

Learning and Behavioral-Long-Term Potentiation: Importance of Controlling for Motor Activity

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A series of brief, high-frequency trains of electrical stimulation delivered to the perforant-path results in long-term potentiation (LTP) of the dentate gyrus as measured by average evoked potentials (EPs). Similar increases in dentate evoked potentials have been reported after natural learning. Previous studies of this behavioral LTP have not adequately controlled for ongoing behavior at the time of recording, even though motor activity also influences the amplitude of EPs. Chronically implanted rats were trained in both a radial-arm maze and an avoidance task using a crossover design. EPs in the dentate gyrus following perforant-path stimulation were recorded daily under 3 different behavioral conditions: immobility, movement, and freely behaving. After completion of both tasks, animals were given tetanizing stimulation of the perforant path. Results indicated strong improvements in the performance of both tasks. Tetanization induced significant LTP, which was still present at the end of 5 d. Significant differences were found between EPs collected during immobility and movement throughout the experiment. No evidence of behavioral LTP was observed, and the EPs remained consistent with baseline measures. These data show the necessity of controlling for ongoing behavior at the time of recording in electrophysiological studies of learning. The data also indicate that the phenomenon of behavioral LTP, as assessed by hippocampal EPs, is not universal to all learning experiences.

Long-term potentiation (LTP) is a term applied to an increase in synaptic efficacy, measured by evoked potentials (EPs), which follows the application of brief, high-frequency trains of electrical stimulation. The functional similarity of LTP to the hypothesized operation of the modifiable "Hebbian" synapse has made it one of the more popular phenomena with which to model and study the neural basis of memory (Teyler and Discenna, 1984; Racine and Kairiss, 1987). However, the exact nature of the relationship of LTP to normal memory processes has yet to be determined (Teyler and Discenna, 1987).

Support linking LTP to learning has come from a variety of sources, one of which is behavioral LTP. Behavioral LTP is a related electrophysiological phenomenon, in which LTP-like changes are reflected in hippocampal EPs as a result of natural

learning (Teyler and Discenna, 1987). Behavioral LTP has been reported during the learning of a classically conditioned nictitating membrane response (Weisz et al., 1982), after the completion of a footshock-motivated discrimination task (Ruthrich et al., 1982), and gradually over the training period of an appetitively motivated operant conditioning paradigm (Skelton et al., 1987).

It has been known for some time that the hippocampal electrocorticogram varies systematically with ongoing behavior (Vanderwolf, 1969). Hippocampal spontaneous electrical activity recorded during "type I" behaviors such as walking, changes in posture, or head movements show rhythmical slow activity (RSA), which differs in frequency and amplitude from the large-amplitude irregular activity (LIA) that can be recorded during "type II" behaviors such as sniffing, immobility, or face washing (Vanderwolf, 1988). Some behavioral sequences, such as grooming, consist of a series of such behaviors as face washing, changes in posture, and licking, and therefore include a mixture of both RSA and LIA (Vanderwolf et al., 1975).

Hippocampal EPs also vary systematically in correlation with behavior (Winson and Abzug, 1978; Leung, 1980; Buzsaki et al., 1981). EPs recorded during "type I" behaviors differ in morphology and amplitude from those recorded during "type II" behaviors. These relationships to ongoing behavior have been found for EPs recorded in the CA1 region (Leung, 1980) and dentate gyrus of the hippocampal formation (Segal, 1978; Winson and Abzug, 1978; Buzsaki et al., 1981; Green et al., 1988).

Recordings taken during training in a learning or memory task display such behavior-related activity, raising the possibility that behavior-related changes can be mistakenly identified as learning-related changes (Vanderwolf and Ossenkopp, 1982; Morris and Baker, 1984). Of the 3 behavioral LTP studies cited above, none included control of ongoing behavior at the time of EP recording. In the work reported here, we wished to reexamine the question of behavioral LTP using strict controls for ongoing behavior at the time of EP recording. EPs were recorded in the hilus of the dentate gyrus following stimulation of the perforant path.

Prominent among theories of hippocampal function is the suggestion of a role in spatial memory (O'Keefe and Nadel, 1978). In light of this, it is surprising that none of the behavioral LTP studies have utilized behavioral tasks with a prominent spatial component. Therefore, in the following study we employed a radial-arm maze task (Olton and Samuelson, 1976). We also utilized a 1-way active avoidance task to observe the effects that the different tasks might have on behavioral LTP and to allow a stronger assessment of behavioral performance.

Received Aug. 7, 1989; revised Dec. 15, 1989; accepted Dec. 20, 1989.

This work was supported by a grant from the Natural Sciences and Engineering Research Council of Canada to D.P.C.

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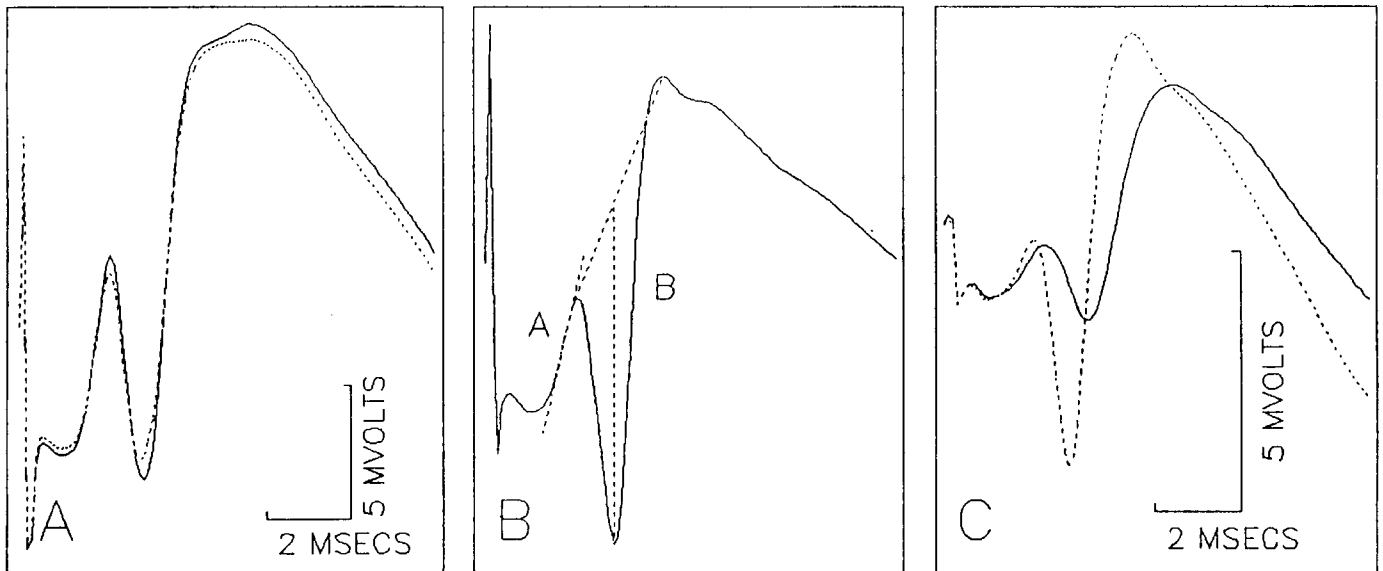


Figure 1. Samples of average EPs. *A*, Differences between average EP collected under immobility (solid line) and movement (dashed line). *B*, EP measures: *A*, maximum slope of the EPSP; *B*, amplitude of the extracellular population spike. *C*, Differences between average EP collected immediately before (solid line) and immediately after (dashed line) LTP.

Materials and Methods

Subjects. The subjects were 24 naive male hooded rats of the Royal Victoria strain, weighing between 300 and 500 gm at the time of surgery. They were individually housed in a colony room where a 12 hr light/dark cycle was in effect, with the lights turned on at 8:30 A.M. and turned off at 8:30 P.M. They had continuous access to food (Purina Lab Chow) and water, except as specified below.

Using pentobarbital anesthesia and conventional surgical techniques, the rats were implanted with stimulating and recording electrodes on the right side of the brain in the perforant path (AP -7.8 mm, L 4.5 mm, V -3.5 mm) and the hilus of the dentate gyrus (AP -4.0 mm, L 2.3 mm, V -3.5 mm). Placements were measured from bregma and lambda in the same horizontal plane. The final depth of the electrodes was determined by electrophysiological methods. Monopolar recordings from the rats included in the study exhibited an extracellular population spike at a stimulation intensity of less than $100 \mu\text{A}$. Additionally, the population spike was negative and the excitatory postsynaptic potential (EPSP) was positive, indicating placement in the hilus of the dentate gyrus. After a week of recovery, the 10 animals meeting these criteria were used in the subsequent study.

Equipment and techniques. EPs were recorded during 3 different behavioral conditions: (1) "immobility," which was defined as standing with weight on at least 3 limbs, head held up against gravity, and eyes open with no discernable movement (Leung, 1980); (2) "movement," which was defined as wheel running; and (3) "freely behaving." In the latter condition, EPs were collected at fixed intervals regardless of the ongoing behavior. Ten EPs were collected during each condition and then averaged separately using a microcomputer. Two measures were obtained by computer from each average EP: the maximum slope of the EPSP, and the amplitude of the extracellular population spike as defined in Figure 1*B*.

Single diphasic, constant-current pulses, each with a pulse duration of 0.1 msec, were used as test pulses. The intensity of the test pulses was 80% of the maximum evoked response as determined for each rat by input/output (I/O) curves recorded during immobility. EPs were triggered manually at an average rate of once every 5 – 10 sec (Racine et al., 1983).

The animals were separated into 2 groups matched for the size and shape of the EP, and the intensity of the test pulse. Electrophysiological measures were taken daily until the EPs were relatively stable, at which time a 5 d period was begun to establish baseline average EP measures for each condition. This was followed by training in 1 of the 2 learning tasks, using a counterbalanced design. Throughout the learning tasks,

EPs were collected on a daily basis during each of the 3 behavioral conditions. Recording sessions occurred 20 – 22 hr after behavioral training.

The 8-arm radial maze had a center that was 31.5 cm in diameter, and each arm was 80 cm long. Each arm was baited with a sunflower seed, and each animal was allowed 1 trial/d for 10 d. All trials were videotaped by a video camera mounted above the maze. The number of arms entered before all the arms had been entered, and the time required to enter all the arms were scored during playback of the tapes. At the beginning of the 5 d baseline period, the rats were placed on a feeding regimen permitting only 15 gm lab chow/d, supplemented with small amounts of sunflower seeds.

The 1-way active avoidance task was carried out in a shuttle-box with a grid floor that could be electrified (1.5 mA scrambled shock). The box was $90 \times 30 \times 60$ cm and divided into a light and dark chamber separated by a sliding partition. The rats were first habituated to the apparatus for 20 min/d for 5 d. At the beginning of a trial, the rat was placed in the dark chamber and the partition was withdrawn, triggering the tone, at which time the animal had 5 sec to leave the dark chamber or receive footshock for a maximum of 5 sec. The tone ceased when the rat left the dark compartment. Training consisted of 10 trials/d for 5 d. The percentage of successful avoidances and the latency to avoid were recorded by a solid-state relay circuit.

Each task took 15 d to complete. The avoidance task was comprised of a minimum 5 d baseline period, a 5 d habituation period, and a 5 d training period. The radial-arm maze was comprised of a minimum 5 d baseline period and a 10 d training period. After the animals had completed both behavioral tasks, they were allowed a 4 d period without recording. After the daily recordings again indicated that the EPs were stable, the rats started a 5 d LTP baseline period. After the recording session on day 5 of the baseline period, each animal received 20 high-frequency trains (400 Hz, 20 msec train duration) composed of diphasic pulses identical to those of the test pulses. The intertrain interval was 30 – 45 sec, and all trains were delivered during behavioral immobility. During this portion of the study, EPs were collected immediately following the potentiating stimulation and every 24 hr thereafter for 5 d.

After completion of the study, all animals were killed with an overdose of sodium pentobarbital and perfused through the heart with a 10% formalin solution. Coronal sections 40 – $60 \mu\text{m}$ thick were then mounted and stained with galloyanin to verify electrode placement.

The data were analyzed through a series of analysis of variance repeated-measure designs (ANOVA). All electrophysiological data were normalized to the average of the immobility and movement conditions on the last day of the baseline period, for each portion of the study.

Results

For 9 of the 10 rats, histological data confirmed that the recording electrode sites were in the hilus of the dentate gyrus, and stimulating electrode sites were in the perforant path. No histological data were available for the 10th rat, but since the morphology of the EP was similar to that of the others, the data from this rat were included.

One rat did not learn the avoidance task (no successful avoidances on the last day of training), so its recording and performance data were excluded from that portion of the analysis; however, it did complete the remainder of the study successfully, so the data were included for those portions of the experiment. During the baseline period of the LTP portion, electrical activity in another one of the rats became difficult to record owing to a failure of the ground connection, and therefore its recording data were excluded from that portion of the study. In total, then, the data from 9 animals were analyzed for the avoidance task and the radial-arm maze, while the data from 8 animals were analyzed for the LTP portion of the study.

Statistically significant differences were found in the EPSP and the population spike between immobility and movement in all 3 portions of the experiment. Significance for the EP data from the radial-arm maze (Fig. 2, *C, D*) was found for the EPSP ($F_{1,7} = 14.82, p < 0.006$) and for the population spike ($F_{1,7} = 45.33, p < 0.0005$). Similarly, the EP data from the avoidance task (Fig. 3, *C, D*) were found to be significant for the EPSP ($F_{1,7} = 64.62, p < 0.0005$) and for the population spike ($F_{1,7} = 26.14, p < 0.001$). Finally, the EP differences from the LTP portion (Fig. 4, *A, B*) were also found to be significant for the EPSP ($F_{1,7} = 16.22, p < 0.005$) and for the population spike ($F_{1,7} = 20.65, p < 0.003$). These results indicate that ongoing behavior at the time of recording significantly affected the EP measures. Figure 1*A* illustrates typical EPs collected during immobility and during movement.

Statistically significant increases in performance during training were found for measures in both learning tasks. Performance measures from the radial-arm maze (Fig. 2, *A, B*) were found to be significant for the number of arms entered before all arms had been entered ($F_{9,63} = 2.49, p < 0.001$) and for the time required to enter all the arms ($F_{9,63} = 8.62, p < 0.0005$). Similarly, the performance measures from the avoidance task (Fig. 3, *A, B*) were found to be significant for the percentage of successful avoidances ($F_{4,4} = 36.00, p < 0.002$) and for the latency to avoid or escape footshock ($F_{4,4} = 19.08, p < 0.007$). These results indicate significant improvements in performance of both tasks as training progressed, demonstrating the occurrence of learning.

However, improvements in performance were not accompanied by LTP-like changes in the average EP measures (Figs. 2, 3). All analyses resulted in nonsignificant *F* ratios. These negative results occurred regardless of whether the learning procedure was the radial-arm maze or the avoidance task. These negative results also occurred regardless of whether the EPs were recorded during the immobility condition, the movement condition, or the freely behaving condition, although the population spike measure did display a nonsignificant trend towards LTP-like changes during the avoidance task under the freely behaving recording condition (Fig. 3*D*). These results indicate that behavioral LTP did not occur, under any of the conditions tested.

Statistically significant differences were found when the 5 d pre-LTP EP measures were compared with the 5 d post-LTP

EP measures (Fig. 4, *A, B*). Significance was found for the population spike ($F_{1,7} = 29.19, p < 0.001$), but only approached significance for the EPSP ($F_{1,7} = 3.72, p < 0.095$). A *post hoc* test comparing the EPSPs of the EPs recorded immediately prior to the tetanizing stimulation to the EPSPs of EPs recorded immediately after the tetanizing stimulation revealed a significance difference ($F_{1,7} = 11.49, p < 0.012$). Overall, these results indicate that the phenomenon of LTP did occur, and in the case of population spike had a recorded duration of at least 72 hr. Figure 1*C* illustrates typical average EP collected immediately before the potentiating stimulation and immediately after the potentiating stimulation.

Observations of behavior made during the course of the learning tasks indicated that the rats were very active throughout maze learning, yet tended to remain immobile much of the time during avoidance training. Data from the freely behaving condition corroborate that this behavioral difference carried forward into the EP recording sessions as well. Figure 2, *C, D* indicates that when recording during maze training the freely behaving condition approximated the movement condition more closely than the immobility condition, while Figure 3, *C, D* indicates that when recording during the avoidance training, the freely behaving condition approximated the immobility condition more closely than the movement condition.

Discussion

The consistent differences in EPSP and population-spike measures between the immobile and movement recording conditions confirm that variations in ongoing behavior at the time of recording can significantly affect the amplitude of the hippocampal EP. These results are in agreement with previous findings relating motor activity to EP amplitude (Segal, 1978; Winson and Abzug, 1978; Leung, 1980; Buzsaki et al., 1981; Vanderwolf et al., 1987). These results specifically agree with those of Brankack and Buzsaki (1986), who found EPs elicited in the dentate gyrus by perforant-path stimulation were significantly greater during immobility than during walking.

Although there was strong evidence of learning in both the avoidance task and the radial-arm maze task, there was no evidence of behavioral LTP. These results disagree with the previous conclusions of Weisz et al. (1982), Ruthrich et al. (1982), and Skelton et al. (1987).

Several possible interpretations of the discrepancy between the present study and the studies by Ruthrich, Skelton, and Weisz should be considered. The first is that behavioral LTP, as assessed by the perforant-path/dentate gyrus EP, did occur in the present study but was not detected. This is unlikely since the difference in EPs between the behavioral conditions of immobility and movement was small but consistent, which attests to the sensitivity and reliability of our recording arrangement. The fact that the rats exhibited good LTP after tetanization of the perforant path also shows that the circuitry studied was fully capable of exhibiting this form of neuroplasticity. It is conceivable that by utilizing a single, high-intensity (80% of maximal effect) test pulse, an optimal intensity for detecting an LTP-like change was overlooked. This is unlikely since the greatest LTP-like effects have been reported at the higher intensities (Racine et al., 1983; Green and Greenough, 1986; Sharp et al., 1987; Skelton et al., 1987). Another possibility is that recording 20–22 hr after the behavioral training sessions may have missed possible LTP-like increases in our rats. However, this seems unlikely since Ruthrich et al. (1982) observed LTP-like increases

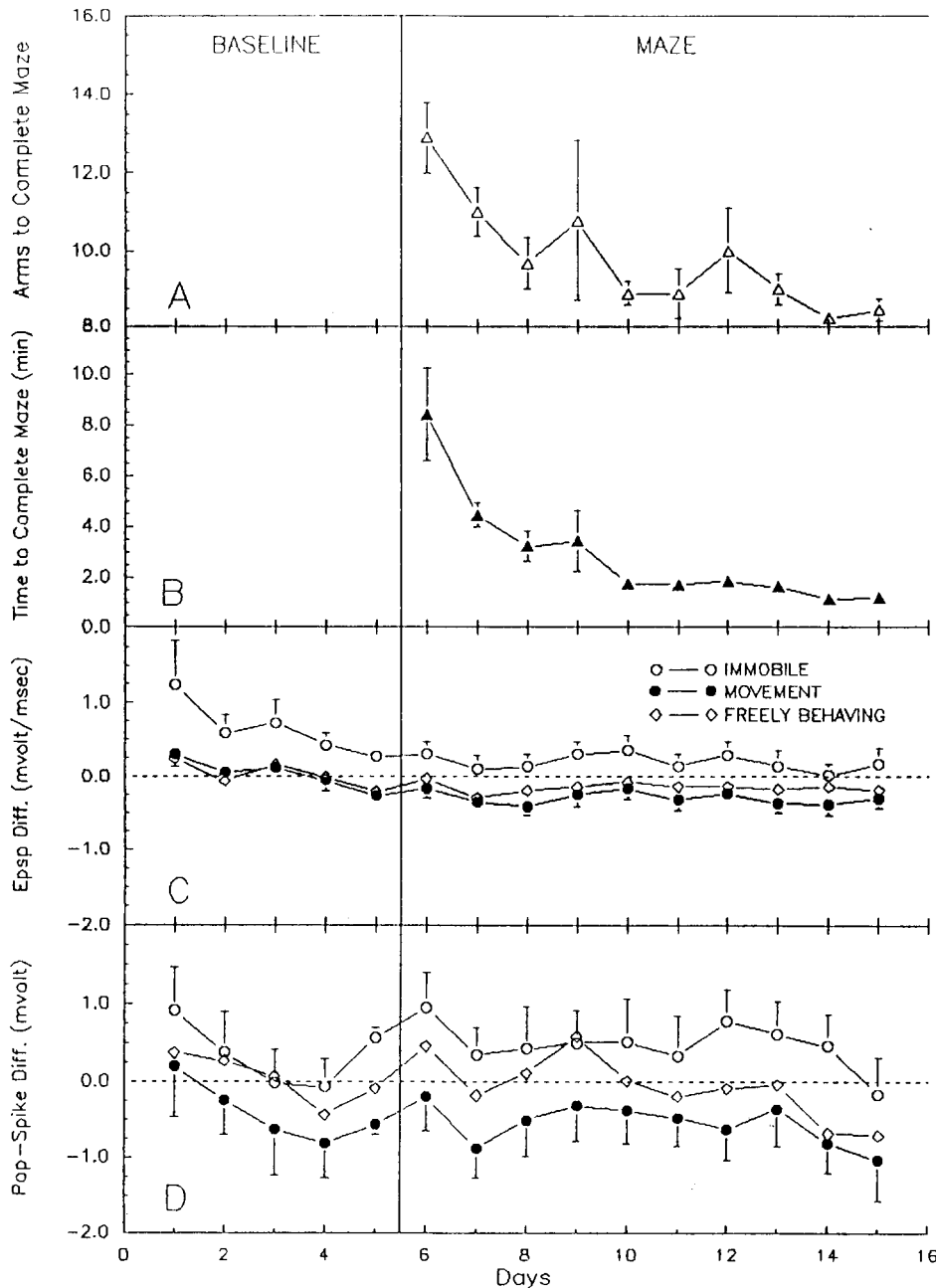


Figure 2. Results of the radial-arm maze ($n = 9$). *A*, Performance measured by the number of arms entered during a session before all the arms have been entered once. *B*, Time taken to complete (*A*). EPSP (*C*) and population-spike (*D*) data collected during the immobility (open circles), movement (closed circles), and freely behaving (open diamonds) recording conditions. Dashed lines represent the average of the data collected during the immobility and the movement recording conditions on the last day of the baseline period. All error bars represent SEM.

at 4 and 24 hr after training, and Skelton et al. (1987) observed increases 22 hr after training.

It may also be possible to explain the failure to detect behavioral LTP as having resulted from the avoidance task and radial-arm maze learning being neurally encoded not as an overall increase in synaptic efficacy, but as a differential weighting of synaptic strengths, or as a strengthening of a much smaller subset of synapses than evoked by the test pulse. Further, the distribution of such synaptic changes may have extended beyond the specific perforant-path/dentate gyrus system studied here. Thus, it is possible that learning-induced neuroplasticity might have occurred in response to the learning of one or both of the tasks used here but not been detected by the particular assay, specifically the hippocampal EP. Such considerations raise the question of whether gross electrophysiological measures such

as the hippocampal EP are optimal in studying the neural plasticity occurring during natural learning. As a consequence, the approach used in this and similar studies of behavioral LTP may not be capable of distinguishing between the presence or absence of learning-induced plasticity in every instance.

The discrepancy between our data and the previous reports of Ruthrich, Skelton, and Weisz illustrates a basic problem in electrophysiological studies of neuroplasticity in intact awake animals. It is assumed that behavioral training produces central alterations in synaptic connectivity that should be demonstrable by EP recording techniques. It is also the case that behavioral training produces systematic changes in motor activity; these changes generally constitute the evidence that learning has occurred. The morphology of EPs varies with motor activity regardless of whether learning has or has not occurred. Therefore,

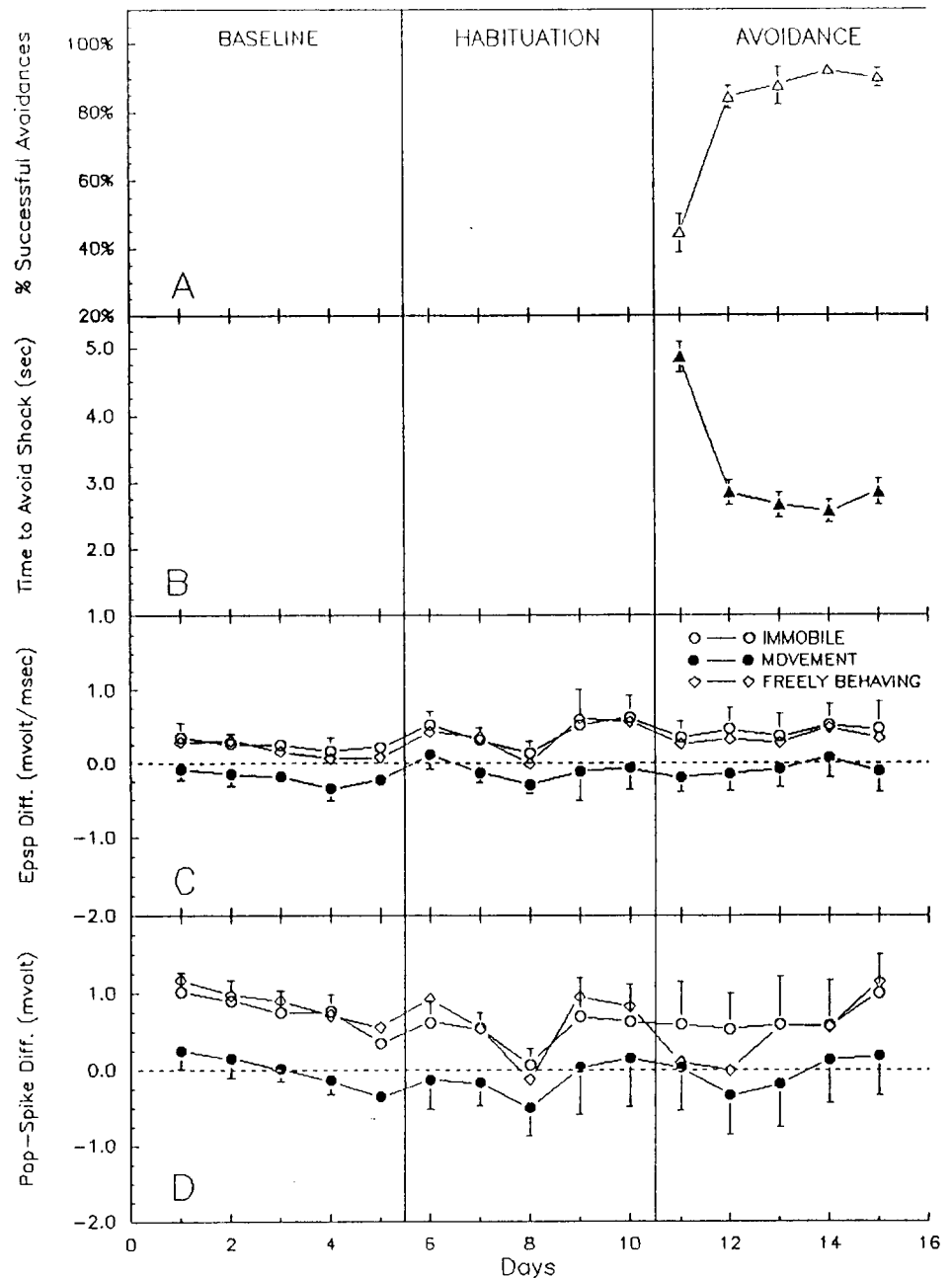


Figure 3. Results of the active avoidance task ($n = 9$). *A*, Percentage of successful avoidances during a session. *B*, Time taken to avoid or escape foot-shock in seconds. EPSP (*C*) and population-spike (*D*) data collected during the immobility (open circles), movement (closed circles), and freely behaving (open diamonds) recording conditions. Dashed lines represent the average of the data collected during the immobility and the movement recording conditions on the last day of the baseline period. All error bars represent SEM.

a change in EPs during the course of behavioral training might be attributable, wholly or in part, to either the correlation with motor activity or to plastic synaptic changes in the system under study. A failure to differentiate these possibilities has invalidated much of the early work on the electrophysiology of learning and memory (Vanderwolf, 1969; Whishaw and Vanderwolf, 1973; Vanderwolf and Ossenkopp, 1982).

One way of distinguishing between movement-correlated activity and memory-correlated activity is to hold one of these factors constant while varying the other. Averaging EPs during the same movement condition both before and after training varies memory while holding movement constant: varying motor activity from one moment to another without intervening training of any kind presumably holds memory constant while varying movement. We have done such experiments and find that the potentials produced in the dentate gyrus vary in cor-

relation with movement but are unaffected by 2 commonly used behavioral training procedures. If the movement and memory factors are both allowed to vary at the same time in an experiment, it is not possible to attribute changes in electrical activity to either factor. The design of such experiments is strictly comparable to conducting a study of the effects of a catalyst on the rate of a chemical reaction without holding the temperature constant, or even recording it.

Weisz and coworkers observed behavioral LTP during the classical conditioning of the nictitating membrane response in rabbits, but did not observe similar changes in control animals that received unpaired CS and US trials. Although this study employed appropriate conditioning controls, and recorded hippocampal EPs within trials and between trials during each training session, no behavioral data other than the records of nictitating membrane movement were reported. However, in a

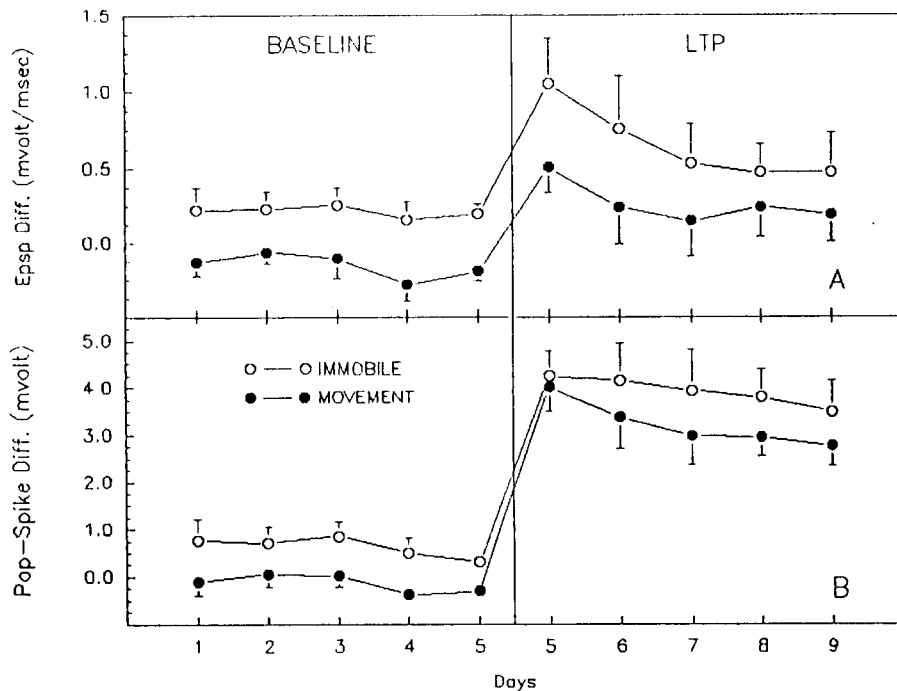


Figure 4. Results of LTP ($n = 8$). EPSP (A) and population-spike (B) data collected during the immobility (open circles) and the movement (closed circles) recording conditions, before (days 1–5) and after LTP (days 5–9). All error bars represent SEM.

discussion of the Weisz et al. (1982) data, Thompson (1983) clearly stated that the hippocampal EEG of a conditioned animal exhibited RSA during the performance of a conditioned eye-blink. From this reported difference in hippocampal EEG, we suggest that the hippocampal EP will reflect a similar difference, as has been previously shown (Winson and Abzug, 1978; Buzsáki et al., 1981; Brankack and Buzsáki, 1986; Green et al., 1988).

Our data recorded under the freely behaving condition, in addition to our behavioral observations, indicate that different training regimens affect the motor activity of animals even in environments that are spatially and temporally distinct from those of training. Figure 2, C, D indicates that when recording EPs during maze training the freely behaving condition approximated the movement condition more closely than the immobility condition, while Figure 3, C, D indicates that when recording EPs during the avoidance training, the freely behaving condition approximated the immobility condition more closely than the movement condition. From the evidence that behavior was affected 22 hr after training, we suggest that the EPs collected during the intertrial interval of Weisz et al. (1982) would be equally contaminated by the differences in ongoing behavior as those collected during the intratrial interval.

Ruthrich et al. (1982), using a foot-shock discrimination task, found significant changes at 4 and 24 hr after training, but not at 1 min or 1 hr after training. Similarly, great care was taken to yoke the amount of foot-shock received by control animals to that received by experimental animals. Yet, there is no guarantee that this procedure ensures similar behavior. In fact, it is highly probable that rats receiving escapable foot-shock (experimental group) will behave very differently from rats receiving inescapable foot-shock (control group) (Fantino and Logan, 1979; Anisman and Zacharko, 1986). One cannot simply assume that since the sum of the stimuli presented to both groups is the same that the subsequent behavior will be the same.

Skelton et al. (1987), using an appetitive operant task and

recording EPs 22 hr after each training session, found population spike increases as performance improved over days. Two groups were run in a counterbalanced fashion through operant and free-feeding regimens. Each animal served as its own control, and the recording of EPs took place in an environment spatially and temporally distinct from that of training. The data recorded from our study, under the freely behaving condition clearly indicate that different training regimens affect the motor activity of animals even in environments that are spatially and temporally distinct from those of training. Yet, behavioral data other than the operant response ratios were not recorded in Skelton et al.'s study, making any comparison of overall activity under the different regimens impossible. Without this critical behavioral data it is difficult to evaluate the differences or similarities between experimental and control groups, which may in part or in whole underlie the observed changes in EPs. Behavior must be recorded in detail.

Movement-correlated changes in hippocampal formation activity appear to be due to the influence of afferent inputs, especially the cholinergic inputs from the basal forebrain and serotonergic inputs from the brain stem (Vanderwolf, 1988). Comparison of evoked potential activity in hippocampal slices taken from trained and untrained animals provides a means of studying neuroplastic changes due to experience without the complicating effects of these inputs. Using this approach, Green and Greenough (1986) have provided convincing evidence that potentials evoked in the dentate gyrus by perforant-path stimulation are enhanced in rats that have been reared in a complex environment in comparison to rats reared in a simple environment. This experiment is perhaps the most convincing evidence currently available that experience can alter functional synaptic connectivity in the hippocampal formation. The reports by Sharp et al. (1985, 1987) suggest that evoked potential enhancement by rearing in a complex environment can also be demonstrated in freely moving animals. However, rigorous distinctions be-

tween Type 1 and Type 2 behaviors do not appear to have been made in this work, and no consistent relation of EP development to concurrent behavior was demonstrated.

At present it is not possible to say why experience-related changes in EPs can be demonstrated following rearing in a complex environment but not following training in a maze or an avoidance apparatus. Perhaps more is learned during lengthy exposure to a complex environment than in daily training by conventional procedures. Perhaps the effect of the environment during development is different from its effect in the adult.

The principal conclusion to be drawn from our work is that it is essential to control motor activity rigorously in studies of the electrophysiology of learning in freely moving animals. We did not observe any electrophysiological evidence of behavioral LTP despite our attempt to maximize the likelihood of obtaining such evidence by (1) recording in the hippocampus after training rats on a task that is known to be dependent on an intact hippocampus (radial-arm maze), (2) confirming behaviorally that learning did in fact occur, (3) training and recording from the animals over a period of days before training and after performance reached asymptote, (4) showing that at the end of the experiment the circuitry under study could undergo normal LTP and that the recording arrangements could detect it, (5) utilizing a test pulse intensity that is conducive to detecting changes in plasticity, and (6) recording 20–22 hr after behavioral training, a time when previous studies indicated behavioral LTP could be found. The data indicate that hippocampal behavioral LTP, as assessed by hippocampal EPs, is not universal to all learning experiences, even when those experiences involve strong spatial components.

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