significance of the auditory stimuli to the subject may be more relevant to the occurrence of the interhemispheric asymmetry in AER's than is the mere use of verbal versus nonverbal materials.

Therefore, many factors that are likely to change the significance of an auditory stimulus become directly responsible for the magnitude of this interhemispheric asymmetry. Attention level (*12*) and conditioning processes (*13*) are examples of such factors. However, the possibility that man's brain also has neuronal mechanisms that respond only to some spectral characteristics of speech sounds cannot be ruled out. Although evidence for such mechanisms was not found in the small area that we investigated, these mechanisms might exist in other areas (*14–16*).

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11. Although the differences between R's for the different conditions were statistically significant, absolute amplitudes (in microvolts) of the W waves obtained under the four conditions, when compared within a hemisphere, gave no statistically significant differences ($P > .40$ for both hemispheres, by Friedman one-way analysis of variance).
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Hippocampal Unit Activity during Classical Aversive and Appetitive Conditioning

Abstract. *Rats were trained with a tone being followed by either food or electric shock, on alternate days. Unit activity during application of the conditioned stimulus was recorded from the dorsal hippocampus. The results indicate differentiation of the hippocampal system. Dentate units respond by augmentation to a conditioned stimulus which leads to food and by inhibition to the same stimulus when it precedes electric shock. The hippocampus proper responds by augmentation in both situations. The intensity of the hippocampal response to the conditioned stimulus on the first day of training is higher if the unconditioned stimulus is food than if it is electric shock. These data cast light on the functions of the dorsal dentate-hippocampal connections and the hippocampus proper during aversive and appetitive conditioning.*

Recent theories of hippocampal functions can be divided between those which consider the hippocampus as functioning in motor mechanisms (*1*) and those which look at the hippocampus as a central information processor influencing perceptual as well as behavioral mechanisms (*2*). A way to distinguish between the theories is to set up a situation where two clearly distinct behaviors are performed, namely, food retrieval versus freezing, as a response to a stimulus which serves as a signal for different reinforcers on different sessions of training. Does the hippocampus have the same response to the same stimulus or does its response correlate with the gross behavior of the animal? The present experiment attempts to answer this question.

Twelve rats with six to eight electrodes implanted in the dentate gyrus and CA-3 and CA-1 fields of the hippocampus served as subjects. Methods of implantation, data collection, and reduction are described elsewhere (*3*, *4*). Six of the rats were trained in the following paradigm. Day 1 consisted of pseudoconditioning: one of three stimuli (two tones and a 45-mg food pellet) randomly selected was presented once every minute for 16 hours. On days 2 and 3, one of the tones, the positive conditioned stimulus (CS+), was correlated with a food pellet, the unconditioned stimulus (US), with a CS-US interval of 1 second. The CS+ was randomly alternated with the second tone (CS−), which was presented without reinforcement. On days 4 and 5, the CS+ was correlated with an electric shock (US) ¼ second in duration (*5*). On day 6, food was served again as the US. The other six rats were trained in the same paradigm except that on day 1 pseudoconditioning consisted of two tones and ¼-second shock presented randomly. On days 2, 3, and 6 the US was shock, and on days 4 and 5 it was food. Between every switch from one US to another there were 2 to 3 hours of extinction and pseudoconditioning—the two tones and the forthcoming US presented randomly. For the daily sessions (involving 300 trials of each CS) an average of the unit activity in the 1-second pre-CS and the 1-second CS-US intervals was plotted. For the averages (pre- and poststimulus histograms) a 10-msec bin width was used, that is, each point indicates the average firing during a particular 10-msec interval. A similar average was prepared on the basis of the gross movement of the whole animal, this being the measure of the overt condi-

tioned response (*6*). Examples of average response curves for single units are shown in Fig. 1.

A total of 33 units (*7*) were recorded from the various hippocampal areas, divided as follows: 13 from the dentate gyrus, 9 from CA-3, and 11 from CA-1 areas of the hippocampus proper (*8*).

For analysis, the 1-second CS-US interval was divided into four successive 250-msec periods. The mean activity in these periods was presented as a deviation from the mean of the 1-second pre-CS period in standard scores. Grand averages, that is, averages of the standard scores for all of the units in each of the various hippocampal areas for the fifth and sixth days of training under the two conditions, are presented in Fig. 2. It shows clearly different gross behaviors in response to the same tone under the two conditions. Units of the dentate gyrus respond by augmentation to the food signal, and by inhibition to the shock signal; CA-3 and CA-1 respond to both signals by augmentation. A two-way distribution-free analysis of variance (*9*) which was made on the first 250 msec in the three areas in the two conditions showed overall significant deviation from randomness ($\chi^2 = 15.81$, $P < .01$), significant difference between the hippocampal areas ($\chi^2 = 10.3$, $P < .01$), and nonsignificant difference between treatments ($\chi^2 = 2.96$, $.05 < P < .10$).

The comparison between days 5 and 6 of both paradigms was chosen in order to compare the responses in animals already trained under the two conditions. A question still exists concerning how the response to the conditioned stimulus was acquired. Is there a difference between the response to a food signal and a shock signal on the first day of conditioning? The gross motor conditioned response as well as the dentate conditioned response were well established in this day. Animals that started the experiment with food as a US show excitatory responses. Those that started with shock as a US had inhibitory responses (Fig. 1). These behaviors were reflected in dentate units. However, a comparison (*10*) between units in the hippocampus proper in rats that started the experiment with food as US and those that started with shock as US showed that there was a more intense response ($U = 19$, $P < .05$), in terms of deviation from background activity, to the food signal than to the shock signal in the hippocampus proper on the first day of conditioning (see also Fig. 1). This result, in combination with the comparison of days 5 and 6, suggests that the hippocampus proper is likely to "learn" a positive (food) rather than a negative (shock) signal, but once the rat has learned to connect the signal to the positive reward, the hippocampus will sustain its response to the signal even if its meaning is changed.

The dentate gyrus was found to be different from the hippocampus proper in a few respects (*11*). It responded by augmentation to the food signal and by inhibition to the shock signal, and seemed to reflect the gross behavior. Unlike behavior, the dentate response to the shock signal could be predicted by the response of some denate units to a "no food" signal (*4*). This fits Amsel's theory (*12*) which equates positive and nonnegative signals, and negative and nonpositive signals, although we did not find the response to the "no shock" signal to be equivalent to the "food" signal. Since the only known output of the dentate gyrus is through the mossy fibers to area CA-3 of the hippocampus (*13*), the two questions might be asked, what is the relation between the two structures, and what makes the CA-3 fire in the same intensity in both situations, although one of its main input stages (dentate gyrus) is inhibited? There is the possibility that under aversive conditioning there was a short circuit through the direct perforant path and/or activation of the hippocampus by input from the medial

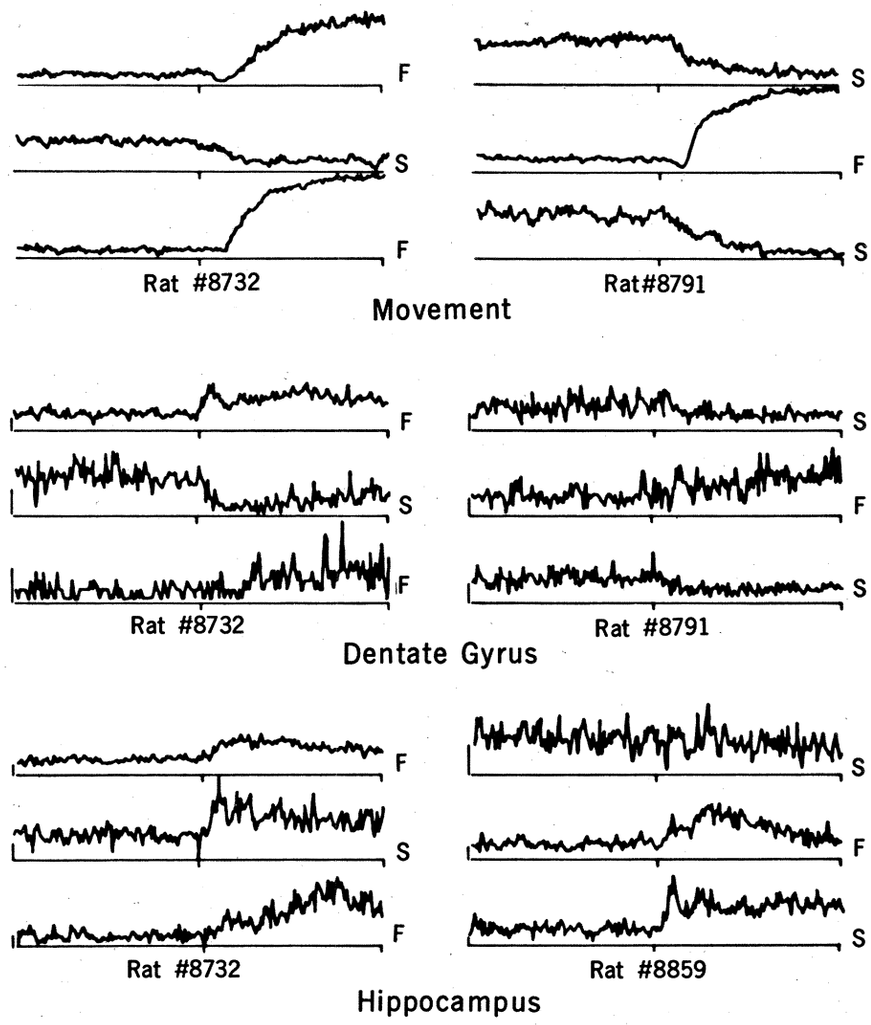

Fig. 1. Computer-averaged response histograms for units and behavior. Every histogram is an average of 300 successive trials. The histogram is divided into halves: the first half is combined of 100 points in the pre-CS period; the second half is combined of 100 points of the CS-US interval. The US is either food (*F*) or shock (*S*). The bar to the left of each histogram represents an average firing probability for a 10-msec interval which is equal to 0.02 (equivalent to two spikes per second). Every set of three histograms represents the same unit, or gross movement of the same animal, under three successive treatments applied in day 2 (first day of conditioning) and days 5 and 6 (days 4 and 5 of conditioning); the left column is taken from a situation in which the unconditioned stimulus is food-shock-food. The right column is shock-food-shock.

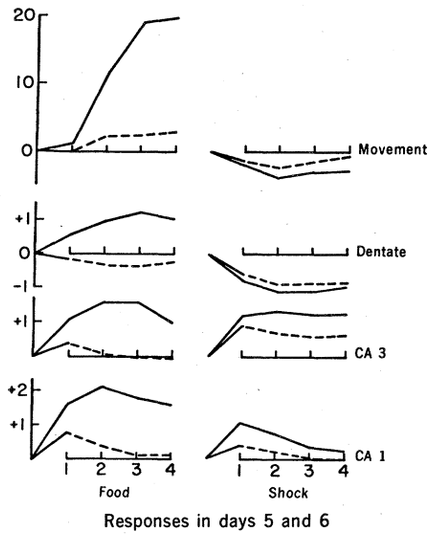

Fig. 2. Averaged response curves in the various hippocampal areas. The data of the kind presented in Fig. 1 were reduced to four periods, 250 msec each, for the 1-second CS-US interval. The amount of activity in each of these periods is presented in terms of deviation from a background level. Figure 2 shows an average of the units in the various areas under the two experimental conditions. Solid line = response to CS^+; dashed line = response to CS^-. The ordinate scale is of standard scores. The sample sizes are: dentate, $n = 13$; CA-3, $n = 9$; CA-1, $n = 11$. Gross movement: $n = 12$ (the total number of animals in the experiment).

septal nucleus (*13*) or directly from the reticular formation. (These possibilities have to be explored in further experiments.) If this were the case, it would mean that the dentate gyrus has to do mainly with positive reward, and that the hippocampus proper is more easily activated through the dentate circuit, in a positive reward situation. In any event our data clearly indicate a differential response between dentate and the CA-3, CA-1 system when a fear-inducing stimulus is supplied, in spite of their similar response to stimulations which could be expected to instigate more positive anticipations. This differentiation of dentate activity from that of the hippocampus into which it projects mitigates the possibility that there is some gross arousal function of the formation which includes both of these large groups of highly organized neurons, and favors a more complex role for this system in the processing of information.

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6. Movement was detected by means of a "noisy" wire attached to the animal's head. Head movements generated potentials in the wire which were amplified and fed through a schmitt-trigger to the computer. For further details see (*4*).
7. A total of 48 (four out of each rat) units was recorded; 15 of them were excluded from the final sample prior to any analysis because of (i) disappearance of the unit during the experimental session (five cases), (ii) various quality criteria [see (*4*)] (three cases), and (iii) units which were found in other structures or were not clearly localized within the hippocampus (seven cases).
8. After termination of the experiment the rats were killed by an overdose of Nembutal. A 10-μa d-c lesion current was applied for 15 seconds through the electrode before perfusion with 10 percent formaldehyde. The brains were sectioned in 60-μ slices on a freezing stage and stained by cresyl violet and Weil methods. Probe tips were easily located.
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Nuclear Magnetic Relaxation Time of Blood and Blood Velocity

Morse and Singer (*1*) reported the nuclear magnetic resonance (NMR) longitudinal relaxation time T_1 of blood samples as 0.4 ± 0.03 second both in vivo and in vitro. They claimed that T_1 is constant, and, based on this value of T_1, they calculated the blood flow velocity. It is not probable for blood to have the same relaxation time both in vivo and in vitro as the milieu interior of the blood may affect the relaxation time of blood in vivo.

There are a few other factors, in addition to velocity, which affect the relaxation time of a fluid, and T_1 cannot be the same for all types of blood. One of us (J.K.) has studied several phenomena of flowing fluids using the NMR technique (*2*). This study showed that the variations in the amounts of oxygen and paramagnetic materials in a fluid would affect T_1 to a considerable extent. The value for T_1 of $0.0015M$ $MnSO_4$ solution was found to be 0.278 second, and that of $0.0005M$ $MnSO_4$ solution was 0.675 second. Similar variations in T_1 were noted for fluids containing $FeCl_3$ or other paramagnetic materials.

Saraf (*3*) reported that changes in concentrations of different ions in a fluid would affect the T_1 of that fluid. He determined that the NMR signal for a solution consisting of 0.1 mole of NaCl per liter of solution was 50 units, and the NMR signal for a solution consisting of 1 mole of NaCl per liter of solution was 38 units.

Therefore, the presence of varying amounts of oxygen, paramagnetic materials, and other salts in blood can give different values of T_1, even though the blood has the same flow velocity. Similarly, blood samples having the same flow velocity may have different values of T_1. It is very important to take into consideration the effects of these factors if the NMR technique is to be used for determining blood flow velocity.

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Kumar and Kumar are correct in saying that the nuclear magnetic resonance (NMR) relaxation time (T_1) of blood does vary. In fact, we have been engaged in a yearlong study of the magnetic relaxation times of blood samples (*1*). However, the measurement of blood flow velocity by means of our techniques (*2*) does not depend on the NMR relaxation time. In order to illustrate this point, I here briefly recapitulate our technique for the measurement of blood flow.