In the first experiment, mice were subjected to cold exposure for periods of 3 or 6 hours. The PNMT activity was significantly elevated (Table 1) at the end of 3 hours; this elevation was sustained at 6 hours.

To determine whether the rapid increase in PNMT activity represented an activation of existing enzyme or an induction of protein synthesis, the following experiment was performed. One hour before the initiation of cold exposure, animals were given 50 mg of cycloheximide per kilogram of body weight intraperitoneally; cycloheximide is an inhibitor of protein synthesis.

Cycloheximide dilutions were prepared in isotonic saline; control animals received an equivalent volume of saline. After 6 hours of cold exposure, the animals were killed, as stated before, and the PNMT in the adrenals was determined. The results (Fig. 1) confirm the rise in PNMT activity seen in the previous experiment (saline plus cold stress). However, cycloheximide completely blocked the stress-mediated rise in PNMT. These results suggest that stress brings about an increase in PNMT activity by stimulating protein synthesis. It remains to be elucidated whether stress induces the de novo synthesis of PNMT, or of some other protein which perhaps activates existing PNMT without increasing the absolute amount of the enzyme.

Our studies represent the first demonstration in any species that acute stress can cause a rapid induction of PNMT. The results also demonstrate species differences; since, in the rat, PNMT induction is important only in response to long-term stress situations (*3, 4, 8, 9*), while in the mouse, PNMT may be important in the acute adrenal medullary stress response. The results raise the possibility that, in the mouse, a relatively rapid change in PNMT activity may be important in the ability of the organism to sustain output of epinephrine. The rapid rise of PNMT activity in the mouse could provide a valuable system for investigation of regulation of catecholamine biosynthesis (*10*).

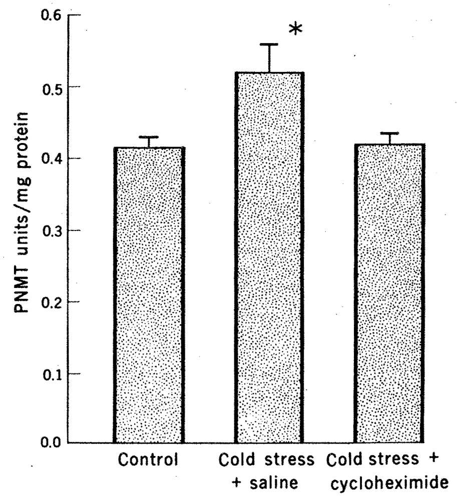

Fig. 1. Effects of cycloheximide on cold stress–mediated increase in PNMT. Animals were treated with saline or cycloheximide, cold-stressed, and killed 6 hours later. $*P < .02$ greater than control.

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Auditory Evoked Response: Meaningfulness of Stimuli and Interhemispheric Asymmetry

Abstract. *Interhemispheric asymmetries of different magnitudes were observed in human cortical auditory evoked responses to speech and sound-effect stimuli. The wave with peak asymmetry occurred 100 milliseconds after signal onset. The amount of asymmetry of the amplitude of this wave was related to the meaningfulness to the subject of the auditory stimulus rather than to the mere use of verbal versus nonverbal materials.*

Differences between the hemispheres in processing verbal as opposed to nonverbal stimuli have been demonstrated in man by clinical, pathological, pharmacological, and psychological techniques (*1*). The presence of specialized auditory areas in each hemisphere has been postulated (*2*), and an anatomical asymmetry between the speech area in the major hemisphere and its counterpart area in the minor hemisphere has been reported (*3*). These findings suggest that similar asymmetries between the two hemispheres might be detected by neurophysiological techniques.

We looked for interhemispheric asymmetries in the transcranially derived gross auditory evoked response (AER) in human subjects who were processing various verbal and nonverbal stimuli (*4*). However, the focus of this report is on the effect of variations in the meaningfulness of the stimulus materials, both verbal and nonverbal.

Using a rosette recording method (*5*) over the parietal, central, and temporal regions of two subjects, we established that the largest asymmetry of AER amplitude (W wave in Fig. 1) occurred about 100 msec after the stimulus. Measurements were made by comparing two bipolar recordings, W_1-P_3 and W_2-P_4. In these recordings, P_3 and P_4 were the left and right parietal locations as given by the standard 10-20 system (*6*), and W_1 was defined as the center of a triangle made by 10-20–system locations P_3, T_3, and T_5. This W_1 placement was presumably close to Wernicke's area. Location W_2 was similarly determined on the right hemisphere.

In some subjects, the interhemispheric asymmetry of the W waves consistently differed in magnitude as a function of the speech or nonspeech character of the stimuli.

We wondered whether these asymmetries in the gross AER were determined by the physical properties of speech and nonspeech sounds or by the significance attached by the subject to these different auditory stimuli. In other words, were these AER asymmetries attributable to the use made of the stimuli by the subject? To answer this question, we studied the AER obtained in the following experimental conditions.

Condition 1: undiscriminated words. Four monosyllabic words (back, tick, bake, and cook) recurred 110 times in all and were interspersed randomly among the nonspeech sounds of condition 2. Subjects were instructed merely to tally with a pencil the total words in the series. Discrimination among the words was not required.

Condition 2: undiscriminated sounds. Four different sound effects, generated by various mechanical noises (*7*), recurred a total of 110 times in random sequence and were interspersed among the words of condition 1. Subjects were instructed to keep a tally of the total noises in the series, that is, they tallied words and sounds concurrently, in separate columns. As in condition 1, discrimination among different words and sound effects was not required.

Condition 3: discriminated sounds. The same four sound effects used in condition 2 were presented without interspersed words, and subjects were instructed to determine how many different types of sounds they could identify.

Condition 4: meaningful speech. Ten sentences of test instructions, totaling 150 words, were delivered in spaced speech.

The conditions were thus designed to contrast low and high significance levels of noises (conditions 2 and 3) and low and high significance levels of words (conditions 1 and 4). The purpose was to compare AER asymmetries obtained from the same subject with stimuli of contrasting meaningfulness. Subjects reported that they assigned verbal labels (for example, "wobbly") to the sounds in condition 3, to aid them in their discrimination task.

All auditory stimuli (words or sounds) were edited by computer (*8*) to 485 msec, except for a few shorter words in the sentences of condition 4. Word length was equalized by eliminating some of the redundant and silent parts of the waveforms; even after 20 percent elimination, all words were still perfectly understandable (*9*).

Subjects were nine right-handed young adults. All stimuli were presented through two balanced speakers, one 25 cm from each ear; 4-second interstimulus intervals were used for all conditions. The subjects sat in a moderately illuminated, soundproof recording chamber and were instructed not to tilt their heads during the experimental session. Trigger pulses to signal the onset of computer sampling of the AER were synchronized with the onset of each word or sound. Random selection of the stimuli was made by the computer, operated on-line. Stimulus intensity was 75 to 85 db above threshold for normal young adult subjects.

The AER's for each of the four conditions were sorted out and summated independently, also by the computer. The AER's to the four words chosen showed no difference in amplitude, latency, or waveform (*4*); hence they were added together (condition 1). Similarly, the AER's were collected for each word in the sentences (condition 4) and added together. The same was done for the four sound effects in conditions 2 and 3.

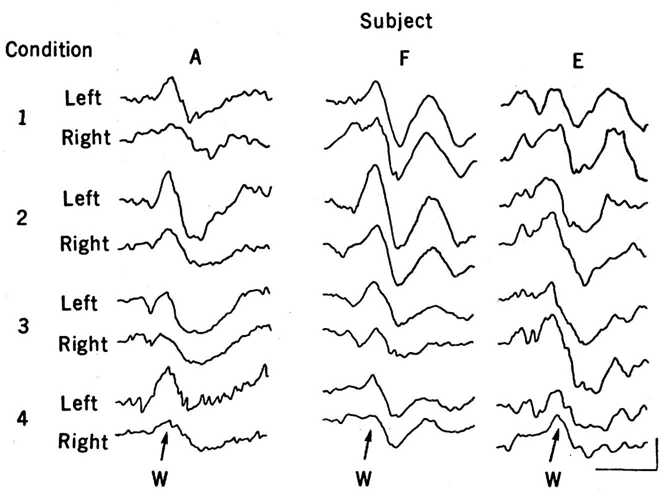
Figure 1 shows the AER's to the auditory stimuli presented under the different conditions. The W wave is larger on the left hemisphere in two-thirds of the subjects (for example, subjects A and F) and is larger on the right in the remaining subjects (for example, subject E).

The asymmetries seen on the W waves for all subjects are shown in Fig. 2. The magnitude of the asymmetry is expressed by the ratio $R = w_l/w_l + w_r$), where w_l is the peak-to-peak amplitude (in microvolts) of the W wave recorded on the left hemisphere and w_r is that recorded on the right hemisphere (*10*). When this ratio is 0.5, the W wave is symmetrical between the hemispheres; when it is larger than 0.5, the W wave on the left is larger; and when it is smaller than 0.5, the W wave on the right is larger.

In all subjects but one, *R* values were largest under condition 4 ($P <$ .01, by two-tailed Wilcoxon matched-pair signed-ranks tests against other conditions). Also, a larger *R* value is generally seen with sounds presented under condition 3 than under condition 2 even though identical sound effects were used in both conditions ($P <.05$). No group statistical significance was found between words in condition 1 and sounds in condition 2 ($P >.05$), although variability was high and differences between these two conditions were large in some objects (*11*).

The latency of the W wave (100 msec after word onset) indicates that the W wave occurs when less than 25 percent of the stimulus word has been heard. Thus, the W wave is probably not a reflection of the meaning intrinsic in the message, but rather of the mental set which the particular conditions imposed on the subject.

When the subject had to use the meaning of each word maximally, the asymmetry was largest (condition 4), but when the subject did not have to understand each word, the word did not produce such large asymmetry (condition 1). Also, the same sound effects produced different magnitudes of asymmetry when different tasks were imposed on the subject (conditions 2 and 3). This suggests that the



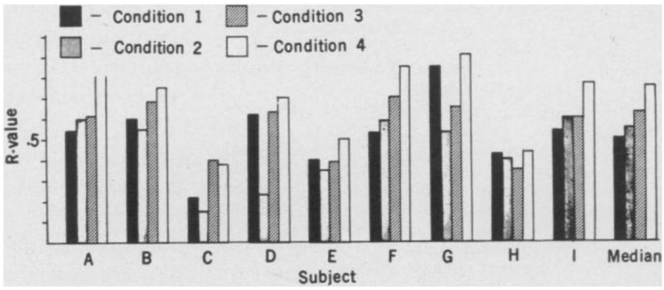


Fig. 1 (left). Auditory evoked responses to various auditory stimuli that differ in meaningfulness. Recordings are from the left and right hemispheres of three right-handed subjects. The W wave, which shows the interhemispheric asymmetry of amplitude, is indicated by *W* and the arrow. The abcissal scale is 100 msec and the ordinal scale is 2.5 μv. Total analysis time per record is 250 msec. The upward direction indicates positivity. Fig. 2 (right). Changes in *R* values with different auditory stimuli.

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-