

Associative Synaptic Potentiation and Depression: Quantification of Dissociable Modifications in the Hippocampal Dentate Gyrus Favors a Particular Class of Synaptic Modification Equations

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ABSTRACT This report further characterizes associative long-term synaptic modification of the ipsilateral and contralateral synapses formed by the bilateral entorhinal cortical (EC) projection to the dentate gyrus (DG). The experimental model is the anesthetized hooded rat. The quantitative results qualify this system as a model for studying the rules of associative synaptic modification formulated in terms of individual synapses. Bilateral DG microelectrodes recorded both ipsilateral and contralateral EC-DG responses before and after brief, high-frequency EC conditioning stimulation. The weak contralateral pathway received high-frequency conditioning before, during, or after similar conditioning of the strong, converging ipsilateral pathway. Statistical analyses revealed two types of significant, dissociated synaptic modifications, which depend on the relationship of the ipsilateral and contralateral afferents. First, contralateral EC-DG responses were potentiated or depressed when the converging ipsilateral responses concurrently either potentiated or remained unchanged. Second, contralateral EC-DG responses potentiated, depressed, or showed no change when the collateral ipsilateral responses concurrently either potentiated or remained unchanged. Correlation and contingency table analyses indicated that changes in the contralateral synaptic responses are not well predicted by changes at either neighboring synapses of the converging ipsilateral pathway or at synapses of the collateral ipsilateral pathway. The contingencies of associated pre- and postsynaptic activation determined by the conditioning paradigm, however, accurately predicted the altered synaptic responses of both ipsilateral and contralateral EC-DG pathways. The results imply that associative synaptic modification in the EC-DG system is specific to individual synapses and requires both appropriate presynaptic and postsynaptic activation. Because this system provides suitable controls for nonspecific effects of conditioning stimulation and because modification of neighboring synapses is dissociable, the EC-DG system can be used to study further those rules of activity-dependent associative modification that are formulated in terms of individual synapses. The discussion briefly considers published rules of synaptic modification, pointing out several rules that are not consistent with the experimental observations and one that agrees with the present results.

INTRODUCTION

Activity-dependent modification of synaptic strength provides a plausible cellular mechanism for memory and learning (Desmond and Levy, 1988; Eccles, 1983; Hebb, 1949; Thompson, 1986). A major theme in neuroscience is understanding the cellular and subcellular bases of activity-dependent associative modification (Barrionuevo et al., 1986; Desmond and Levy, 1983; Dolphin et al., 1982; Fifkova and Van Harreveld, 1977; Golet et al., 1986; Lynch et al., 1983; Stanton and

Sarvey, 1984). A related theme, which motivates the present work, is understanding how the spatiotemporal

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contingencies of synaptic activity determine associative modification so that biologically plausible rules of associative synaptic modification can be postulated. Such rules relate activity at an individual synapse to consequent changes in the strength of synaptic transmission there. By conducting electrophysiological studies of associative long-term potentiation (LTP) and long-term depression (LTD) at the entorhinal cortical (EC) *M* dentate gyrus (DG) synapses, our aim is to select the proper form(s) of the synaptic modification rule at these synapses.

Associative synaptic modification and the specific rules governing such modification at individual synapses are central to most systems neurodynamic models of concept formation, learning, and perceptual development. Examples of such models include studies by Rosenblatt (1962), Anderson (1968), Anderson and Mozer (1981), Amari (1977), Amari and Takeuchi (1978), Kohonen (1982, 1984), Bienenstock et al. (1982), Cooper et al. (1985), Grossberg (1976), Marr (1971), and Klopff (1982) (see Hinton and Anderson, 1981; Levy et al., 1985; for additional references). The form of such rules is often the single most distinguishing characteristic of the various systems neurodynamic theories. Because theorists disagree on the rules of associative synaptic modification [compare equations by Amari (1977), Bienenstock et al. (1982), and Kohonen (1982)], experiments that elucidate the properties of associative synaptic modification should help to select a physiologically appropriate rule.

Critical to relating electrophysiological observations to the selection of an appropriate synaptic modification rule is the question of the individuality of associative modification. That is, can we infer that individual EC-DG synapses are individually modified as a consequence of the pattern of associated pre- and postsynaptic activity? Previously we demonstrated that simultaneous but different synaptic modifications (i.e., synaptic LTP and synaptic LTD) can be observed in the bilateral EC-DG system (Levy and Steward, 1979, 1983). By inducing activity in the large, ipsilateral EC-DG pathway concurrent with relative inactivity or delayed activity in the sparse, converging contralateral pathway, LTD of the contralateral response occurs even though the ipsilateral response itself potentiates (Burger and Levy, 1983; Levy and Steward, 1979, 1983). If ipsilateral activation is concurrent with, or slightly delayed relative to, activation of the converging contralateral pathway, then potentiation of both the ipsilateral and the contralateral responses occurs.

These results offer some support for the inference that individual EC-DG synapses are individually modified as a consequence of the pattern of associated pre- and postsynaptic activity. However, technical shortcomings in our previous reports compromise the strength of this inference and, as a consequence, limit its usefulness for evaluating different synaptic modification rules governing individual synapses. First, only simultaneous measurement of the modifications occurring bilaterally at the ipsilateral and contralateral EC-DG synapses in each animal can provide the data for complete correlational and contingency table analyses and thus provide the firm groundwork needed to qualify the EC-DG system for studies of synaptic modification rules. In our previous experiments, the number of stimulating and

recording electrodes varied between different animals. Moreover, even when there were two stimulating and two recording electrodes, the technical limitations of our data archiving prevented statistical evaluation of all four EC-DG responses within a single animal. As a result of these two limitations, our previous analyses could not quantitatively assess the changes in synaptic strength and their statistical dependency for all four EC-DG synaptic responses of each individual animal. Finally, recirculating electrical activity through the EC was rarely eliminated in our previous studies. Consequently, the contribution of multisynaptic loops to differential synaptic modification could never be excluded in the statistically analyzed data. Here, in every experiment, the use of local tetrodotoxin (TTX) injections effectively isolated the monosynaptic EC-DG pathways.

The present report overcomes the limitations of our earlier studies in order to make the strongest possible inference about individual synaptic modification in the EC-DG system. Using two recording and two stimulating electrodes in animals in which recirculating activity is blocked by TTX, we extend the qualitative observations of Levy and Steward (1979, 1983) using a quantitative statistical evaluation. With this statistical approach and by independently manipulating the conditioning stimulation of the converging contralateral and ipsilateral EC-DG pathways, the effects of the conditioning stimulation on neighboring synapses and on collateral synapses are fully dissociated in individual animals. Two different conditioning paradigms increase the generality of the results presented here as compared to our previous reports. Finally, statistical evaluation of control observations reported qualitatively in previous reports (Levy and Steward, 1979, 1983; Wilson et al., 1981; Levy et al., 1983) confirms their adequacy. Taken together, these improvements strengthen the credibility of the EC-DG system as a model system for evaluating synaptic modification rules in terms of individual synapses. These improvements thus provide a firm groundwork for considering the various synaptic modification rules, introduced above, within the constraints imposed by the present electrophysiological results. Portions of the data in this paper were reported in preliminary form (Lopez et al., 1985).

MATERIALS AND METHODS

The experiments used 29 male Long-Evans rats weighing 150–400 g. The animals received chloralose/urethane anesthesia intraperitoneally (55 mg/kg and 0.2–0.5 g/kg, respectively), with supplemental doses given as needed. A hot water heating pad maintained body temperature between 36.5° and 37.5°C.

TTX injections

To prevent spontaneous activity and activity recirculating through the limbic system, multiple, bilateral injections of 10^{-5} M TTX totaling 1.2–1.8 μ l were made into the EC in each animal immediately prior to the experimental procedure. The TTX injections proved to be much more reliable than the knife cuts and electrolytic lesions previously used (Levy et al., 1983) for the same purpose.

An epoxylite-insulated (outside only) Hamilton syringe needle delivered the TTX injections and confirmed their effectiveness by acting as an auxiliary stimulating

electrode. At each of 12 locations along three dorsal-ventral tracks, 50 nl of TTX were injected. The coordinates of the three tracks were 10.2 mm posterior to bregma and 4.4, 3.9, and 3.4 mm lateral to the midline. To follow the septotemporal extent of the EC, the tracks angled 20° anterior to the coronal plane and 10° lateral to the sagittal plane at the sagittal suture. A DG response evoked by stimulation at a depth of 3 mm initially confirmed the needle's position in the EC. The 12 injection depths at each mediolateral position extended from 2 mm to 5 mm ventral to the brain surface. The needle remained at each injection site for at least 15 sec.

Two observations confirmed that TTX effectively blocked EC activity. First, in 23 of 40 cases examined, the final location of the angular bundle stimulating electrode was 0.4–1.1 mm anterior to its standard location (see below) because stimulation at the usual location failed to elicit a DG response. Since DG responses could be generated prior to TTX injection, the inability of the initial angular bundle site to generate DG potentials was attributed to blocking the initiation or conduction of impulses at that site in the angular bundle. Second, in six animals, stimulating electrodes reintroduced into the EC at the conclusion of the experiment failed to elicit a DG response at the experimental stimulus intensity (Burger, 1987).

Electrophysiology

The general electrophysiological methods were described previously (Levy and Steward, 1979, 1983). Figure 1 is a schematic representation of the experimental system. In all experiments, bipolar twisted-wire stimulating electrodes were positioned bilaterally in the angular bundle (bite bar at –5 mm, initially 4.4 mm lateral to the midline, 8.1 mm posterior to bregma). The TTX injections into the EC often necessitated repositioning the stimulating electrodes to more rostromedial positions within the angular bundle as it courses toward the hippocampus (see above). The electrophysiological effectiveness of the stimulation in generating field responses in both the ipsilateral and contralateral DGs determined the final depth of each stimulating electrode.

The bilateral extracellular recordings used micropipettes filled with normal saline (resistance 10–70 MΩ). Initial placements were 2.5 mm posterior to bregma and 1.3 mm lateral to the midline. Potential maps across the DG and audio monitoring of cell firing determined the final location of each recording electrode in the ventral leaf of the DG. We required the ipsilaterally and contralaterally evoked population excitatory postsynaptic potentials (pEPSPs) to have similar potential maps

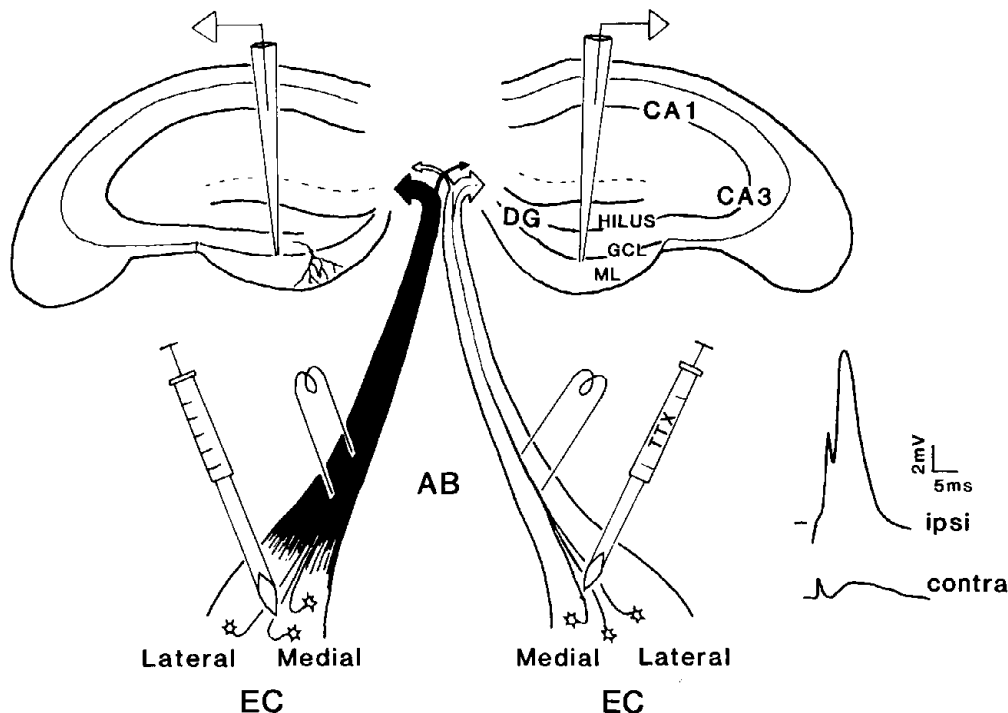


Fig. 1. Schematic of the experimental system. Recording electrodes are placed bilaterally in the granule cell layer (GCL) of the ventral leaf of the dentate gyrus (DG). The bilateral projections from the entorhinal cortex (EC) to the DG illustrate the relative sizes of the ipsilateral and contralateral projection and the convergence of the sparse contralateral projection from one EC with the dense ipsilateral projection from the other EC. A bipolar stimulating electrode in each angular bundle

(AB) delivers test and conditioning stimulation to the EC axons. The syringe in each EC indicates the TTX injections used to reduce spontaneous and recirculating activity. Representative ipsilateral and contralateral DG responses recorded in one GCL following stimulation of the right and left AB are illustrated at the right. Note that the dense ipsilateral pathway evokes a strong response, and the sparse contralateral pathway elicits a weak response.

across the DG, positive in the somatic and hilar layers and negative in the molecular layers. The final depth of each recording electrode optimized the positive-going potential. At the conclusion of every experiment, the responses were again mapped to ascertain that there was negligible electrode movement during the experiment.

Previous studies indicate that electrophysiological criteria are reliable indicators of electrode position within the DG (Andersen et al., 1966; Lomo, 1971; Steward, 1976). Even so, electrode tracks were confirmed histologically in several animals. There was close agreement between the histological and physiological maps.

There were four measurable EC-DG responses, two in each DG. Test stimulation of one angular bundle evoked two short-latency pEPSPs: 1) a response recorded in the DG ipsilateral to the stimulated angular bundle, an "ipsilateral" response, and 2) a response recorded in the DG contralateral to the stimulated angular bundle, a "contralateral" response. In each DG, the large ipsilateral pathway from one EC converges with the sparse contralateral pathway from the other EC. Therefore, a strong ipsilaterally evoked postsynaptic response converges with a much weaker contralaterally evoked postsynaptic response.

Separate experiments, not included here, demonstrated the stability of population potentials over a typical 4–5 hr experiment (Burger, 1987). Slope measurements of the contralateral pEPSP remained constant in the absence of conditioning stimulation (see Fig. 2).

Experimental protocol

For all experiments, the stimulation protocol consisted of five sequential stages: 1) a preconditioning, baseline test period; 2) a first conditioning period; 3) an intermediate test period; 4) a second conditioning pe-

riod; and 5) a final test period. To monitor synaptic efficacy, the angular bundles alternately received test stimulation once every 24.5 sec (i.e., each angular bundle received test stimulation every 49 sec). Test stimulation was a single monophasic, constant current, square pulse of 0.1 msec duration. Stimulation intensity was above the threshold for eliciting an ipsilateral population spike and was sufficient to produce at least a 0.5 mV contralateral pEPSP. The preconditioning test period lasted 20 min. The intermediate and final test periods each had a duration of 7–12 min. In all experiments, a train of conditioning stimulation consisted of eight pulses of 17.5 msec duration at 400 Hz. The intensity of test and conditioning pulses was identical.

Conditioning paradigms

There were two conditioning paradigms: the asynchronous conditioning paradigm and the unpaired/paired paradigm. The asynchronous conditioning paradigm used bilateral trains applied asynchronously to the angular bundles (see Fig. 3). The leading train was delivered to one angular bundle 20.5 msec prior to delivery of the trailing train to the other angular bundle. Because each train was 17.5 msec long, the first pulse of the trailing train began 3 msec after the last pulse of the leading train (see Fig. 3). Activation of the leading and trailing trains converges in each DG because of the bilateral EC-DG projection. Moreover, the asynchrony of converging activity is reversed in each DG (see Fig. 3).

Each conditioning period in the asynchronous conditioning paradigm consisted of 30 bilateral asynchronous trains with an intertrain interval of 145 sec. The second conditioning period differed from the first only by reversing which side of the brain received the leading train of the asynchronous pair of trains. For example, the angular bundle that initially received the leading train received the trailing train in the second conditioning period. The asynchrony of converging activity in the

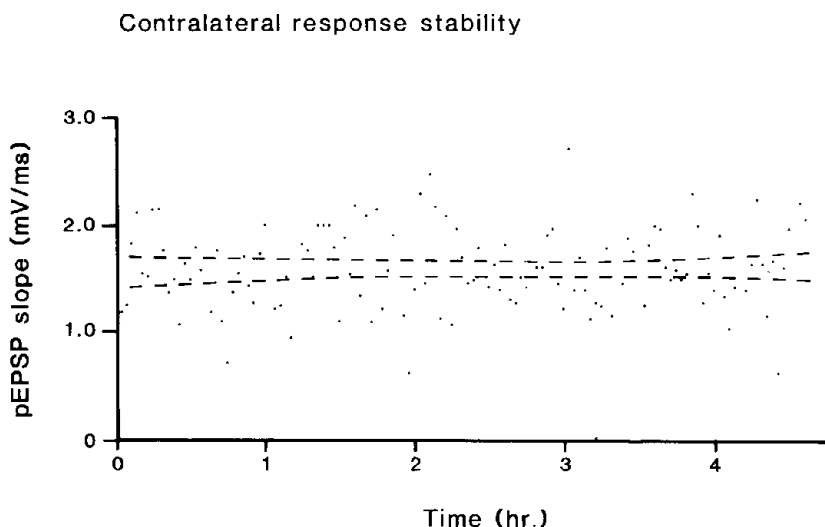


Fig. 2. Stability of the contralateral evoked response over time. The mean and variance of the pEPSP slope, measured over 4.5 hr of test stimulation, are relatively constant. Test stimulation was delivered 1/2.25 min over the interval with each response plotted as a point in the

figure. The dashed lines indicate the 95% confidence interval for a regression line calculated using all of the points. Data are from a single animal with bilateral TTX injections.

ASYNCHRONOUS PARADIGM

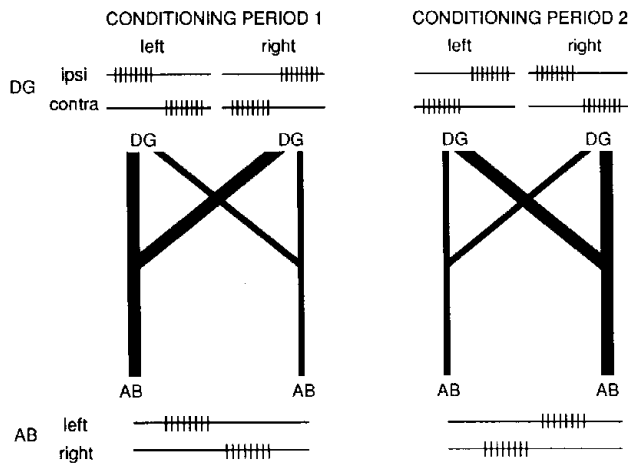


Fig. 3. Schematic of the asynchronous conditioning paradigm illustrating the timing of the stimulation activating the ipsi- and contralateral EC-DG pathways that converge in each DG during the two conditioning periods. An asynchronous stimulus pair consists of two 17.5 msec, 400 Hz trains presented asynchronously to the angular bundles (AB) on each side of the brain. Thicker lines depict the pathways that receive the temporally leading train of the asynchronous pair; thinner lines indicate the pathways that receive the trailing train of the asynchronous pair. Note that the side that leads in conditioning period 1 is the side that trails in conditioning period 2. Three milliseconds separate the end of the leading train from the beginning of the trailing train. The top of the figure illustrates how the ordering of each ipsi/contra stimulus pair changes with side of the brain. Ipsilateral and contralateral AB conditioning converge asynchronously in each DG during each stimulus pair with little change in timing since the conduction delay between ipsilateral and contralateral inputs differs by only 0.2–0.4 msec.

DGs during the second conditioning period was thus opposite that during the first conditioning period (see Fig. 3).

In the asynchronous conditioning paradigm, the order in which the strong (ipsilateral) and weak (contralateral) converging pathways receive the asynchronous conditioning trains motivated our nomenclature for the four EC-DG responses. The ipsilateral response of the pathway that received the leading train in the first conditioning period and the trailing train in the second conditioning period is the lead/trail ipsilateral response (LT ipsilateral). The response of the contralateral pathway that is the collateral of the LT ipsilateral pathway, and thus received the same conditioning as the LT ipsilateral pathway, is the lead/trail contralateral response (LT contralateral). The response of the ipsilateral pathway that received the trailing train in the first conditioning period and the leading train in the second period is the trail/lead ipsilateral response (TL ipsilateral). The response of the contralateral pathway that is the collateral of the TL ipsilateral pathway is the trail/lead contralateral response (TL contralateral). The nomenclature thus indicates the order of conditioning of the two pairs of strong and weak converging responses: 1) LT ipsilateral and TL contralateral and 2) TL ipsilateral and LT contralateral responses.

The second conditioning paradigm, the unpaired/

paired paradigm, examined the effect of either unilateral or simultaneous bilateral postsynaptic activation on synaptic modification (see Fig. 4). The first conditioning period consisted of 30 unilateral trains; the second conditioning period consisted of 30 bilateral synchronous trains. Train delivery occurred every 145 sec.

In the unpaired/paired paradigm, the nomenclature for the evoked responses reflects the conjoint or individual conditioning of the strong (ipsilateral) and weak (contralateral) converging pathways. The ipsilateral response of the pathway that received conditioning during the first and second conditioning periods is the conditioned/conditioned ipsilateral response (CC ipsilateral). Because the collateral contralateral pathway also receives these two periods of conditioning, the collateral contralateral response is the conditioned/conditioned contralateral response (CC contralateral). The ipsilateral response of the pathway receiving no conditioning in the first conditioning period and conditioning in the second conditioning period is the unconditioned/conditioned ipsilateral response (UC ipsilateral). The collateral contralateral response of the UC ipsilateral response is the unconditioned/conditioned contralateral response (UC contralateral).

The CC ipsilateral and the UC contralateral responses are converging responses, as are the UC ipsilateral and the CC contralateral responses.

Data collection and statistical analyses

The responses were fed through high-impedance preamplifiers to AC-coupled amplifiers and then into a digitizing, Nicolet 1070 computer with a sampling period of 45 μ sec and low-pass filter settings at 10 kHz.

UNPAIRED / PAIRED PARADIGM

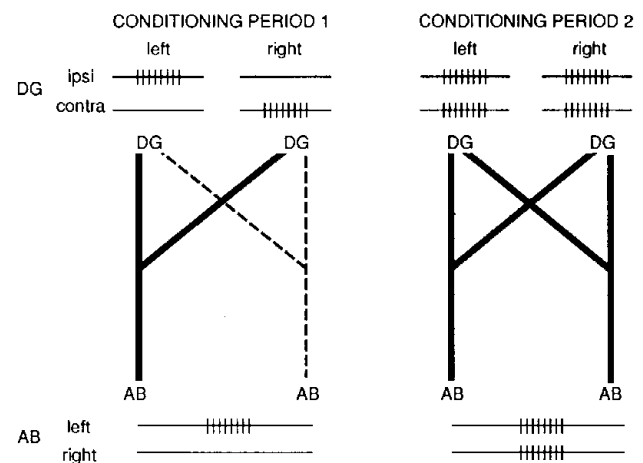


Fig. 4. Schematic of the unpaired/paired conditioning paradigm illustrating the differing activation of the ipsilateral and contralateral EC-DG pathways during conditioning period 1 (left half of figure) and conditioning period 2 (right half of figure). Conditioning stimulation of the angular bundle (AB) consists of 30 unilateral trains in conditioning period 1 and 30 bilateral synchronous trains in conditioning period 2. Solid lines indicate the pathway(s) receiving conditioning stimulation; the dashed line indicates the unconditioned pathway. The top of the figure illustrates the differing activation in each dentate gyrus (DG) occurring with unpaired and paired conditioning.

Photographic records were taken from the on-line oscilloscope before analog-to-digital conversion.

Quantification of the digitized responses consisted of off-line measurements of the initial slope (within the first 4 msec of the stimulus artifact) or amplitude of the positive-going pEPSPs. In a few animals (~20%), quantification of the contralateral responses was difficult either because of their small size (0.5–2 mV) or because of contamination by volume-conducted potentials generated simultaneously on the other side of the brain by ipsilateral activation. This simultaneous, large high-frequency component only appeared late in the experiments as the ipsilateral responses potentiated. This contamination was identified at the conclusion of an experiment by its failure to map as a positive and negative voltage and by the temporal congruence of ipsilateral and contralateral high-frequency components. The contaminated contralateral responses could frequently be quantified by measuring response amplitude rather than slope. Contaminated contralateral responses in which neither amplitude nor slope measurements were possible were not included in the results (six of 51 contralateral responses).

The means of the evoked responses recorded during each test period were the initial, intermediate, and final test period values for each of the four EC-DG responses. The results section reports the mean percent change of the evoked responses.

Although brief, high-frequency conditioning stimulation consistently yielded long-term modifications in our previous studies, we assessed the long-term nature of the modifications induced here using linear regression analysis. Assuming a linear function, the time required for the modified response to return to baseline was calculated from the mean intercept and slope for each response during the intermediate and final test periods. The calculated time interval ranged from 41 to 294 min, clearly justifying the statement that associative potentiation and associative depression are both long-term modifications.

Statistical analysis consisted of four procedures for each paradigm. A Wilcoxon matched-pairs, signed-ranks test (see Siegel, 1956; SAS Institute, 1982) compared the mean responses in the preconditioning and postconditioning test periods to evaluate the effect of conditioning on each EC-DG response. A Kruskal-Wallis repeated measures analysis of variance by ranks (see Siegel, 1956; SAS Institute, 1982) compared the effects of conditioning across the four EC-DG responses of each experiment to evaluate whether the conditioned responses differed statistically. This design took into account the interdependent nature of the four EC-DG test responses recorded from each animal.

If the analysis of variance yielded significant *F* values, then two additional statistics assessed whether contralateral pEPSP changes statistically depended on changes of the ipsilateral synapses or on the associative contingencies of conditioning stimulation. First, Pearson's *r* coefficients estimated the linear correlation between the effects of conditioning on converging ipsilateral and contralateral response pairs and on collateral ipsilateral and contralateral response pairs (SAS Institute, 1982). Second, a Bayesian test with a uniform prior for probable dependency (Tribus, 1969) was applied to the data after its assembly in 2×2 contingency tables. The Bayesian test estimated the probability that con-

tralateral pEPSP changes statistically depended on 1) changes of converging ipsilateral synapses, i.e., those synapses on the same granule cells as the contralateral synapses; 2) changes of collateral ipsilateral synapses, i.e., synapses formed by afferents originating in the same EC; and 3) the associative contingencies of the conditioning stimulation, i.e., the presence or absence of contralateral activation in the presence of strong postsynaptic activation provided by converging ipsilateral conditioning stimulation.

Contingency table analyses offer several advantages when compared with correlation analyses. The evaluation of statistical independence via contingency tables does not require a Gaussian assumption and thus complements the more restricted assumptions of the correlation analysis. In addition, contingency tables provide a means to examine the dependency of pEPSP changes on categorical, nonnumerical data such as the associative contingencies of conditioning stimulation.

RESULTS

Asynchronous conditioning paradigm

The strong ipsilateral responses on both sides of the brain potentiated after the first period of asynchronous conditioning (Fig. 5A) and showed negligible further increases after the second period of asynchronous conditioning (Fig. 5B). The LT ipsilateral response, i.e., the ipsilateral response of the pathway that received the leading train of the asynchronous pair, increased 118.0% after the first asynchronous conditioning period (left half of Fig. 5A; $P = .0015$, $n = 17$). The second period of asynchronous conditioning increased the LT ipsilateral response only 7.2% (left half of Fig. 5B, $P = .4407$, $n = 17$). The ipsilateral response of the pathway that received the trailing train, the TL ipsilateral response, increased an average of 103.6% (right half of Fig. 5A; $P = .0004$, $n = 18$) after the first conditioning period. The TL ipsilateral response increased only 11.1% after the second conditioning period (right half of Fig. 5B; $P = .223$, $n = 18$).

The two weak contralateral responses potentiated or depressed depending on the timing of the contralateral conditioning relative to the converging ipsilateral conditioning. A contralateral response potentiated if this contralateral pathway received the leading train during conditioning, i.e., the LT contralateral response after the first conditioning period and the TL contralateral response after the second conditioning period (see Fig. 5). Conversely, when a contralateral pathway received the trailing train during conditioning, this contralateral response showed depression, i.e., the TL contralateral response after the first conditioning period and the LT contralateral response after the second conditioning period (see Fig. 5).

The LT contralateral response potentiated after the first conditioning period and depressed after the second conditioning period (Fig. 5). LT contralateral test responses increased 64.6% on average from the initial baseline test period to the intermediate test period ($P = .0002$, $n = 18$). Following the second conditioning period, the LT contralateral response decreased 25.6% as compared with the intermediate test period ($P = .0011$, $n = 18$). Figure 6 (lower row) illustrates the potentiation and subsequent depression of the LT contralateral response from one animal.

Simultaneously, on the other side of the brain, the

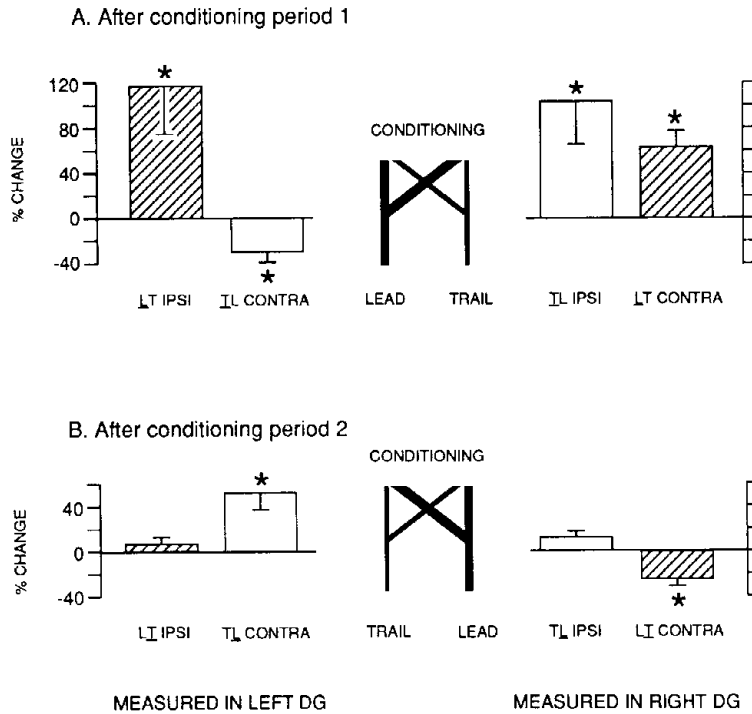


Fig. 5. Effect of asynchronous conditioning on EC-DG synaptic responses after conditioning period 1 (A) and conditioning period 2 (B). The schematics of the EC-DG pathways in the center of the figure indicate the conditioning paradigms used in A and B. Thick lines indicate the EC-DG pathways receiving the leading train of the asynchronous pair; thin lines indicate EC-DG pathways receiving the trailing train of the asynchronous pair (see Fig. 3). Values plotted are the mean (either + or - sem) percent change in the pEPSP slope as compared to the immediately preceding baseline. The left bar graph in A illustrates that asynchronous conditioning potentiates the LT ipsilateral response (shaded bar) and depresses the converging TL contralateral response (open bar). The right bar graph in A illustrates that asynchronous conditioning potentiates both the TL ipsilateral response (open bar) and the converging LT contralateral response (shaded bar). Reversing the temporal order of the asynchronous condi-

tioning (B) potentiates the previously depressed contralateral response (TL contra) and depresses the previously potentiated contralateral response (LT contra). Neither ipsilateral response is potentiated further. The results for collateral responses are similarly shaded. The open bars in A show contralateral depression (TL contra) with collateral ipsilateral potentiation (TL ipsi). The shaded bars in B show contralateral depression (LT contra) accompanied by no change in the collateral ipsilateral response (LT ipsi). LT, pathway that leads during conditioning period 1 and trails during conditioning period 2. TL, pathway that trails during conditioning period 1 and leads during conditioning period 2. Underlined letters (L, lead; T, trail) indicate the temporal position of synaptic activation during the most recent conditioning period. The left half of A and B are recorded from the same DG electrode. The right half of A and B are recorded from the same DG electrode. Asterisks indicate statistical significance of $P < 0.05$.

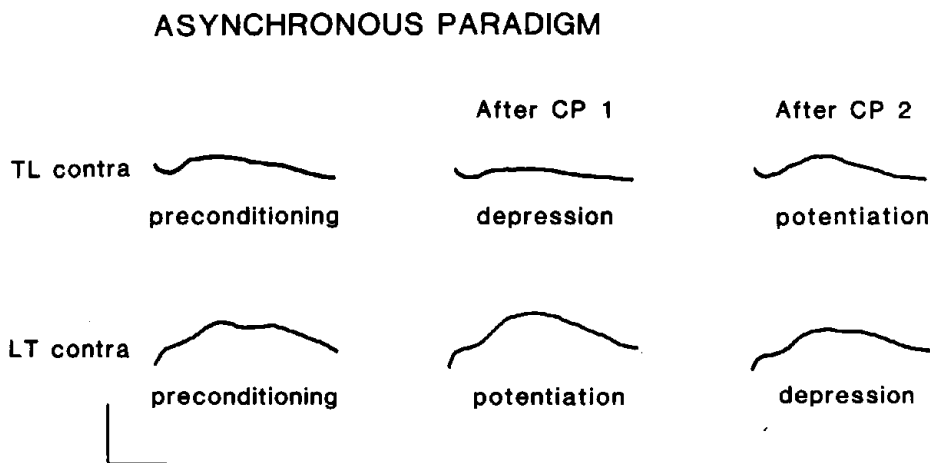


Fig. 6. Effect of asynchronous conditioning on individual contralateral synaptic responses. The TL contralateral pEPSP (top row) decreases after conditioning period 1 (CP1) and subsequently increases

after conditioning period 2 (CP2). The LT contralateral pEPSP (bottom row) increases after CP1 and then decreases after CP2. See text for definition of each response. Scale, 2 mV/5 msec.

average TL contralateral response depressed after the first conditioning period and potentiated after the second conditioning period (Fig. 5). Following the first conditioning period, the mean TL contralateral response decreased 30.1% from the preconditioning baseline to the intermediate test period ($P = .0035$, $n = 16$). After the TL contralateral pathway received the leading train in the second conditioning period, the mean TL contralateral response increased 51.3% relative to the intermediate test period ($P = .0100$, $n = 16$). The upper row of traces in Figure 6 shows the depression and subsequent potentiation of one TL contralateral response.

A weak contralateral EC-DG response thus either potentiates or depresses when the strong converging ipsilateral response simultaneously either potentiates (Fig. 5A) or is unchanged (Fig. 5B). Moreover, synaptic modification is not the same either at all collateral synapses of one EC neuron or at all the synapses converging upon one postsynaptic DG neuron.

Unpaired/paired paradigm

Unilateral (i.e., unpaired) conditioning potentiated the ipsilateral test response of the conditioned pathway, i.e., the CC ipsilateral response, and depressed the test response of the converging, unconditioned pathway, i.e., the UC contralateral response (see Fig. 7A). After the first conditioning period, the average CC ipsilateral response increased 166.3% from its preconditioning baseline value ($P = .0050$, $n = 10$). The average UC contralateral response decreased 19.0% relative to its preconditioning baseline average ($P = .0460$, $n = 10$).

Simultaneously, neither of the converging responses on the other side of the brain, the UC ipsilateral response and the CC contralateral response, changed significantly (Fig. 7A). In the intermediate test period, the average UC ipsilateral response increased only 8.2% relative to its preconditioning baseline value ($P = .4070$, $n = 9$). The average CC contralateral re-

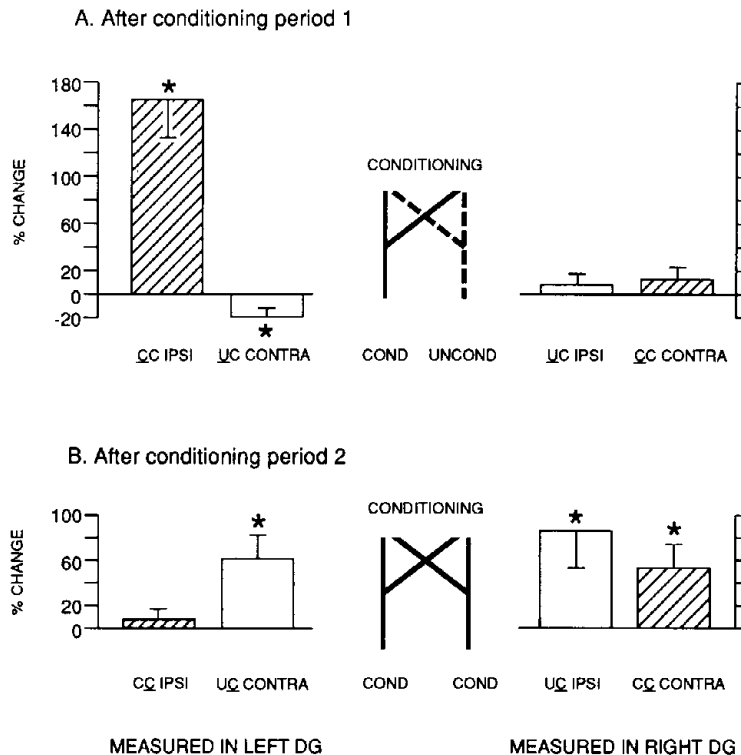


Fig. 7. The effects of unpaired (A) followed by paired (B) conditioning stimulation demonstrate that modification of EC-DG synaptic responses is independent of both neighboring and collateral synapses. Schematics in the center of the figure indicate the paradigm for each conditioning period. Solid lines indicate the conditioned EC-DG pathways; broken lines indicate the EC-DG pathways unconditioned during conditioning period 1 (see Fig. 4). Values plotted are the mean (either + or - sem) percent change in pEPSP slope as compared to the immediately preceding baseline. A: Unilateral conditioning potentiates the CC ipsilateral response (hatched bar) and depresses the UC contralateral response (open bar). Simultaneously neither the CC contralateral response (hatched bar) nor the UC ipsilateral response (open bar) is altered by the unilateral conditioning. B: Effects of

bilateral conditioning on the same responses. Hatched bars indicate collateral pathways that receive conditioning stimulation in both conditioning periods; the CC ipsilateral response is unchanged while the CC contralateral response now potentiates. Open bars identify collateral pathways that are unconditioned in conditioning period 1 and conditioned in conditioning period 2; both collateral responses now potentiate. UC, unconditioned during conditioning period 1 and then conditioned during conditioning period 2. CC, conditioned during conditioning period 1 and then conditioned during conditioning period 2. Underlined letters indicate if the pathway is either conditioned (C) or unconditioned (U) in the most recent conditioning period. Asterisks indicate statistical significance of $P < 0.05$.

UNPAIRED/PAIRED PARADIGM

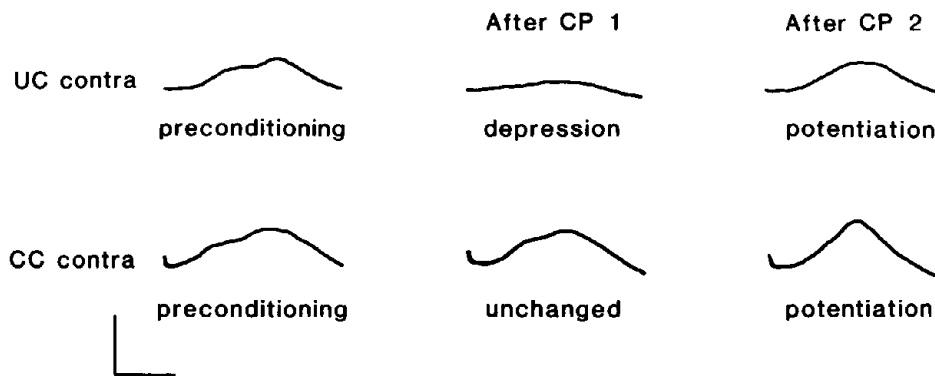


Fig. 8. Effect of unpaired/paired conditioning on individual contralateral synaptic responses. The UC contralateral pEPSP (top row) decreases after unilateral conditioning in conditioning period 1 (CP1) and then increases after bilateral conditioning in CP2. The CC con-

tralateral pEPSP (bottom row) is unchanged after CP1 and increases after CP2. These are average responses from a single animal. See text for definition of each response. Scale, 3 mV/5 msec.

tration similarly increased only 12.7% relative to its preconditioning baseline average ($P = .2720$, $n = 7$).

Bilateral (i.e., paired) conditioning did not significantly alter the previously potentiated CC ipsilateral response but did potentiate the other three test responses (Fig. 7B). The CC ipsilateral test response increased only 7.5% from the intermediate test period to the final test period ($P = .3583$, $n = 10$). The previously depressed UC contralateral response increased 60.6% on average from the intermediate test period to the final test period ($P = .0110$, $n = 10$). The UC ipsilateral and the CC contralateral responses increased 85.4% and 53.0%, respectively, from the intermediate to the final test period ($P = .0090$, $n = 9$; $P = .0230$, $n = 8$). Figure 8 shows average contralateral responses from a typical experiment.

Like the asynchronous conditioning paradigm, the unpaired/paired conditioning paradigm demonstrates that synaptic modification can be different at different synapses on a single postsynaptic neuron and at collaterals of a single axon. There is thus both a dissociation between collateral synapses (see hatched bars in Fig. 7) and between converging synapses (see hatched and unhatched pairs in Fig. 7).

Analysis of variance

The conditioning stimulation of each paradigm differentially altered the four EC-DG evoked responses. For the asynchronous paradigm, both the first and second conditioning periods significantly altered the four evoked responses ($F = 3.75$, $df = 37$, $P < .05$; $F = 1.89$, $df = 37$, $P < .05$, respectively). Similarly, for the unpaired/paired paradigm, the two conditioning periods each differentially changed the four evoked responses ($F = 5.56$, $df = 18$, $P < .05$; $F = 3.54$, $df = 17$, $P < .05$, respectively).

Correlation analysis

The quantified dissociations of synaptic modification presented above are consistent with the view that indi-

vidual EC-DG synapses independently change their strength. Linear correlation analyses support this view statistically for both paradigms (see Tables I and II). The linear correlation between the observed pEPSP changes of the collateral contralateral and ipsilateral responses was 0.10 for the unpaired/paired paradigm (Fig. 9). For converging ipsilateral and contralateral response pairs in the unpaired/paired paradigm, the correlation coefficient was -0.09 (Fig. 10). For the

TABLE I. Correlation of collateral and converging contralateral response changes with ipsilateral response changes in the asynchronous paradigm¹

	Collateral response pairs		Converging response pairs	
	LT ipsi/ LT contra	TL ipsi/ TL contra	LT ipsi/ TL contra	TL ipsi/ LT contra
After CP1	0.043 (16)	0.505 (15)	0.087 (16)	0.152 (17)
After CP2	0.554 (16)	-0.162 (15)	-0.163 (16)	0.158 (17)

¹Values are Pearson's r coefficients (number of response pairs). CP1, conditioning period 1; CP2, conditioning period 2. LT, pathway receives leading train during CP1 and trailing train during CP2. TL, pathway receives trailing train during CP1 and leading train during CP2. Figure 3 and Materials and Methods provide further details of the asynchronous conditioning paradigm.

TABLE II. Correlation of collateral and converging contralateral response changes with ipsilateral response changes in the unpaired/paired paradigm¹

	Collateral response pairs		Converging response pairs	
	CC contra/ CC ipsi	UC contra/ UC ipsi	UC contra/ CC ipsi	CC contra/ UC ipsi
After CP1	0.097 (8)	0.019 (7)	-0.666 (9) ²	0.505 (7)
After CP2	0.706 (8)	-0.107 (7)	0.344 (9)	0.847 (7) ²

¹Values are Pearson's r coefficients (number of response pairs). CP1, conditioning period 1; CP2, conditioning period 2. CC, pathway conditioned during CP1 and CP2; UC, pathway unconditioned during CP1 and conditioned during CP2. For further details of the unpaired/paired paradigm, see Figure 4 and Materials and Methods. ²Correlation predicted by the associative contingencies of the conditioning paradigm.

Correlation of modification at collateral synapses

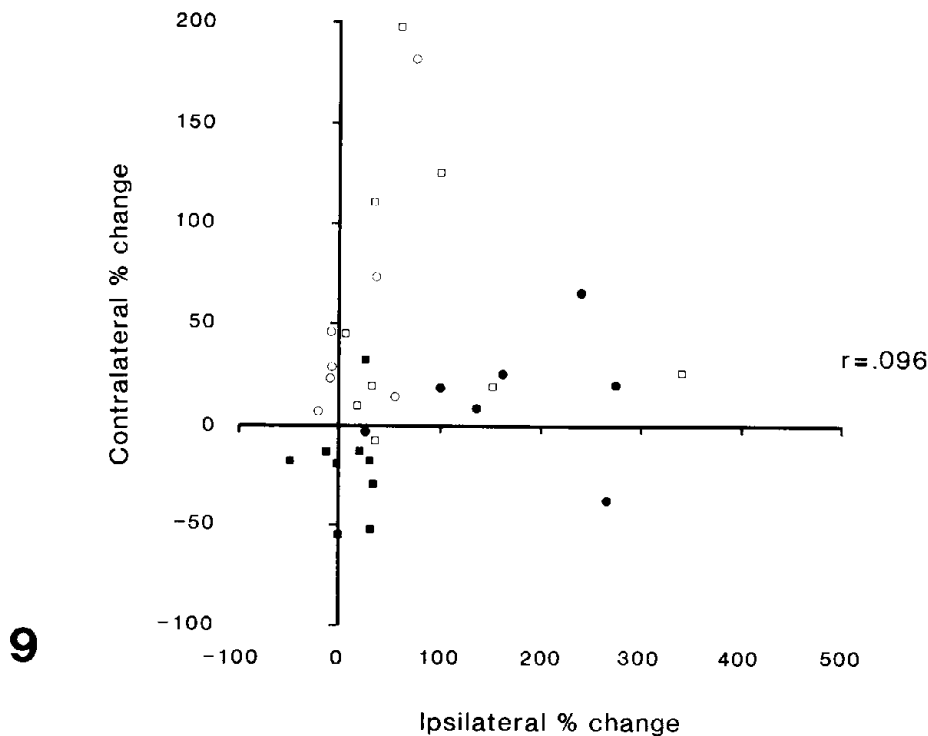


Fig. 9. Scatterplot of the change in each contralateral pEPSP plotted against the change in its simultaneously evoked collateral ipsilateral pEPSP in the unpaired/paired conditioning paradigm. The correlation is very poor ($r = 0.096$), implying that synapses made by a single axon can be differentially modified. Each experiment contributes two collateral response pairs tested after each of the two conditioning periods.

Squares indicate collateral response pairs unconditioned in conditioning period 1. Circles indicate collateral response pairs conditioned in conditioning period 1. Responses after conditioning period 1 are indicated by solid symbols; responses after conditioning period 2 are indicated by open symbols.

asynchronous paradigm, the correlation was 0.00 for collateral ipsilateral and contralateral response pairs and was 0.03 for the converging response pairs. All these correlation coefficients are near enough to zero that we can consider the response modifications as uncorrelated and, with the typical Gaussian hypothesis of linear correlations, as independent.

Contingency table analysis

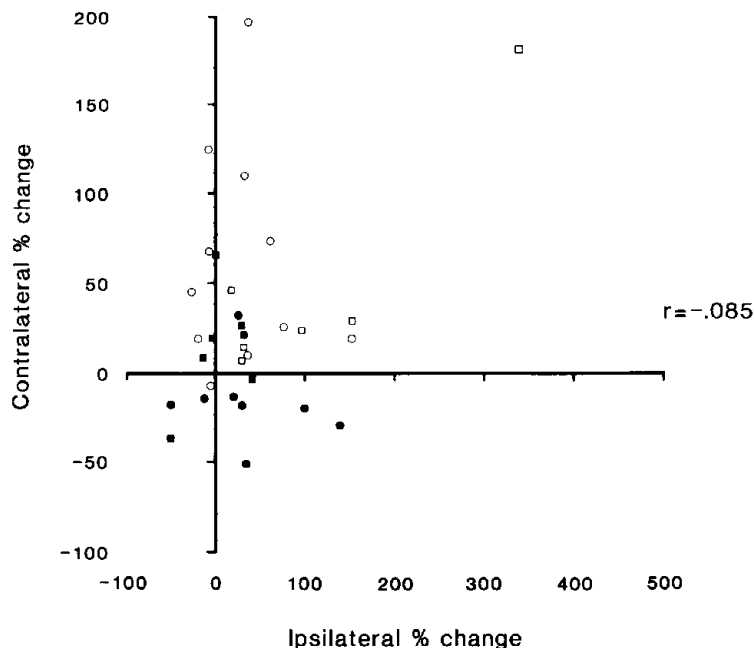
In this statistical analysis, the information present in the graded nature of the responses is of no relevance because modifications are treated as dichotomous variables (increase or decrease, with no "no changes"). The contingency table analysis examined the statistical dependence of modification of the weak contralateral pEPSP on modification of the strong ipsilateral pEPSP and on the associative contingencies of each conditioning paradigm. Unlike the correlation analysis, the validity of inferences of statistical dependency from a non-parametric analysis of contingency tables does not depend on any particular distributional assumption, e.g., the Gaussian assumption inherent in correlation analysis.

The dependence of contralateral response modification on each conditioning paradigm far exceeds its dependence on ipsilateral response modification. The probability that contralateral response modification de-

pends on modification of the converging ipsilateral response was only 0.29. The probability of contralateral modification depending on collateral ipsilateral modification was 0.73. Thus the direction of modification of the contralateral response is poorly predicted by modification of the converging ipsilateral response and is predicted only partially by modification of the collateral ipsilateral response. On the other hand, the probability of contralateral modification depending on the associative contingencies of converging contralateral and ipsilateral conditioning was 0.99 for the unpaired/paired paradigm and 1.00 for the asynchronous paradigm. Thus the direction of modification of the contralateral response can be predicted totally by the contingencies of contralateral activation and converging ipsilateral activation.

DISCUSSION

The present study extends our partial quantification of synaptic modification (Levy and Steward, 1979, 1983; Levy et al., 1983; Wilson et al., 1979, 1981) by quantifying the dissociated, but simultaneous, synaptic changes of all four EC-DG responses after brief, high-frequency conditioning stimulation. This complete quantification statistically contrasts and compares the effects of conditioning on the responses of the converging and collateral EC-DG pathways. These statistical comparisons fully



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Fig. 10. Scatterplot of the change in each contralateral pEPSP plotted against the change in its converging ipsilateral pEPSP in the unpaired/paired conditioning paradigm. The correlation is very poor ($r = -0.085$), implying that neighboring synapses can be independently modified. Each experiment contributes two converging response pairs tested after each of the two conditioning periods. Squares indicate

converging response pairs in which the ipsilateral response was unconditioned in conditioning period 1. Circles indicate converging response pairs in which the contralateral response was unconditioned in conditioning period 1. Responses after conditioning period 1 are indicated by solid symbols; responses after conditioning period 2 are indicated by open symbols.

qualify the bilateral EC-DG system as a model for studying the spatiotemporal and activity dependencies of associative synaptic modification and thus for formulating synaptic modification equations. The quantitative data suggest that changes in the contralateral EC-DG pEPSP may be extrapolated to the modification of an individual contralateral EC-DG synapse, a point critical to many published synaptic modification equations.

Specificity of synaptic modification

The argument for the specific modification of individual synapses rests on the spatial proximity of ipsilateral and contralateral EC-DG synapses converging on the same granule cells. The data supporting the spatial proximity of the EC-DG synapses are anatomical. At least 93% of the synapses in the distal two-thirds of the molecular layer are EC-DG synapses (Steward and Vinsant, 1983). Further, the terminals of the ipsi- and contralateral EC-DG pathways are not spatially segregated but are intermingled (Davis et al., 1988; Goldowitz et al., 1975; Steward et al., 1976a).

Electrophysiological observations further document the convergence of ipsilateral and contralateral EC-DG pathways in each DG. Stimulation of the contralateral EC-DG pathway evokes a short-latency synaptic response with the same location of current sources and sinks as does stimulation of the ipsilateral pathway (White et al., 1988), thereby demonstrating the spatial convergence of the two pathways. EC-evoked single unit firing in the DG demonstrates that granule cells can be

driven by both the ipsilateral and the contralateral pathways (Fig. 11; see also Wilson, 1981); this observation shows convergence of both inputs onto the same cell. Indeed, each of the few contralaterally activated granule cells we have observed is also fired by the ipsilateral input. Therefore the ipsi- and contralateral inputs that converge to the same side of the brain also converge on the same region of the molecular layer and onto some of the same granule cells. This cellular convergence explains why the excitation provided by the ipsilateral input is interpreted as the postsynaptic excitation controlling the induction of associative LTP and LTD at each individual neuron (Levy and Steward, 1979) or even just a portion of an individual neuron's dendritic tree (Moore and Levy, 1986; White et al., 1986, 1988).

The poor correlation between modification of converging ipsilateral and contralateral responses shows that these alterations do not reflect nonspecific, nonsynaptic changes in the DG, e.g., increases or decreases in the excitability of the DG granule cells or changes in resting membrane potential. Nonspecific and many nonsynaptic mechanisms predict the alteration of many synapses in the same terminal region; this is not observed. The poorly correlated changes of converging ipsilateral and contralateral responses (see Tables I and II) thus indicate that broad postsynaptic changes cannot account for the changes in synaptic field potentials observed here.

A similar argument about the specificity of synaptic modification exists for collateral ipsilateral and contralateral synapses as well. Both the anatomical orga-

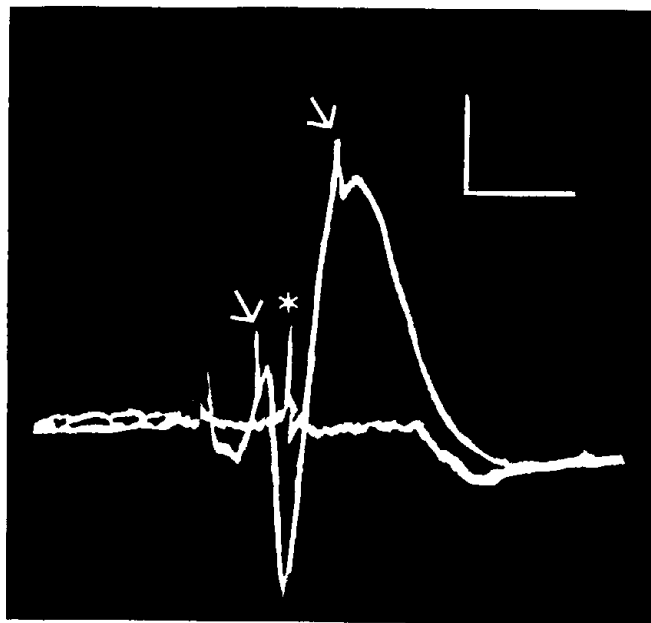


Fig. 11. Unit firing in the DG evoked by both ipsilateral and contralateral angular bundle stimulation. High-frequency spikes, indi-

cating unit firing, occur on the rising phases of both the ipsilateral (arrows) and contralateral (asterisk) pEPSPs. Scale, 2 mV/5 msec.

nization of the bilateral EC-DG system and the physiology of long-term modification are not consistent with synaptic modifications stemming from changes in the afferents themselves (e.g., changes in axonal conduction, excitability, or branch point safety factor), since such changes would similarly affect both the collateral ipsilateral and contralateral responses. This result is not the experimental observation. Anatomically branches of the same EC axons form synapses in both the ipsilateral and contralateral DGs (Steward and Vinsant, 1978). Electrophysiologically synaptic modification of the collateral ipsilateral and contralateral systems is dissociable, and changes of the contralateral response are not well predicted by changes of the collateral ipsilateral response (see Tables I and II).

The specificity argument is further emphasized if we consider the intermingling of synapses in quantitative detail. Anatomical studies estimate that the ratio of ipsilateral to contralateral EC-DG synapses is 19:1 (Steward et al., 1976a; Steward and Vinsant, 1983). Given the random distribution of contralateral EC-DG synapses in the molecular layer (Goldowitz et al., 1975; Davis et al., 1988) and the estimated density of synapses there (Desmond and Levy, 1986), a cube of molecular layer less than 2.5 μm on a side contains 20 synapses. If such a cube is centered on a single contralateral synapse, then 19 ipsilateral synapses surround the one contralateral synapse. Therefore, the dissociated changes in converging contralateral and ipsilateral field potentials show that depression or potentiation of synaptic efficacy can occur within less than 1 μm of synapses that either remain unchanged or potentiate. Thus both potentiation and depression possess remarkable specificity.

Synaptic modification rules

The most simple interpretation of the dissociations of synaptic modification reported here is that individual EC-DG synapses are individually modifiable and that this modification is a function of both pre- and postsynaptic activity. The contingency table analysis supports this view by demonstrating that the effect of conditioning stimulation on a contralateral response is only well predicted by the associative contingencies of the conditioning paradigm. These findings thus favor those theories hypothesizing the existence of individually modifiable synapses (Amari, 1977; Anderson, 1968; Cooper et al., 1985; Grossberg, 1976; Kohonen, 1982). That is, the rules governing synaptic modification operate at the level of the individual synapse, and such rules should be constructed with reference to individual synaptic connections (see, e.g., Levy, 1982; Levy et al., 1983; Levy and Desmond, 1985, 1988).

Although the contralateral test system contains many EC-DG axons, we interpret test responses of this system as equivalent to the qualitative test response of a single afferent. This interpretation is justified by the fact that qualitative results are all that are needed to distinguish among major classes of synaptic modification rules and by the following observation. If stimulation initially evokes a small contralateral conditioning and test response and then stimulation strength is decreased to obtain an even smaller response, associative LTP and LTD still are observed, provided ipsilateral conditioning is sufficiently strong. That is, with decreasing stimulation strength, there is no intensity dependence in the contralateral system. So long as a contralateral response is measurably above noise levels

all of the phenomena of associative potentiation and depression are observed (see, e.g., Burger and Levy, 1987; Levy and Steward, 1983; Levy et al., 1983). These observations invite the following extrapolation: If we decrease stimulus intensity so that only a single EC axon is activated, then all the phenomenology still obtain.

By combining the controls discussed above with this extrapolation to a single afferent, it is clear how the bilateral EC-DG system can be used to study synaptic modification rules formulated in terms of single synapses. Specifically, the contralateral input in these rules corresponds to a single presynaptic input, whereas the net amount of ipsilaterally induced excitation, which is highly nonlinear (Burger and Levy, 1987; Levy and Burger, 1987) and varies monotonically with the intensity and frequency of ipsilateral activation, corresponds to the postsynaptic term in these rules.

Synaptic modification equations

If we juxtapose our experimental observations in the EC-DG system against some of the published synaptic modification equations, we find that some of these equations do not fit the data. The critical data are the contingencies controlling the qualitative changes of the contralateral response.

Two equations are fundamental to the mathematical statement of synaptic modification rules. The first equation merely formulates change almost as a plasticity experiment might: The synaptic strength after the experiment is just the synaptic strength before the experiment plus the change in synaptic strength:

$$W_{ij}(t+1) = W_{ij}(t) + \Delta W_{ij}(t). \quad (1)$$

Here $W_{ij}(t)$ stands for the strength of a single synapse ij at time t ; $(t+1)$ indicates some later time and Δ indicates change. The ij label occurs because we think of a single afferent named i making a single synapse with a neuron named j .

The second equation defines $\Delta W_{ij}(t)$, the change in synaptic strength, and is the heart of the issue.

One such equation, perhaps the simplest mathematical interpretation of Hebb's (1949) associative proposal, is

$$\Delta W_{ij} = \epsilon X_i Y_j, \quad (2)$$

where X_i is the activity of afferent i and Y_j is the measure of postsynaptic excitation in neuron j . (Time t has been left out for notational simplicity and will remain implicit.) Typically, X_i is interpreted as frequency (however, see Colbert and Levy, 1988) so that its values range from zero to some maximum. ϵ is a positive number between 0 and 1 and produces a stochastic averaging function (Geman, 1981). From the experimental perspective, we consider ϵ akin to arousal or septally induced theta rhythm, i.e., a nonspecific excitation that is the same for all cells and synapses in a given region.

The terms of equation 2 may be defined in terms of the bilateral EC-DG system, where i is a contralateral afferent, X_i is the contralateral input frequency during conditioning, and Y_j is the postsynaptic excitation induced at granule cell j by high-frequency ipsilateral activation. The simple associative equation 2 does not

predict synaptic depression when X_i is zero and $Y_j > 0$, i.e., contralateral inactivity associated with converging ipsilateral activation. Rather the rule predicts no change, $\Delta W_{ij} = 0$. Furthermore, neither the classic error corrector equations (e.g., Widrow-Hoff; see Barto et al., 1981) nor the rule proposed by Bienenstock et al. (1982) of the form

$$\Delta W_{ij} = \epsilon X_i f(Y_j) \quad (3)$$

predicts depression when $X_i = 0$. Thus several synaptic modification equations are not consistent with the experimental observations in the EC-DG system.

The simplest equation consistent with these (and other) electrophysiological observations is

$$\Delta W_{ij} = \epsilon f(Y_j)(X_i - W_{ij}c), \quad (4)$$

where c is a constant. This equation is a variant of Kohonen's (1982) equation and is consistent with both Amari's (1977) and Grossberg's (1976) suggestions. We previously summarized our research in terms of this equation (Levy, 1982, 1985; Levy and Desmond, 1985) and analyzed the simplified form using a linear postsynaptic term [$f(Y_j)$] (Levy and Geman, 1982; Levy et al., 1983) instead of a more realistic sigmoid expression. The very fact that contralateral activation alone is ineffective in inducing its own LTP demands a highly nonlinear $f(Y_j)$. [The same argument applies to intensity studies in the ipsilateral system (see, e.g., McNaughton et al., 1978; Wilson et al., 1980, 1981), although the use of linearity for explanatory and analytic simplification sometimes obscures this point (Levy and Geman, 1982; Levy et al., 1983; Kohonen, 1984)]. More recent studies of contralateral LTP and LTD confirm the nonlinear nature of the permissive event $f(Y_j)$ (Burger and Levy, 1987; Levy and Burger, 1987).

The generality of the present findings remains to be determined. It does seem likely that different classes of synapses will be governed by different modification rules. However, judging such differences is problematic at present because almost any differences noted between the work here and that conducted in other systems might be attributed to technical and paradigmatic differences rather than to fundamental differences in synaptic function (e.g., in vivo vs. in vitro, train lengths and frequencies). Moreover, it does seem possible that the rule presented here for the EC-DG synapses is incomplete. We have recently proposed that there are two rules governing a single synapse (see Levy et al., 1989; for discussion of this proposal). This perspective allows us to unify our observations on depression with those of Pavlides et al. (1988) and Stanton and Sejnowski (1989) without contradicting the analysis presented above.

Relating contralateral associative potentiation/depression to ipsilateral LTP

We believe that there is no fundamental difference between an individual ipsilateral and an individual contralateral synapse. Ipsilateral and contralateral synapses are indistinguishable ultrastructurally (Davis et al., 1988) and electrophysiologically (Harris et al., 1978; Steward et al., 1976b). The apparent difference between ipsilateral and contralateral synapses with regard to long-term potentiation and depression is a

function of the coactivity that can be evoked in each pathway (see Levy, 1985; Levy and Steward, 1979; Wilson et al., 1979, 1981).

The critical observation for understanding the apparent difference between ipsilateral and contralateral LTP is the intensity dependence of LTP (McNaughton et al., 1978; see also Wilson, 1981; Wilson et al., 1979, 1981; for more detailed replications). With only a small amount of synaptic activation, neither the ipsilateral nor the contralateral EC-DG system can self-potentiate. If the ipsilateral system is made to produce a large response by increasing the stimulus intensity or if the contralateral system is enlarged via experimentally induced sprouting (Wilson et al., 1979), then LTP can be induced in either system.

The remaining apparent dissimilarity between the ipsilateral and contralateral systems is the absence of experiments that report LTD in the ipsilateral system. Because LTD requires spatial (i.e., local dendritic) convergence between the test system and the requisite powerful permissive input (White et al., 1988), the missing ingredient for ipsilateral LTD is a powerfully excitatory converging input that can be activated without activating the ipsilateral test pathway. In fact, pilot studies from our laboratory indicate that the contralateral system can induce depression in the ipsilateral system if the contralateral system is made more powerful in its influence on DG cells. For example, if a partial ipsilateral EC lesion is made in a neonate, the adult animal then has a sprouted, powerfully excitatory contralateral input and a weak ipsilateral input. In this situation, the contralateral input can provide a suitable permissive event to induce ipsilateral depression. Thus, there appear to be no fundamental differences between individual ipsilateral and contralateral EC-DG synapses, and inferences made based on contralateral synaptic modification presumably apply equally well to ipsilateral synaptic modification.

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