attrition of the hippocampal region in food-storing birds.**

The hippocampal region (dorsomedial cortex) of the avian brain plays a role in spatial memory, including the memory for cache sites in food-storing birds (1–3). Comparisons among passerines birds (4–7) have shown that the hippocampal region is larger relative to the rest of the telencephalon in food-storing species than in nonstorers. Here we show that volume of the hippocampal region relative to the rest of the telencephalon in the food-storing marsh tit (*Parus palustris*) is dependent upon food-storing experience. This effect is not seen in another forebrain region taken as a control. Experience of storing and retrieving food, independent of age within the range tested (35–138 days), causes growth of the hippocampal region. Growth does not increase in proportion to the amount of food-storing experience, suggesting that there may be a threshold effect. Control birds, prevented from storing and retrieving food but otherwise given identical behavioral experience, show a cumulative decrease in volume of the hippocampal region with increasing time over which storing is prevented. In addition to their smaller hippocampal volume, compared with experienced birds, controls have fewer neurons in the hippocampal region and a higher proportion of apoptotic cells, suggesting that one effect of experience of food-storing may be to reduce programed cell death.

METHODS

The subjects were 47 hand-raised, postfledging juvenile marsh tits (taken under Nature Conservancy Council license). At nutritional independence (day 35 posthatch), birds were divided into groups that were exposed to different kinds of behavioral experience (Table 1). In food-storing trials, birds were deprived of food overnight and tested individually the following morning for their ability to store sunflower seeds and remember the spatial locations of these seeds. Trials were carried out in a 3.5 × 4.0 × 2.8 m room that contained four "trees" supported in plastic basins on the floor and a platform with water and a bowl of sunflower seeds. On each tree there were eight, individually numbered storage sites (a hole 5 mm in diameter × 5 mm deep) with a wooden perch 5 mm below each hole. When the birds searched for their caches, the storage sites were covered by a string knot to prevent the birds from seeing the stored seeds (8). In the first phase of a food-storing trial the bird was provided with a bowl containing sunflower seeds and allowed to store for 20 min. Following a retention interval of 2 hr in the home cage (each cage was connected to the test room by an individual trapdoor), the bird was allowed back into the room for a 10-min second phase, during which it could search for its caches.

Control birds were treated in an identical way except that in phase I of each trial they were given powdered sunflower seed that they could eat but not store. In phase II, the birds flew and perched in the room but did not retrieve because they had not cached seeds. The durations of the two phases for control birds were matched with those of the experienced birds. To control for experience in handling and eating seeds, all birds were given one seed in their home cage after every trial.

The experiment was divided into three stages according to age of the birds (Table 1). Group EEE birds were exposed to food-storing/retrieval experience every third day in all three stages and a subset of the birds was sacrificed after each stage. In stage I, groups E_H and E_L were included to investigate the effects of elevated or reduced levels of experience. Group E_H birds stored ad lib every day instead of storing once every third day, while group E_L birds were allowed to store only one seed per day. Group CEE birds were given control experience in stage I (until day 60) but they were transferred to storing/retrieval for stages II and III. Group CCE birds were given control experience in stages I and II (until day 115), and they were transferred to the storage/retrieval treatment for stage III. Group CCC birds remained as controls throughout all three stages. In addition to the 45 brains derived from these treatments, two naive birds were sacrificed before the start of the experiment (day 35) to provide a baseline measure of relative hippocampal volume before any storing or control trials.

The logic of the experimental design is as follows. Previous behavioral work has shown that young marsh tits start to store at day 44 and that storing reaches an asymptote by day 59 (8). Therefore comparison of the experienced (group EEE) and control (group CEE) brains at the end of stage I (day 59) is a test of whether or not the behavioral transition from nonstoring to storing is accompanied by changes in the relative volume of the hippocampal region. The birds in groups E_H and E_L test the effect of amount of experience of storing and retrieving food during stage I. Group E_H birds had enhanced experience, compared with group EEE, by storing and retrieving ad lib every day, while group E_L birds had reduced experience by storing and retrieving only one seed per day.

The remaining treatment groups were designed to test whether or not any effect observed in the comparison of

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Table 1. Experimental design

Group	n	Stage of experiment (age, days posthatch) I (35–59)	II (60–83)	III (115–138)
1	15	**E (6)**	**E (6)**	**E (3)**
2	3	**E (3)**	—	—
3	3	**E (3)**	—	—
4	15	**C (6)**	**E (6)**	**E (3)**
5	6	**C**	**C (3)**	**E (3)**
6	3	**C**	**C**	**C (3)**

The purpose of the experiment was to expose birds to their first experience of storing and retrieving food at different ages, while holding other aspects of experience constant (see text for a description of *experienced* (E) and *control* (C) procedures). The behavioral procedure to which each group was exposed at each stage of the experiment and the number of birds sacrificed for brain measurement at the end of each stage (in parentheses) are indicated. Note that for the brain measurements there were 11 samples from the six groups, as shown in boldface type. Each stage lasted for 24 days in order to allow the full development of storing and retrieval by birds exposed to storing for the first time. Note that groups 1–3 in stage I all included birds that had experience from day 35–59. These groups differed in the amount of experience: group EEE stored/retrieved ad lib every third day; group E_H stored/retrieved ad lib every day; group E_L stored/retrieved one seed per day. Stage II of the experiment followed immediately after stage I. However, there was a gap of 32 days between stages II and III, during which the birds were exposed to their appropriate behavioral trials once per week. The gap was included so that the third stage of the experiment was carried out at the time when wild birds would normally have been at their autumn peak of storing. The aim was to test whether birds that were prevented from storing until this late age would still develop normal storing and any associated changes in the brain.

experienced and control birds at day 59 is restricted to a "sensitive phase" in early life. To test this hypothesis, birds were transferred from the control to the experienced condition at different ages to see if the behavioral transition from nonstoring to storing that normally occurs at day 44 could be reproduced at different ages by providing the opportunity to store. At the same time, the treatments test whether changes in the brain are caused by changes in behavioral experience independent of age. To achieve these comparisons, some control birds were transferred to the experienced condition at the start of stage II on day 60 (group CEE birds) and others at the start of stage III on day 115 (group CCE birds). The experimental design allows one further set of comparisons to test whether or not there is a cumulative effect of either experience or control treatments. Birds in group EEE were sacrificed at the end of all three stages (days 59, 83, and 138), while birds in group CEE, which had experience from day 60 onward, were sacrificed at the end of stages II and III (days 83 and 138). Control birds were sacrificed at the end of all three stages (days 59, 83, and 138), allowing a test of the possibility of cumulative effects of the control treatment.

To place the timing of the three experimental stages in the context of the overall life-span of the birds, note that before the first stage (day 35) marsh tits are fully grown but have not reached sexual maturity. By the start of the third stage, the birds have molted into adult plumage and are fully sexually mature. The three stages cover more than a third of the average expected life-span of an 11-g bird such as the marsh tit.

Brains were treated in an identical way to control for effects of shrinkage. At the end of each stage, birds were perfused transcardially following a lethal interperitoneal overdose of sodium pentabarbitone (4). The brains were cut as 25-μm frozen coronal sections. Every 10th section was stained with cresyl violet. The volume of the hippocampal region [defined by a combination of techniques (4–6, 9–11)] (Fig. 1) and the remainder of the telencephalon were traced and digitized to compute the volumes using standard techniques (4–6). Neuron numbers were estimated using the same protocol as in previous measurements on the avian hippocampal region (7). Apoptotic cells, identified in the cresyl violet-stained sections by their densely stained spherical chromatin (sometimes fragmented) and lack of cytoplasm, were counted in every third section. All measurements were done blind.

RESULTS

At all three stages, experienced birds started to store and retrieve food after 7–10 days of exposure to seeds in the storing arena. In all cases, there was a transition from not storing to storing over two to three trials, after which the amount of storing remained relatively constant. Memory performance, measured by plotting the cumulative number of seeds found as a function of number of sites visited in phase II of each trial, improved more gradually over the period of experience (12).

Results of the volumetric analysis of the brains are illustrated in Fig. 2. Following the methods used in previous studies (4–7), volume measurements were logarithmically transformed and analyzed using the residuals of a regression of hippocampal volume on telencephalon volume (i.e., relative hippocampal volume). Fig. 2*A* combines experienced (excluding groups E_H and E_L because they were tested daily) and control birds from the different treatment groups, while Fig. 2*B* shows the different experienced groups at each stage of the experiment. Data were analyzed by a one-way ANOVA on the 11 samples indicated in boldface type in Table 1. Particular comparisons between groups were carried out by nonorthogonal contrasts (for further details of statistical comparisons and significance levels, see legend to Fig. 2). Results can be summarized as follows: (*i*) At all three stages, experienced birds had a relatively larger hippocampal region than did controls. (*ii*) Control birds showed cumulative attrition of the hippocampal region with increasing length of deprivation of food-storing experience. There was no trend across stages in the experienced birds. (*iii*) Group E_H birds did not have a larger hippocampal region than group EEE at day 59, although they had stored every day instead of every third day; group E_L birds, which stored only one seed per day, had a smaller relative hippocampal region than group EEE birds at the same stage. This suggests that the amount of experience required to trigger growth of the hippocampal region is greater than storing and retrieving one seed per day and that above this threshold there is no dose dependence. (*iv*) The effect of experience on hippocampal volume did not change with age. Group EEE birds had a similar relative hippocampal volume in all three stages, birds exposed to their first storing experience at day 60 (group CEE) did not differ in relative hippocampal volume from those exposed from day 35, and those exposed at day 115 (group CCE) did not differ from birds starting at day 60.

In summary, the results demonstrate that two processes affect relative hippocampal volume in marsh tits. (*i*) Control birds, with no food-storing experience, show gradual attrition of the hippocampal region as a function of time in the control condition. (*ii*) In contrast, experienced birds show an increase in relative hippocampal volume compared with the control birds. The effect of experience is independent of age and is not cumulative.

Fig. 2 shows deviations from the regression of hippocampal region on telencephalon and therefore does not give an indication of the absolute magnitude of the effects. The mean volume of telencephalon for all experienced groups (excluding group E_L because these birds, which stored and retrieved only one seed per day, differed significantly in relative hippocampal volume from the other experienced groups; see

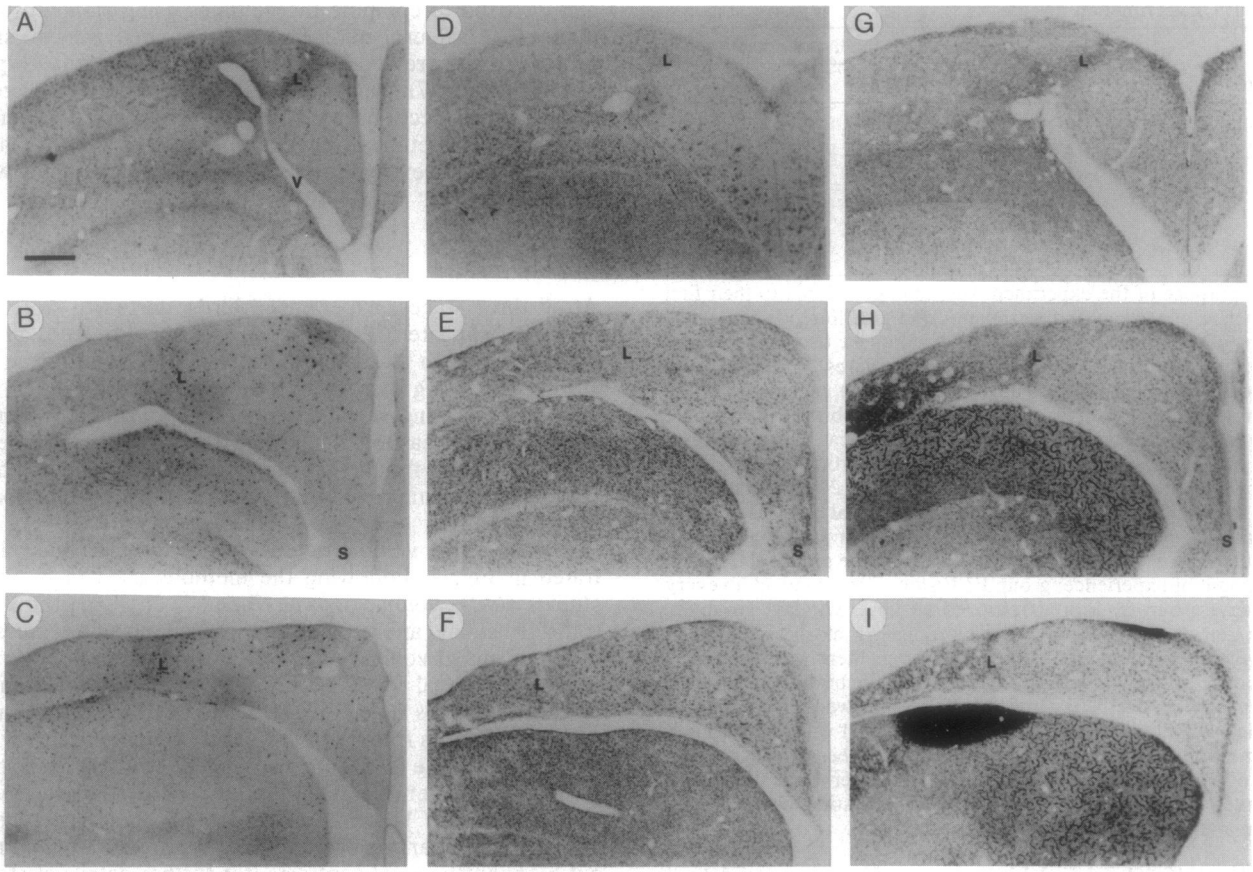

FIG. 1. Photomicrographs to illustrate the boundaries of the hippocampal region in the marsh tit in three different coronal sections (rostral, middle, and caudal, from top to bottom of each column), using three different staining techniques. (*A–C*) Calbindin immunocytochemistry (10). (*D–F*) Cresyl violet (4). (*G–I*) Acetylcholine esterase (11). The middle and righthand series are from the same bird and are from similar planes of section; the lefthand series is from a different individual and the plane of section is not identical to that of the other two series. The hippocampal region lies on the dorso-medial surface of the telencephalon above the lateral ventricle (V) and is a paired structure. Here, only the left side is shown, although in the top row part of the right side can be seen. The lateral boundary (L) is indicated in calbindin-stained sections by a band of densely stained neuropil (10), cresyl violet-stained material by a change in cell density (4), and acetylcholine esterase-stained material by a densely stained band of neuropil (11). The septohippocampal boundary (S) is indicated by an abrupt change in the staining pattern in all three stains. Quantitative analysis of the volume of the hippocampus stained by the different methods shown here indicates that the three stains reveal the same boundaries. (Bar = 500 μm.)

legend to Fig. 1) was 46339 mm^3 and the hippocampal volume was 2206 mm^3. For the control groups combined, the figures were 49060 mm^3 and 1718 mm^3, respectively. Thus the telencephalon of experienced birds was 94% of the volume of control birds ($t_{37} = 0.79$, $P = 0.41$), while the hippocampal region was 128% that of the controls ($t_{37} = 3.06$, $P = 0.004$). In other words, the average overall difference between experienced and control hippocampal volumes was about 28% and the difference relative volume of the hippocampal region of experienced and control birds arose because the telencephalon did not differ between the two groups while the hippocampal region was larger in experienced birds.

The analysis in Fig. 2 showed that food-storing experience does not induce general growth of the telencephalon, because values are expressed relative to the telencephalon as a whole. As a further check of the specificity of the effect on the hippocampal region, an analysis identical to that summarized in Fig. 2 was carried out on ectostriatum, a telencephalic nucleus similar in size, and not directly connected, to the hippocampal region (14). Ectostriatum is a visual nucleus receiving afferents via the tectofugal pathway and is considered to be equivalent to the mammalian peristriate cortex (15). Relative ectostriatum volume did not differ between the experimental groups ($F_{10,34} = 1.73$, $P > 0.05$), supporting the conclusion that the effect of experience is specific to the hippocampal region.

Figs. 3 and 4 show estimates of neuron number and proportion of apoptotic cells in the hippocampal region of the experienced and control groups referred to in Fig. 2. The following effects are apparent (statistical analysis and significance levels are in the figure legends). (*i*) There were more neurons and fewer apoptotic cells in the hippocampal region of experienced birds than in control birds. (*ii*) There was an overall decline in neuron number and apoptosis with stage of the experiment, although the patterns for the two variables do not match closely. (*iii*) Birds with reduced experience in stage I (group E_L) had fewer neurons and more apoptotic cells than group EEE or group E_H birds, supporting the idea that there is a threshold for the amount of experience required to induce changes in the hippocampal region. As with the volumetric difference involving group E_L, these effects are only marginally significant and should be tested further. (*iv*) Comparison of birds starting to store at different ages supports the view that there is not a sensitive phase for effects of storing on the hippocampal region.

DISCUSSION

Although the results in Figs. 2–4 show that experienced birds have a larger hippocampal region, more cells, and less apoptosis than controls, it is not clear yet how these three variables are interrelated. The details of the changes in experienced and control groups across the three stages of the

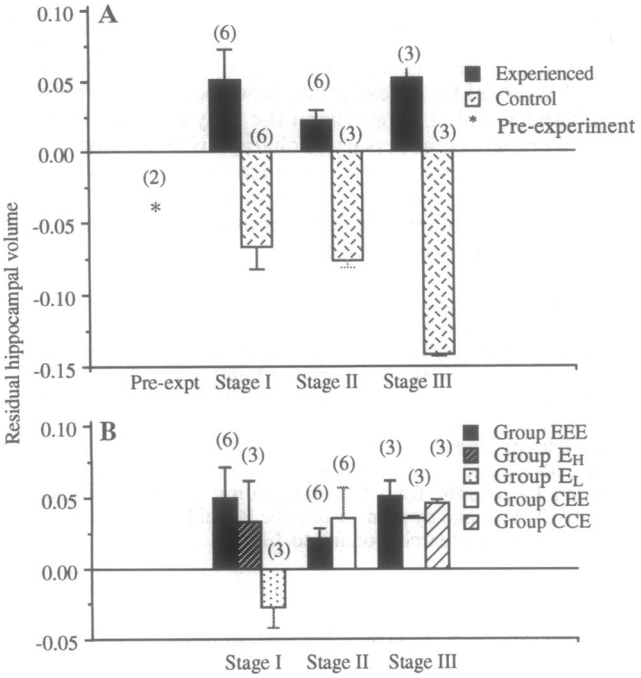

FIG. 2. (*A*) Mean values (±SE) of relative hippocampal volume of experienced and control birds at the three different stages of the experiment (see Table 1). Solid histograms represent birds that had food-storing/retrieval experience once every 3 days; hatched histograms represent birds that had control experience every 3 days (i.e., all 35 birds sacrificed from groups EEE, CEE, CCE, and CCC in Table 1 are shown). The pre-experimental baseline birds are indicated by an asterisk. Sample sizes in each group are shown by numbers in parentheses. (*B*) Mean values (±SE) of birds with different levels of experience (groups EEE, E_H, E_L, CEE, and CCE in Table 1). Different shading patterns refer to the different treatments in Table 1. Values are the residuals from a regression of hippocampal volume on telencephalon volume. A stepwise multiple regression with hippocampal volume as the dependent variable and telencephalon volume and body weight as the independent variables showed that there was a significant association between telencephalon and hippocampal volume ($r^2 = 0.54$, $F_{1,45} = 56.378$, $P < 0.001$) but no significant association between body weight and hippocampal volume ($r^2 = 0.11$, $F_{1,45} = 5.936$, $P > 0.05$). (These analyses included all 47 birds.) The residuals were analyzed by one-way ANOVA to compare the effects of food-storing experience on relative hippocampal volume, the birds from each group having been matched for weight and clutch. An overall ANOVA on the 11 samples indicated in Table 1 [group EEE after stages I, II, and III (3 samples), groups E_H and E_L after stage I (2 samples), group CEE after stages I, II, and III (3 samples), CCE after stages II and III (2 samples), and group CCC after stage III (1 sample)] was significant ($F_{10,34} = 6.24$, $P < 0.0001$). Selected groups were compared with *a priori* nonorthogonal contrasts to test particular hypotheses. All of these contrasts use the error mean square from the overall ANOVA and therefore have t values with 34 degrees of freedom. There are two general approaches to making nonorthogonal comparisons. One is to compensate the critical value of t for the overall number of comparisons to a set level of experimentwise error rate [here we used the method of Dunn (13)]. This reduces the chance of a type 2 error but increases the chance of a type 1 error. An alternative is to balance the two kinds of error by adopting a more stringent level of significance than usual, but not applying compensation to the critical value of t. Unless indicated, whether or not the results are significant is unaffected by the approach taken. (*i*) The harmonic mean of group EEE birds (experienced) differed from their relevant controls (group CEE after stage I, group CCE after stage II, and group CCC after stage III) ($t = 5.75$). (*ii*) The three sets of control birds showed a significant quadratic trend with increasing time ($t = 3.10$), while experimental birds in group EEE showed no trend across the stages ($t = 0.97$ and 0.40 for linear and quadratic contrasts, respectively). (*iii*) To test for an age-dependent effect of experience, the mean of group EEE was compared with the mean of group CEE after stages II and III and the mean of group CEE was compared with group CCE after stage III.

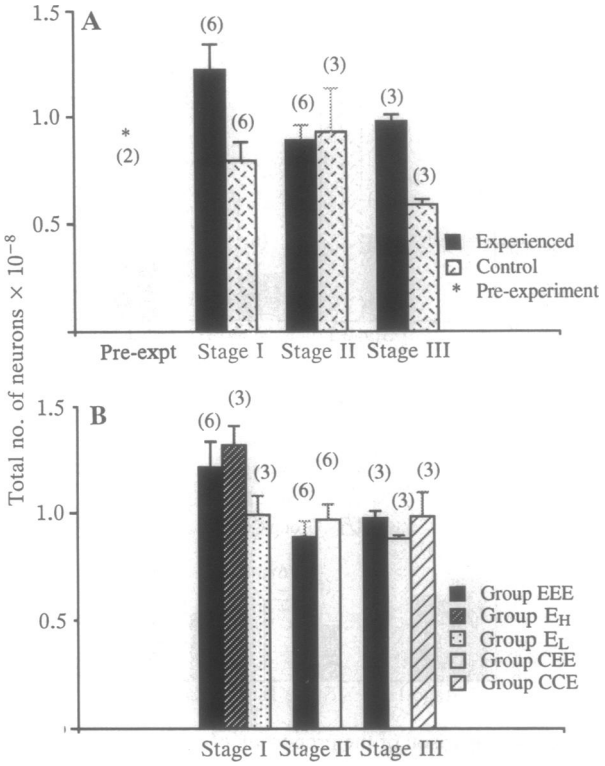

FIG. 3. (*A*) Estimates of total neuron number (mean per group ± SE) in the hippocampal region of experienced and control birds exposed to the treatment every 3 days (groups EEE, CEE, CCE, and CCC from Table 1), as in Fig. 2*A*. (*B*) Estimates of mean neuron number (±SE) in the five experienced groups of birds (groups EEE, E_H, E_L, CEE, and CCE in Table 1). Analysis was similar to that described in the legend to Fig. 2. The overall ANOVA was significant ($F_{10,34} = 4.21$, $P < 0.001$) and the contrasts (t with 34 degrees of freedom) were as follows. (*i*) The harmonic mean of group EEE birds (experienced) differed from their relevant controls (group CEE after stage I, group CCE after stage II, and group CCC after stage III) ($t = 4.13$). (*ii*) The experimental birds in group EEE showed a linear trend across the stages that was significant at the 2% level but not with full compensation ($t = 2.42$), while controls did not ($t = 1.37$). (*iii*) The mean of group EEE did not differ from the mean of group CEE after stages II and III, nor did the mean of group CEE differ from group CCE after stage III ($t = 1.25$ and 0.27, respectively). (*iv*) Group EEE did not differ from group E_H after stage I but had more neurons at the 1% level (but not with complete compensation) than group E_L ($t = 1.17$ and 2.81, respectively).

experiment show that changes in volume cannot be totally accounted for in terms of changes in cell number and that, similarly, changes in cell number do not always correlate with levels of apoptosis. Therefore, it seems likely that other processes, including the recruitment of cells, are involved.

The experimental design aimed to ensure that experienced and control birds differed only with respect to storage and retrieval of food. Although further work will be necessary to demonstrate exactly which aspects of storing and retrieval experience are crucial in causing the observed changes in the hippocampal region, behavioral data showed that the experienced and control groups did not differ either quantitatively or qualitatively in activity (number of sites searched during a trial) and food intake (estimated by body mass). Other measures are described elsewhere (12).

Both comparisons were nonsignificant ($t = 0.45$ and 0.65, respectively). (*iv*) To test for a dose dependence during stage I, group EEE was compared with group E_H and with group E_L after stage I. The first comparison was not significant ($t = 0.18$) while the second was significant at the 2% level but not with full compensation ($t = 2.46$).

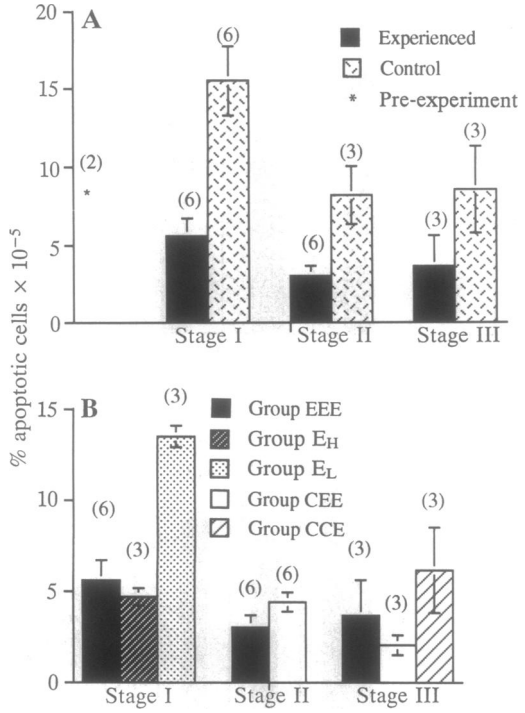

FIG. 4. Comparison of the proportion of cells that are apoptotic in the hippocampal region of the various treatment groups (mean per group ± SE). Details as in Figs. 2 and 3. The overall ANOVA was significant ($F_{10,34}$) = 7.95, $P < 0.001$) and the contrasts (t with 34 degrees of freedom) were as follows. (*i*) The harmonic mean of group EEE birds (experienced) differed from their relevant controls (group CEE after stage I, group CCE after stage II, and group CCC after stage III) ($t = 6.04$). (*ii*) The experimental birds in group EEE showed a linear trend across the stages ($t = 3.17$) while controls did not ($t = 0.78$). (*iii*) The mean of group EEE did not differ from the mean of group CEE after stages II and III ($t = 0.04$) and the mean of group CEE did not differ from group CCE after stage III ($t = 2.17$). (*iv*) Group EEE did not differ from group E_H after stage I but had fewer apoptotic cells than group E_L [at the 2% level but not with full compensation ($t = 1.48$ and 2.79, respectively)].

Previous studies have shown that the developing brain of birds and mammals, including the mammalian hippocampal region, is plastic in response to specific kinds of sensory input or experience and to hormonal influences (16–23), but the present results are unique in having the following combination of features. (*i*) The effect of experience is independent of age within the range tested, in contrast to, for example, effects of visual experience on the development of the visual cortex in mammals (16). (*ii*) The effect is specific, in terms of experience (controls and experimentals did not differ in experience other than the specific task of storing and retrieving food) and in terms of the localization of the effect [it is not a general effect as seen in effects of diverse kinds of enrichment on cortical growth in rats (17)]. (*iii*) The results suggest that one effect of experience is to prevent cell loss through apoptosis, while experience-dependent changes in the mammalian cortex referred to above reflect changes in dendritic arborization and those associated with imprinting and passive avoidance learning are at the synaptic level (22, 23). Changes in certain song control nuclei in the zebra finch are associated with apoptosis (21), but it is not known how these changes are affected by experience.

Apoptosis is thought to be a significant process in the developing nervous system, but to date its role in changes in the adult central nervous system, the kinds of stimuli that induce or prevent it, have not been established (24–26). The present results suggest that the avian hippocampal region is a valuable model for investigating how specific environmental influences inhibit apoptosis in the fully developed brain. Future work will be necessary to characterize more precisely the quantity and quality of experience that will prevent cell death and the consequences for memory as well as to characterize the other cellular processes that underlie the volumetric changes reported here.

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