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Discriminative long-term retention of rapidly induced multiunit changes in the hippocampus, medial geniculate and auditory cortex

Jean-Marc Edeline, N. Neuenschwander-El Massioui and G. Dutrieux

Département de Psychophysiologie, Laboratoire de Physiologie Nerveuse, CNRS, Gif-sur-Yvette (France)

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Multiunit activity was chronically recorded in the hippocampus (CA3 field), the magnocellular medial geniculate (MGm) and the auditory cortex (AC) of rats during acquisition (12 daily sessions, 10 trials per session) and long-term retention of differential classical conditioning (tones paired with footshocks). Marked increases of multiunit discharges to CS + presentations were first detected in the MGm (5–10 trials) followed (10–20 trials) by the emergence of discriminative responses in the hippocampus and in the AC. During long-term retention tests, 45 days after the end of conditioning, CS + selective responses were observed in the 3 structures. We propose that learning-induced changes in the conditioned stimulus (CS) sensory pathway can have the same temporal stability as the sensory plasticity observed during development or post injury in adult animals.

INTRODUCTION

In the past 15 years, a number of studies have reported learning-induced changes in the sensory pathway for the conditioned stimulus (CS) during the acquisition of different types of conditioning[11,16,32,34,39,47–49]. The appropriate controls (such as differential effects to a CS + compared to a CS −, or comparisons between conditioned and pseudoconditioned animals) have firmly established the associative nature of such changes. Moreover, recent studies[9,18,47] have demonstrated that these associative changes can take place in considerably fewer conditioned trials than those used in the pioneering work of Olds and his co-workers[32]. Thus, it seems unlikely that these changes are only a passive reflection of cellular modifications occurring in associative (non-sensory) structures. In fact, the large diversity of preparations in which these sensory alteration responses can be detected (see Weinberger and Diamond[49], for review) suggests that this phenomenon occurs each time a sensory stimulus acquires a predictive value.

Considering the other circumstances where sensory plasticity occurs — during development and following peripheral injury in adult animals — it is remarkable that in both of these cases the reorganization which takes place is expressed over months, and perhaps, during all of the animal's life. Recent data suggest that cortical re-

Correspondence: J.-M. Edeline, Present address until end October 1990: Center for the Neurobiology of Learning and Memory, Bonney Center, University of California. Irvine, CA 92717, U.S.A. Permanent address from November 1990: Département de Psychophysiologie, Laboratoire de Physiologie nerveuse, CNRS, 91190 Gif-sur-Yvette, France.

organizations take place in the S_I map of monkey following behavioral training[22]. However, as these changes occurred after months of training, the question can be raised about the stability of cellular changes detected in a sensory pathway after conditioning with less extensive training.

At the behavioral level, it is well-known that the predictive value of a CS in aversive conditioning can last over a long-term retention interval[41,50]. In a first attempt to link the retention of the predictive value with the sensory plasticity, we have reported that 45 days after conditioning, multiunit changes in the magnocellular medial geniculate (MGm) can be correlated with the retention of a behavioral response[13]. However, even if little or no forgetting is generally detected in rats on conditioned emotional response (CER) paradigms[3,5,15,42], some data suggest that an alteration of the representation of precise features of the CS can occur after a long retention delay[21,44]. As a consequence, it is possible that all acoustic stimuli presented after a long retention delay could be able to trigger the cellular responses we have observed. Until now, no attempt was made to test the specificity of the cellular retention after similar delays to those used in behavioral studies.

To address this question in the present study, we have trained rats in a discrimination paradigm and tested the selectivity of the cellular retention 45 days after conditioning. We have recorded in the MGm and the auditory cortex (AC), which are the two auditory structures showing the most consistent conditioned changes during learning. With regard to these two structures, the hippocampus was chosen as a neural index of acquisition and retention of conditioning since: (1) some studies have already observed long-lasting cellular changes in this structure[6,12,13,24,30,33]; (2) the extensively studied hippocampal long-term potentiation (LTP) phenomena support the notion that persistent changes can take place in this structure; and (3) it seems possible to find a high degree of correlation between the development and the retention of cellular changes in this structure and the acquisition and retention of the predictive value of a CS[25,26].

MATERIALS AND METHODS

Six male Sprague-Dawley rats, weighing 300–350 g at time of surgery were used as subjects. Electrodes were stereotaxically implanted while the animals were under deep anesthesia (sodium pentobarbitone, 50 mg/kg). After surgery the animals were placed in individual cages under a natural dark–light cycle. At least a week of recovery was allowed before the start of the experiment.

Implantation and recording procedure

The implantation and recording procedure were previously described in detail[13]. Briefly, two electrodes (62 μm diameter Nichrome wires sharpened under microscopic control, between 250 and 900 kΩ at 150 Hz) were inserted in a stainless-steel guide microtube whose non-insulated extremity was used for differential recording. The electrodes, connected to 3 miniature sockets were implanted independently for each brain area. The stereotaxic coordinates derived from Paxinos and Watson's atlas[35] were -3.8 mm from Bregma, 3.5 mm lateral to midline, 6 mm vertical from CA3; -5.8 mm from Bregma, 3.2 mm from midline, 4 mm vertical from MGm and -4.8 mm from Bregma, 6.5 mm lateral to midline, 5 mm vertical from the AC (the electrodes were lowered with an angle of 35° vertical from AC). For the two auditory structures, click probes delivered via the hollow ear bar were used during the final adjustment of the electrodes to obtain the best auditory response.

During the experiment, multiunit activity (MUA) was recorded through field effect transistors placed on the animal's head, fed to a preamplifier (300 Hz–10 kHz) and sent through a high-pass filter (cut-off at 400 Hz). The output of this filter, displayed on an oscilloscope, was recorded on magnetic tape during the 5 s pre-tone and the 10 s tone period.

Apparatus and experimental procedure

The experimental box (23 × 23 × 47 cm) was placed in a sound-attenuating chamber where an exhaust fan provided a background noise of 45 dB. The chamber was equipped with a 2 W

light at the top of the left wall and a loudspeaker (Siare, 6 cm in diameter, bandpass 20 Hz–20 kHz) on the rear wall. The grid floor was made of stainless-steel rods 0.5 cm in diameter spaced 1.5 cm center to center. Counterbalanced recording cables were connected to the animal and relayed at the top of the box through a multichannel rotating connector.

Animals were first familiarized to the experimental box and cables for 4 days before the beginning of the experiment. Two tones of 1 and 7 kHz (70 and 67 dB, respectively) were used in this experiment. During two habituation sessions the two tones (10 s in duration) were presented in a pseudo-random order with 3 min mean intertrial interval (ITI) (range 2–5 min). During the subsequent conditioning sessions one of the two frequencies, designated as the reinforced conditioned stimulus (CS +), was followed by an electrical footshock (0.35 mA, 0.5 s in duration) delivered via the grid floor. The other frequency was the non-reinforced conditioned stimulus (CS –), and was never followed by the footshock. For half of the animals, the CS + was the 1 kHz tone and for the other half the CS + was the 7 kHz tone. Twelve conditioning sessions (45 min in duration) were conducted during which 5 CS + and 5 CS – were presented in a pseudo-random order with a mean ITI of 3 min. Such distributed conditioning (12 sessions with 10 trials per session) was chosen in order to optimize the retention after a long time period. Forty-five days after the end of conditioning, the animals were refamiliarized during two sessions of 30 min with the experimental box and cables in order to avoid unconditioned fear to the experimental context. Then, two test sessions (40 min in duration) were carried out (in extinction) consisting in 5 CS + and 5 CS – presentations in a pseudo-random order (ITI 3 min on average). For half of the animals the first stimulus presented was the CS + and for the other half the first tone was the CS – .

The entire experiment (stimulus presentations) was controlled by a microcomputer, which was also used for the off-line analysis of the cellular data.

Data analysis

During the off-line analysis, the MUA was fed into a voltage window discriminator to select the largest spikes (signal-to-noise 2/1). The output pulses were stored on each trial in successive 20 ms bins for 400 ms pre-tone (20 bins) and the first 800 ms of tone (40 bins). Standard computer programs allowed construction of individual histograms, then group histograms for the CS + and the CS – were created by averaging CS + and CS – trials across animals. The same procedures as those previously described were used to avoid neural or non-neural feedback from the animal movements. We discarded trials where movements were observed (about 5% of the trials) and electrical artifacts were ruled out (on the basis of magnitude and rise-time) by a two-threshold trigger[7]. Moreover, for each electrode placement, the pre-tone firing rate was submitted to an analysis of variance across sessions to detect eventual shifts in firing rate across days.

For each structure, the neuronal data were submitted to an analysis of variance[36], with the recorded electrodes as subject factor ($n = 6$) and orthogonal repeated measures factors of sessions (14 levels: 2 habituation and 12 conditioning sessions), type of trials (2 levels: CS + /CS –) and time bin after tone onset. In the hippocampus, for each session, the number of spikes per bin during the pre-tone period (20 bins) was compared to the number of spikes per bin of tone period (40 bins). In the two auditory structures, in order to compare the sensory response to tones (3–4 bins after tone onset) across sessions, z-scores were computed by subtracting the mean frequency in the 20 preCS bins from the frequency of the first 3–4 bins following tone onset and then dividing this difference by the standard deviation of the preCS activity. These z-scores were compared across sessions to determine changes in the evoked responses. In order to be sure that the response modifications were due to learning, all comparisons were done with the first habituation day as reference, on which the sensory responses were highest due to stimulus novelty.

Histology

At the end of the experiment, the animals were perfused under deep sodium pentobarbital anesthesia with 0.9% saline followed by 10% formalin (intracardiac perfusion). The brains were placed in 10% formalin for 2 weeks, frozen and sliced at 60 μm, then stained with Cresyl violet for Nissl preparation.

RESULTS

Hippocampal data

As shown in Fig. 1 (left panels), no hippocampal response was observed on the second habituation session during the presentation of the 1 kHz tone ($F_{1,5} < 1$ on the first 400 and the first 800 ms of tone) or the 7 kHz tone ($F_{1,5} = 1.263$ on the first 800 ms and $F_{1,5} < 1$ on the first 400). As early as the first conditioning session, a hippocampal response was detected to CS + presentations ($F_{1,5} = 33.32$, $P < 0.01$ on 400 ms and $F_{1,5} = 12.6$, $P < 0.05$ on 800 ms) and also to CS − presentations ($F_{1,5} = 22.14$, $P < 0.01$ on 400 ms and $F_{1,5} = 11.08$, $P < 0.05$ on 800 ms). At this session no statistical difference was observed between the response to the CS + and the response to the CS − ($F_{1,5} = 1.42$, ns on 400 ms and $F_{1,5} = 4.182$, ns on 800 ms). In contrast (as shown in the middle panels of Fig. 1), at the second discrimination session the response to the CS + was statistically larger than that observed to the CS − ($F_{1,5} = 7.085$, $P < 0.05$ on 400 ms and $F_{1,5} = 19.227$, $P < 0.05$ on 800 ms). This discrimination effect was observed during the subsequent sessions until the last conditioning session ($F_{1,5} = 7.54$, $P < 0.05$ at the twelfth session).

During the first test sessions, 45 days after the end of conditioning, hippocampal responses were detected both to the CS + and to the CS −, and the magnitude of the response was greater for the CS + than for the CS − ($F_{1,5} = 7.24$, $P < 0.05$ on

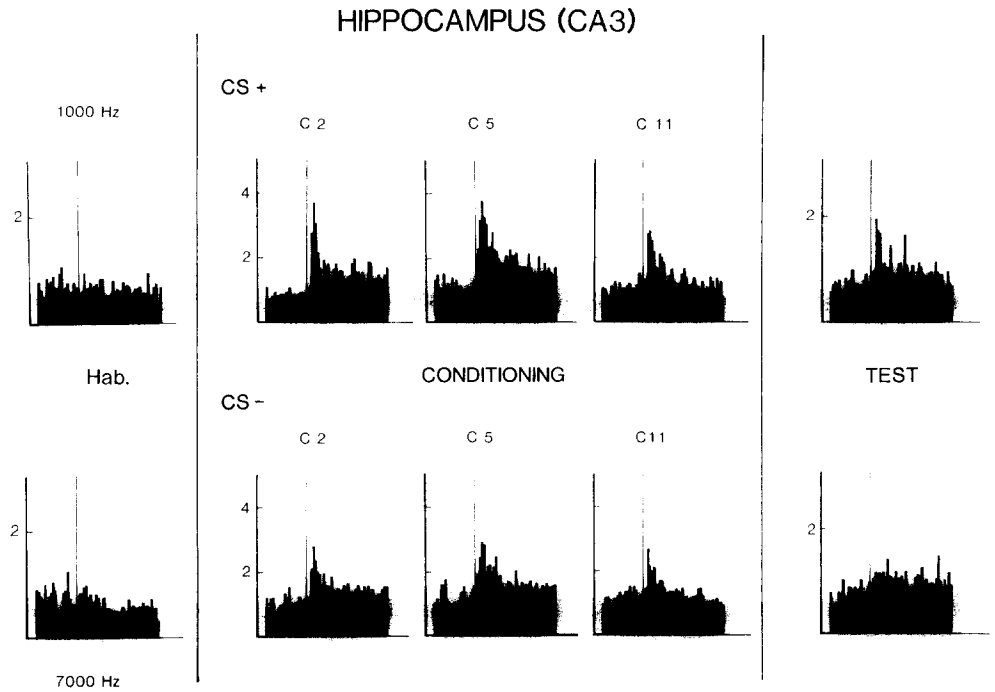

Fig. 1. Averaged group histograms ($n = 6$) of MUA recorded in the hippocampus (CA3) during habituation (Hab), sessions 2, 5, and 11 of conditioning, and retention tests (test 2). Each histogram represents the number of spikes per bin of 20 ms during the 400 ms pre-stimulus period and the first 800 msec of tone. Note the larger response to the CS + compared to CS − at the second conditioning session, which remained until the end of conditioning, and the clear differential effect during the long-term retention tests.

400 ms, and $F_{1,5} = 13.31$, $P < 0.05$ on 800 ms). Moreover, as shown in Fig. 1 (right panels), this discrimination was also observed the second day of the test when the CS + still elicited a significant response ($F_{1,5} = 31.33$, $P < 0.01$ on 400 ms) whereas no statistical response was detected to the CS − ($F_{1,5} = 4.46$, ns).

Medial geniculate data

As shown in Fig. 2 (left panels), during the habituation sessions no difference could be detected between the sensory response elicited by the 1 kHz tone and that elicited by the 7 kHz tone ($F_{1,5} < 1$ on the first as well as the second bin of tone). Within the first conditioning session, a significant increase of the 'on' response evoked by the CS + can be detected (Figs. 2 and 3) whereas only a slight increase of response to the CS − was observed. The statistical analysis confirmed that the averaged z-scores obtained for the CS + on the 2 first bins of tone were statistically greater than those obtained at the first habituation session ($F_{1,5} = 8.175$, $P < 0.05$ and $F_{1,5} = 6.848$, $P < 0.05$, respectively, for the first and the second bin of tone); and that a significant interaction existed on these two first bins between the CS + and the CS − ($F_{1,5} = 14.184$, $P < 0.05$). As shown in Fig. 3, during the subsequent sessions, the increase of the 'on' response observed to the CS + was maintained until completion of the conditioning, and the difference between the z-scores to CS + presentations and to CS − presentations was statistically significant except at sessions five ($F_{1,5} = 4.11$, ns) and eight ($F_{1,5} = 5.05$, ns).

As shown in Figs. 2 and 3, during the retention tests a clear difference of reactivity can be observed between the responses to CS + and to CS − . Even if the sensory response elicited by the CS + is smaller than that detected at the end of conditioning, a clear 'on' response can still be observed whereas a very weak response was detected to CS − . The statistical analysis confirmed that a difference in response is present at the first day of test, on the first ($F_{1,5} = 11.54$,

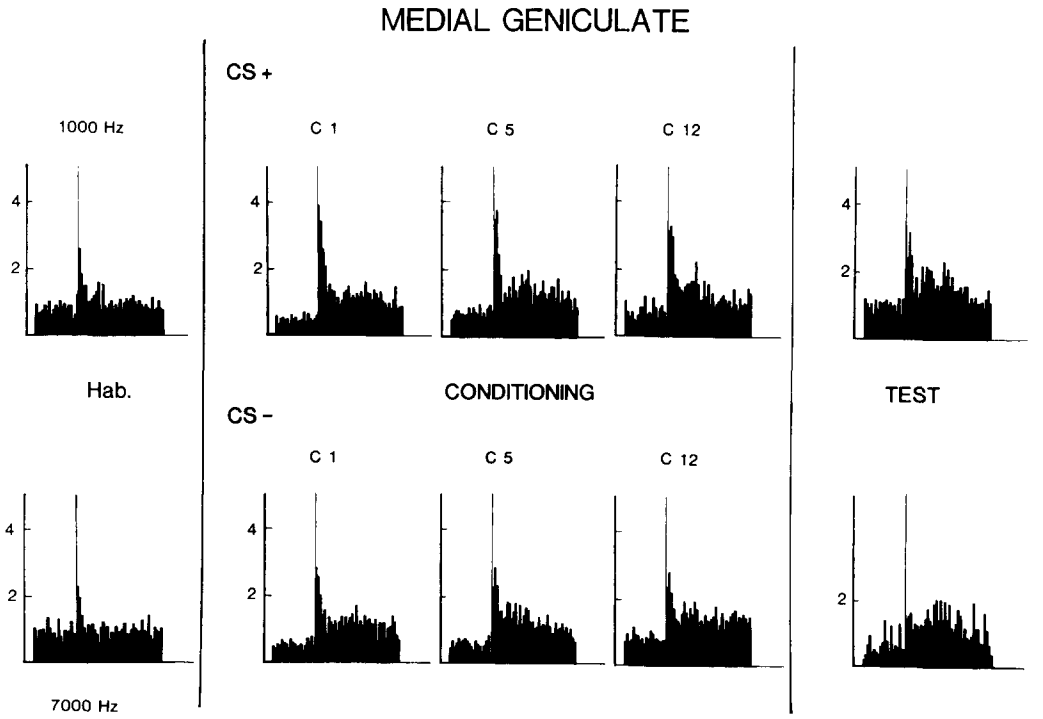

Fig. 2. Averaged group histograms ($n = 6$) of MUA in the MGm during habituation, conditioning, and long-term retention tests. Labeling conventions are as in Fig. 1. Note the similar responsiveness to both tones during the habituation and the increase of the 'on' response for the CS + during the first conditioning session (C1). This increase was maintained until the last session (C12). Note also the clear difference of responsiveness to the CS + and the CS − during the long-term retention tests.

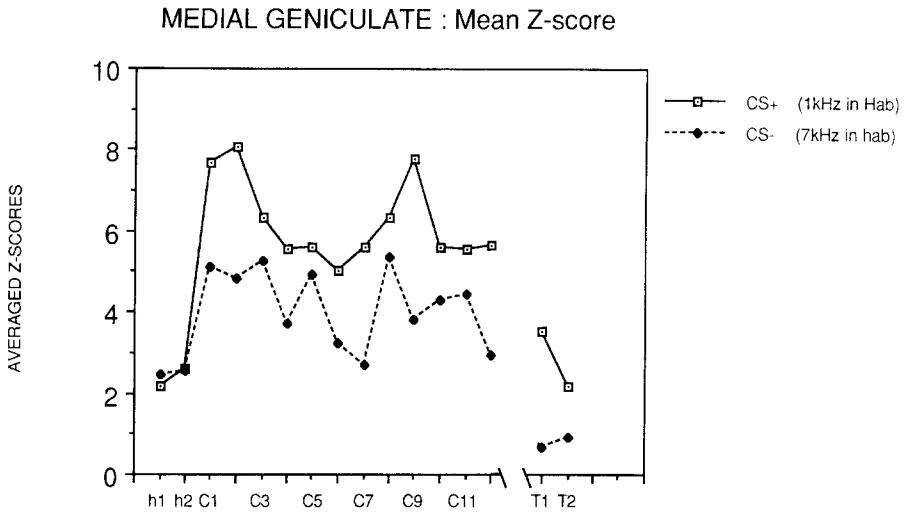

Fig. 3. Mean z-scores obtained from the MGm on the two first bins (20 ms/bin) after tone onset during habituation sessions (h1, h2), conditioning sessions (C1–C12), and the two retention sessions (T1, T2). Note the marked increase of response during conditioning and the larger responses to CS + compared to CS − . Note also the clear discriminative effect during the long-term retention tests.

$P < 0.05$) as well as the second bin of tone ($F_{1,5} = 16.507$, $P < 0.05$).

Auditory cortex

As shown in Fig. 4, only slight responses were observed in habituation to presentations of both the 1 and 7 kHz tones. Possible reasons for this are provided in the Discussion section. During the first conditioning session, a clear increase in response was observed both to the CS + and to

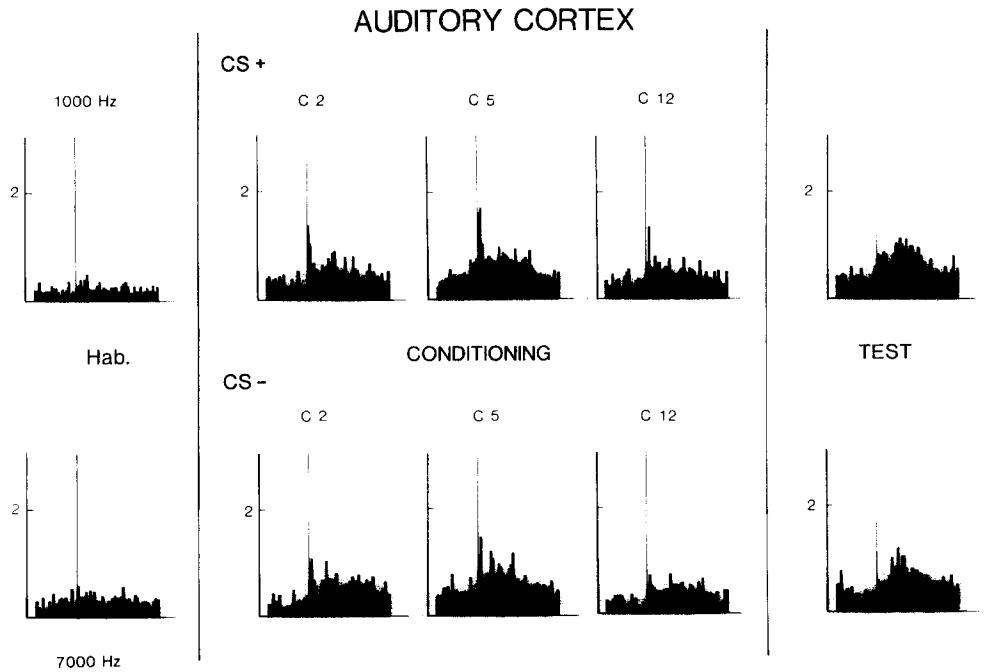

Fig. 4. Averaged group histograms ($n = 6$) of MUA in the AC during habituation (Hab), conditioning (C2, C5, C12) and long-term retention tests. Labeling conventions are as in Fig. 1. Note the larger responses to CS + during conditioning and the discriminative effect on the onset response during the long-term retention tests.

the CS −, and the statistical analysis confirmed that at this session, the responses were greater than during the first habituation session ($F_{1,5} = 7.078$, $P < 0.05$ for the CS + and $F_{1,5} = 8.409$, $P < 0.05$ for the CS − on the two first bins of tone period). However, a differential effect occurred only at the second session of conditioning when comparing the z-scores of the CS + and the CS − ($F_{1,5} = 6.049$, $P < 0.05$ on the first bin of tone). On the next sessions, the cellular discrimination became progressively larger (Fig. 5), and the difference in response between CS + and CS − remained statistically significant across sessions except at session five ($F_{1,5} = 1.083$, ns) and nine ($F_{1,5} = 1.89$, ns).

As shown in Fig. 4 and 5, 45 days after the end of conditioning, a discriminative effect can be detected. An 'on' response can still be observed during the CS + presentations, whereas no clear response was observed to CS − presentations. Only a long latency (about 120 ms) response, which was also detected for the CS +, occurred to CS − presentations. The statistical analysis performed on the 2 first bins of the tone period confirmed that a difference in response to the CS + and the CS − is significant at the first ($F_{1,5} = 10.43$, $P < 0.05$) as well as the second day of testing ($F_{1,5} = 7.45$, $P < 0.05$).

Histology

For all the 6 animals included in this experiment, correct electrode placements were determined (Fig. 6). The hippocampal electrode placements derived from the CA3 field of the hippocampus, at or near the pyramidal layer. In the thalamus, acute tip locations were in the magnocellular division of the medial geniculate ($n = 4$), and in the suprageniculate ($n = 2$); no difference was detected in the responsiveness of the two locations. The cortical recordings were from homogeneous placements which correspond, at least partially, to the area of the MG projections described by Ledoux et al.[29]. This area is more anterior than the coordinates for the temporal cortex in the Paxinos and Watson atlas[35], but correspond to the area TE1 of the Zilles atlas[51].

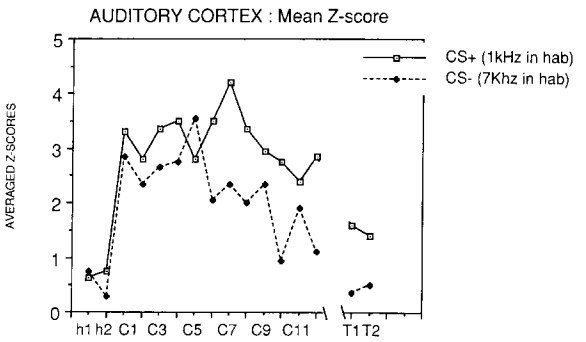

Fig. 5. Mean z-scores obtained from the AC on the two first bins (20 ms/bin) after tone onset during habituation (h1, h2), conditioning sessions (C1–C12), and retention tests (T1, T2). Note the discriminative effect occurring during conditioning, which is maintained during the long-term retention.

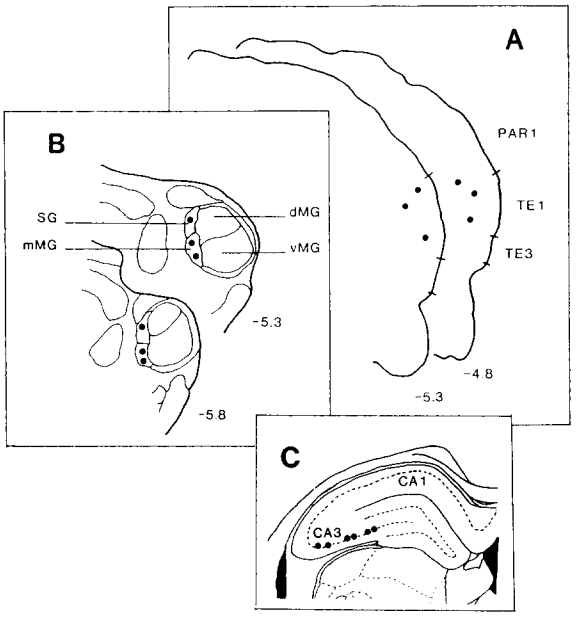

Fig. 6. Outlines showing the placements of the recording electrodes in the auditory cortex (A), the medial geniculate (B) and the CA3 field of the hippocampus (C). The boundaries between the cortical areas come from Roger and Arnault[38] and the MG subdivisions from Ledoux et al.[29].

DISCUSSION

The main results of the present experiment can be summarized as follows: pairing a previously habituated tone with an electrical footshock rapidly induced modifications of multiunit responses in the CA3 field of the hippocampus, the MGm and the AC, and discriminative effects

occurred since the responses to the CS + were larger than those to the CS − . Moreover, 45 days after the end of conditioning a discriminative effect could still be observed in the 3 structures.

We are aware that recording MUA in freely moving animals always raises some methodological problems since it is impossible to precisely control the sensory input constancy. We have previously discussed these problems[13], and we will just emphasize here that the action of the middle ear muscles has a latency of 35–70 ms in the cat at rest[4], and can only account for decreases of evoked responses[43]. In addition, in a discriminative paradigm the animals cannot know if the next stimulus will be a CS + or a CS − , so it is unlikely that they can adopt a specific location or orientation with regard to the speaker before the occurrence of one of these two stimuli. Finally, it is quite difficult to attribute the present results to a startle response at the CS + presentations since it is unlikely that the startle response (6-16 ms in latency; see Davis[8] for review) can affect the neural responses of the two auditory structures on the first bin after tone onset and affect the hippocampal activity only at the third bin after tone onset.

In this study, as well as in a number of previous multiunit[1,11,14,17,32,34] or single unit studies[9,48] using a discrimination paradigm, increases of responses were observed to both the CS + and the CS − , with greater increases of responses to the CS + . Two different explanations can be advanced for these results: (1) responses to CS − can reflect a generalized fear to all acoustic stimuli which always occurs at the beginning of a discrimination; or (2) they can reflect that the CS − of all discriminative paradigms can become a safety signal, and thus it also acquires a 'predictive value' (it predicts the absence of shock). In the present experiment, as well as in other studies, the magnitude of changes to the CS − presentations decreased as the training progressed. Thus, it is more likely that the increased responses to CS − reflect a general fear to all acoustic stimuli which progressively decreased across sessions. However, the significant differences observed between the responses to the CS + and to the CS − lead us to interpret the increased response to CS + as the consequence of the acquisition of the CS + 'predictive value'. During the acquisition, the MGm was the structure showing the more rapidly conditioned changes and discriminative effects. Thus, these results confirmed the associative nature of discharge plasticity observed in the MGm by several authors after very few conditioning trials[16,39,47].

The acquisition observed for the CA3 field of the hippocampus is comparable to that previously observed using the same conditioning procedure[2,13,25], except that in the present study it is a discriminative effect which emerges in 10–20 trials. Furthermore, the time course of the changes observed in the present work corroborates our previous observations: during acquisition, conditioned changes can be detected more rapidly in the MGm than in the hippocampus[13].

The lack of responses at the cortical placements during habituation is surprising, since both the short latency responses observed during conditioning and surgery, and the histological verifications have confirmed correct electrode placements in an auditory cortical area. The comparison with data obtained in similar conditions does not give more insight: Olds et al.[32] have reported a mean z-score of 0.87 for their cortical recordings and Disterhoft and Stuart[11] a 'probability of firing' of 0.1, which in both cases indicates weak responses to auditory stimuli at the cortical placements. In fact, some work strongly suggests that the different cortical areas considered as auditory in man, monkey and cat (areas 41,40, 39, 20, 36) are perhaps very polymodal in rats. For example, electrolytical lesions of MG do not induce massive degeneration in any layer of rat temporal area[46]. This polymodality of the rat auditory cortex is proposed by Harrison and Howe[19,20] based upon the anatomical properties of the MG cells. Thus, it is possible that in freely moving rats the somesthetic information severely depressed the auditory responses. It is perhaps also possible that masking noises, from the animals' movements or breathing, masked more strongly the auditory responses at the cortical level than at the subcortical level.

Whatever the reasons for this weak respon-

siveness during habituation, the cortical results are consistent with some previous studies concerning this structure. At the multiunit level, Oleson et al.[34], have observed conditioned changes in 5–20 trials, then a discrimination after an average of 11 additional trials. In our experiment, if an increase of responsiveness was detected within the first 10 trials, a differential effect to the CS + compared to the CS − was detected only in 10–20 trials. Thus, compared with the MGm data, the cortical results obtained here suggest that the auditory thalamus can be more rapidly involved in the detection of significant acoustic stimuli. Of course, this claim is based on MUA data and single unit studies certainly have reported different acquisition rates in the MGm[47] as well as in the AC[9,10,23,48]. Nonetheless, the MGm plasticity observed here occurs in fewer trials than conditioned suppression observed under similar training conditioning[13], while the cortical changes occur in more trials. This might make the MGm a more likely candidate to be involved in fear learning than the auditory cortex. Of course, neurophysiological conditioning in a brain structure does not indicate that the structure is required for behavioral learning. As an example, the hippocampal conditioned response forms a 'model' of the CR during nictitating membrane conditioning[45], but its removal does not affect learning of this response[37,40] except in special paradigms[31]. However, Ledoux and colleagues[27,28] have demonstrated that MG lesions but not cortical lesions prevent fear conditioning. Thus, the rapid multiunit changes observed in the MGm in the present study can support the idea of the pivotal importance of this structure in the acquisition of all conditioning using tones as CS, at least when it is the frequency dimension of the stimuli which is relevant for learning.

Even if the responses were smaller than at the end of conditioning (probably due to a decrease of recording sensitivity) 45 days after the end of conditioning, a discriminative effect was observed in the 3 structures. At the cellular level, retention of discrimination has previously only been reported by Oleson et al.[34], who observed a discriminative effect in the auditory cortex and in the dorsal cochlear nucleus 6 days after conditioning.

Our observation, 45 days after conditioning, of discriminative effects definitively establishes the fact that sensory alteration responses are not transient changes which disappear with time, since here, during the long-term retention tests, the same populations of cells have shown a reactivity which is a function of the meaningfulness of the stimulus during conditioning. Thus, the present results indicate that there is no reason to postulate that a particular 'associative' structure of the brain is involved in the long-term retention of significant stimuli. Rather, they suggest that learning-induced changes can last over time in many structures of the brain where cellular conditioned changes can be detected during learning.

There is a conceptual reason to stress the fact that learning-induced changes in sensory systems endure over a long time period. It is perhaps possible that the plasticity which takes place in the CS pathway during a particular learning task can be used subsequently whenever the CS occurs, whatever the context and the specific motor response required by the situation. Such an hypothesis can be easily tested by recording CS-evoked responses in different contexts other than the learning context. Thus, the sensory plasticity which develops during learning could be used to detect, recognize and react to significant stimuli whatever the conditions. As pointed out in the Introduction section, knowing the time course of both the developmental and postinjury sensory plasticity, it seems necessary now to look for long-term effects of learning-induced plasticity. The present results, the first evidence of specific long-term retention of conditioned changes in a vertebrate sensory system, suggest that the learning-induced sensory plasticity can contribute to the maintenance of detection of significant stimuli.

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