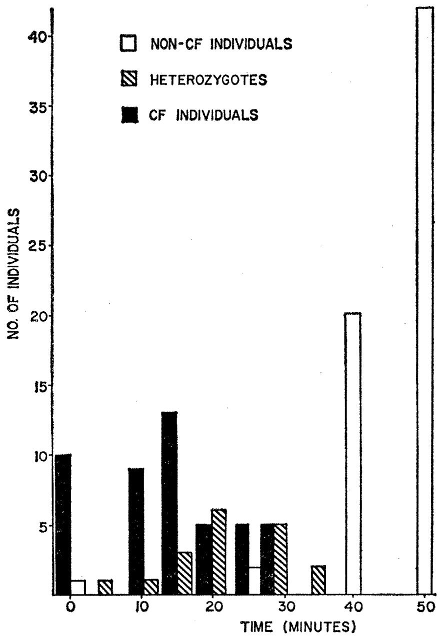

Fig. 2. Number of individuals (CF patients, heterozygotes, and normal individuals) whose serums stopped oyster cilia at intervals from 0 to 50 minutes.

gotes and heterozygotes except for the serums from two healthy individuals which caused the cilia to stop in less than 30 minutes. It is not known whether these two individuals are heterozygotes for cystic fibrosis; however, serums from 19 heterozygotes did cause the ciliary action to stop in less than 5 to 35 minutes. Although the population sampled was small, the results from the serums of these two individuals without CF are compatible with the estimated heterozygote frequency of approximately 2 to 10 percent. None of the serums from CF patients or their parents permitted ciliary action as long as serums from the normals. Serums from 47 CF patients stopped ciliary action in periods ranging from the time of exposure to within 30 minutes after contact. Neither age, sex, nor clinical severity of CF influenced the time of ciliary cessation.

When cystic fibrosis serum was diluted with seawater at ratios of 1:1, 1:2, and 1:3, the first, but not the second concentration, caused the cilia to stop before 35 minutes. The inhibitory activity was present in serum from CF patients after dialysis against seawater in Visking tubing 8/32. Saliva from CF patients, but not from normal individuals, also inhibited ciliary action. Twenty minutes of exposure to saliva from CF patients caused ciliary cessation.

Additional results indicate that the factor in CF patients and heterozygotes responsible for cessation in oyster cilia shares properties in common with the CF factor found by Spock *et al.* (*1*) and by Mangos *et al.* (*2*). It is nondialyzable, heat-labile, and has a molecular weight between 75,000 and 180,000 as indicated by gel filtration. Mangos and McSherry found significant inhibition of transductal reabsorption of sodium in the rat parotid after it was exposed to saliva and sweat from CF patients, in addition to solutions of the following compounds (all bases)—polylysine, polyornithine, and protamine sulfate (*2*). The effects of these compounds were also observed on oyster cilia preparations. After exposure to dilute concentrations of these solutions (*5*), oyster ciliary action stopped immediately after administration of polylysine and polyornithine. Protamine sulfate did not stop the cilia before 40 minutes; but immediately after exposure, there was a moderate expulsion of debris from the gill mounds, an indication of tissue injury produced by this compound. Although the mechanism of these basic compounds and the CF factor which inhibits ciliary activity is not yet understood, it is interesting that the same synthetic compounds which mimic the inhibitory effect of saliva and sweat from CF patients on sodium reabsorption in the parotid also inhibit oyster ciliary action.

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4. Serums from CF patients attending clinics at the Texas Rehabilitation Hospital, Houston, and the University of Minnesota Medical School, Minneapolis, were provided by Drs. G. Harrison, R. Doggett, and W. J. Warwick, respectively. Controls included serums from 13 healthy children in the Head Start Programs of LaMarque and Texas City, Texas; 26 healthy adults; and 25 children suffering from allergic rhinitis and bronchial asthma were provided by Dr. A. Goldman.
5. Polylysine hydrobromide, molecular weight 40,000 to 100,000 and polyornithine hydrobromide, molecular weight 60,000 to 120,000 (Pierce Chemical Company) were prepared to the concentration of 1 mg/ml with filtered seawater. Protamine sulfate (Upjohn) was prepared as 1 mg/ml in normal saline.
6. Supported by PHS grant HD 03321; by special project 409, Children's Bureau of the Department of Health, Education, and Welfare; and by grant allocation from The National Foundation. We thank L. Nicholson and S. Anderson for technical assistance.

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Averaged Evoked Responses in Vigilance and Discrimination: A Reassessment

Abstract. *With the use of monopolar recordings for averaged evoked responses, detected signals in a vigilance task are associated with a late positive component which is absent for undetected signals as well as nonsignals. Bipolar recordings obscure the late positive component associated with detected signals. The data suggest that the late positive component represents cerebral processes associated with evaluation of unpredictable changes in stimulation.*

Although human averaged evoked responses (AER) vary in a lawful manner with changes in stimulus parameters (*1*), and in some instances with perceptual variables (*2*), as yet no portion of an AER can be specifically attributed to processes underlying the perception or evaluation of a stimulus. Discrimination tasks, in which errors of stimulus perception occur, provide an opportunity to observe differences in AER to stimuli which are physically identical but are perceived differently. Several experiments of this sort have been reported, but only one by Haider *et al.* (*3*) assessed the AER to both correct and incorrect responses to the *discriminanda*. In this study the observer was required to detect small changes in stimulus intensity (signals) randomly interspersed among more frequent standard stimuli (nonsignals). The forms of the AER for detected and undetected signals did not differ, although the amplitude was greater for the detected signals. Since the AER amplitude to nonsignals in successive blocks of stimuli over the entire experiment tended to decrease and correlated with the proportion of signals detected within each block, the changes in the signal AER appeared to reflect alterations in subjects' alertness rather than processes specifically related to detection of the signals.

In contrast to these results of Haider *et al.* (*3*), we found (*4*) that, when subjects were reading, unpredictable onset of stimulation as well as stimulus changes randomly embedded in a series of standard stimuli elicited AER containing a prominent late positive component (LPC), usually highest between 300 and 350 msec after presentation of the stimulus. Although the standard stimuli were ignored by the subjects, the unpredictable stimulus changes were perceptually obtrusive and caused momentary shifts of attention to the stimuli. (We subsequently found that the latency of the LPC varies from 300 to 550 msec, depending on the qualitative and quantitative aspects of the stimulus changes used.) Since the stimulus contingencies which elicited the LPC were closely allied to those that produce orienting responses (*5*), we suggested that the occurrence of the LPC could be a cerebral correlate of the orienting response. In that the arrangement for randomly interspersed stimulus changes used in our studies was similar to that of the vigilance experiment by Haider *et al.*, we attributed the absence of an LPC in their study to differences in attentional set. We reasoned that in vigilance tasks the observer actively attends to all stimuli so that shifts of attention or orienting responses to the signals might not occur.

This interpretation, however, does not account for the results of experiments by Sutton and colleagues (*6*) and by Donchin and Cohen (*7*) in which LPC was obtained in response to stimuli presented under conditions in which attention was actively sustained. This discrepancy seemed totally inexplicable and prompted us to review the conditions of all of these experiments. In replication of the experiment by Haider *et al.*, we obtained results reported below which permitted a reinterpretation of the significance of the LPC concordant with all of the experimental findings.

Both auditory and visual discrimination tasks were used. In the visual condition, flashes were delivered once every 3 seconds (*8*). The standard flash (6.8 millilamberts) was replaced in random fashion on the average of one in ten stimuli by a slightly dimmer flash (signal). The subject pressed a small switch whenever he detected a signal. The auditory condition was similar except that the stimuli were tone bursts at 1200 cycle/sec (50 msec), with the standard stimuli (nonsignals) at approximately 40 db and the signals at 35 db. The electroencephalogram (*9*) was recorded from electrodes placed above the left eye, at the vertex (Cz), and 2.5 cm lateral to the standard midoccipital placement (Oz), all referred to a chin electrode. A bipolar linkage between the vertex and occipital leads as described in Haider *et al.* (*3*) was also used.

The results for all subjects were similar (*10*). In the referential recordings, the detected signals elicited AER recorded from the vertex and occipital leads which contained a prominent late positive component (Fig. 1). Since the LPC was common to both leads, the bipolar linkage failed to disclose it, which would account for its apparent absence in the study by Haider *et al.* Furthermore, in the auditory condition, in which stimulus parameters similar to those of Davis (*11*) were used in a discrimination task, the detected signals had LPC with peaks in the range of 450 and 550 msec. Since his analysis was limited to a 375-msec epoch, Davis could not have observed these longer latency changes in auditory stimuli (*12*). An additional result is apparent in Fig. 1. In the bipolar recording for the visual condition and the monopolar vertex recording for the auditory condition, the AER of undetected signals and nonsignals had similar waveforms.

Several additional experiments have been performed to exclude other possible explanations for the results and to assess their generality. Even though the motor response to the detected signals was small and not time-locked to the stimulus, we ruled out the possibility that the LPC might represent a motor potential in two ways. In one condition the subject was instructed to withhold his response for at least 1 second after detecting a signal, and in another he responded to the nonsignals and withheld his response to the signals. In both instances comparable LPC was elicited by the detected signals.

The data reviewed so far suggest that the LPC is a correlate of detection of a change in stimulation. But we have found that when the difference between the signal and nonsignal is made very

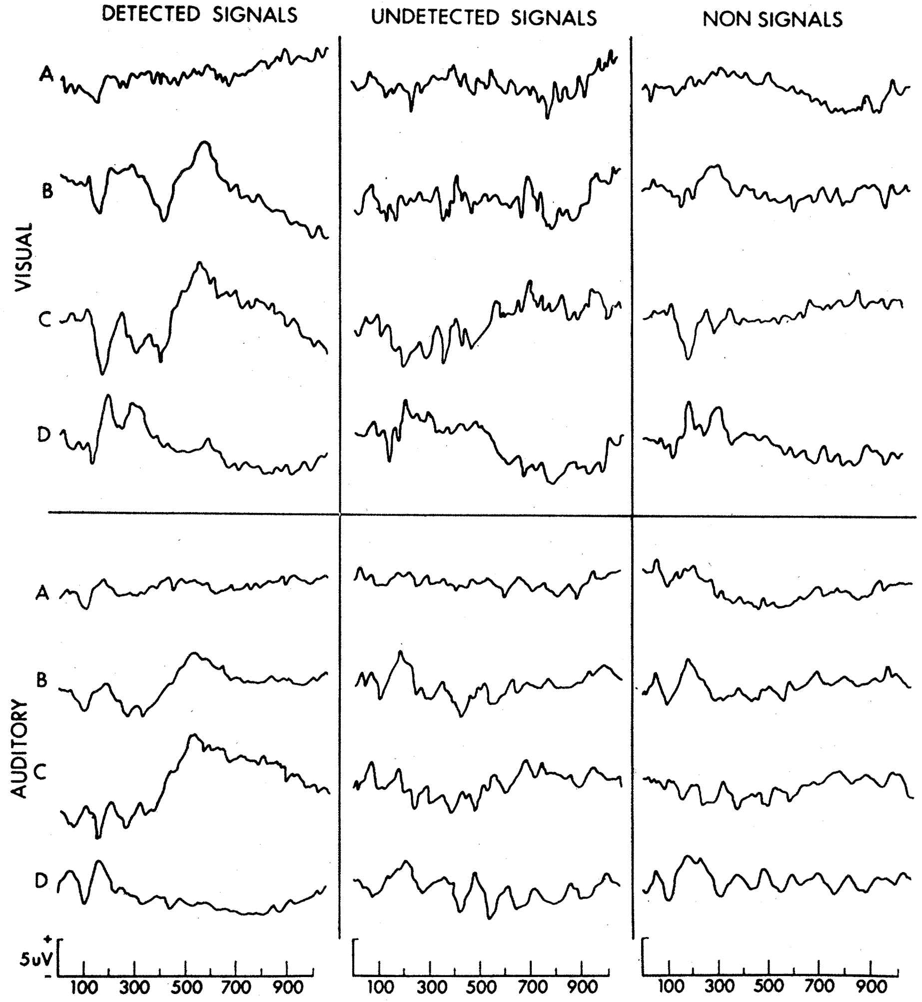

Fig. 1. Averaged evoked responses to detected signals, undetected signals, and nonsignals for one subject. Electrode placements: (*A*) Left supraorbital to chin; (*B*) vertex to chin; (*C*) right occipital to chin; (*D*) vertex to right occipital. Trace begins with stimulus onset. In the visual condition, the averages are based on 33 detected signals, 11 undetected signals, and 33 nonsignals. In the auditory condition, the averages are based on 62 detected signals, 22 undetected signals, and 62 nonsignals. Averages for nonsignals were obtained by randomly sampling from each condition.

difficult, the LPC is found for all stimuli, whether detected signals, undetected signals, or nonsignals. Although the subjects' detection rates remained quite good, they reported far greater concentration on and evaluation of each stimulus compared to an easy discrimination condition. Furthermore, we found that an easy discrimination in a go, no-go reaction time experiment results at first in LPC to both stimuli, whereas after the task has become routinized the LPC is absent. In this connection, Sokolov (*5*) has reported that when a subject is given the task of responding to one of two stimuli, and the discrimination between these stimuli is made very difficult, orienting responses persist to both stimuli for hundreds of trials. When the discrimination is easy, the orienting response begins to disappear once the required response becomes stabilized.

The presence of the LPC for unpredictable changes in stimulation when the subject is not attending to the stimuli (the usual paradigm for the orienting response) as well as for discrimination tasks in which the subject actively attends to the stimuli, suggests the operation of a neurophysiological mechanism common to both situations. Since the orienting response represents a relatively primitive capacity of organisms to respond selectively to changes in the environment, it is possible that the processes which underlie it may form the basis for more complex mechanisms of perceptual selectivity. In both situations stimulus information must continually be stored and compared with incoming stimuli. In the usual orienting situation (when stimuli match the template for information to be disregarded established by prior experience and the current needs of the organism), they are processed routinely and elicit no special notice (*13*). However, when an unexpected mismatch occurs, a shift of attention to the stimulus is elicited, and additional perceptual and cognitive mechanisms are called into play to evaluate the significance of the mismatch. Although no shift of attention is necessary in a discrimination task where the stimuli are actively attended, the determination of match or mismatch might still be made by the same comparator mechanism that operates in orienting responses. With a relatively easy discrimination, as in our main vigilance task, the comparator mechanism might suffice to call forth further evaluation of mismatches (the LPC thus being a correlate of the evaluative process) and failures to register mismatch would be associated with lack of evaluative (LPC) processes. Thus, the physiological processes underlying the LPC cannot represent activity of the comparator mechanism itself, since the LPC was absent for the nonsignals; nor can it be a correlate of conscious detection of a mismatch, since it is present for all stimuli, whether match or mismatch, in a difficult discrimination. In the latter situation, the comparator mechanism is apparently incapable of adequately differentiating the relevant stimuli, and cognitive processes for more complex evaluation are directed to all stimuli. When the stimuli to be discriminated alternate frequently, as in a go, no-go situation, ease of discrimination is associated with establishment of a reliable operation of the comparator mechanism, leading to routinization of response and eliminating the need for special evaluation (reflected in disappearance of the LPC).

The LPC, then, can be elicited in different situations; but whether it is elicited by conditions associated with orienting responses or when the subject is actively engaged in stimulus discrimination, the LPC appears to be a correlate of central processes for cognitive evaluation of stimulus significance.

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8. Photic stimuli were circles (5°), 10 msec in duration, presented to the left eye. Fixation was maintained on the center of a dim red cross.
9. Subjects sat in an electrostatically shielded, sound-attenuated booth positioned on a biteboard during photic stimulation and sitting unrestrained during auditory stimulation. The strain on the subject of remaining positioned on the biteboard, made it necessary to confine the visual condition to a period of about 25 minutes. The auditory condition lasted about 45 minutes. Electroencephalogram (amplifier band pass, 0.06 to 600 hz) was recorded on a frequency-modulated analog magnetic tape, summated with a modified Mnemotron CAT 400 and written out on a Mosley X-Y plotter.
10. Four subjects participated in the visual condition, two of whom were retained for the auditory condition.
11. H. Davis, *Science* **145**, 182 (1964).
12. Davis (*11*) did report that one of six subjects had a 300-msec positive component for the AER to the comparison tone.
13. Our formulation is derived from Sokolov's hypothesis of "neuronal models," but departs from his presentation in that he places central emphasis on the relationship of conditioned orienting responses and conditioned motor responses.
14. Supported by grants ID-2TI-MH-6418, NB-03356, MH-06723, and k-K3-NB-31,816 from the U.S. Public Health Service.

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Gaussian Behavior of the Electroencephalogram: Changes during Performance of Mental Task

Abstract. *The probability distribution of the amplitude of scalp electroencephalogram has been investigated in an adult subject in the idle state, and during performance of a mental arithmetic task. Based on a large sample, the electroencephalogram in this subject in the idle state follows a Gaussian (normal) probability function 66 percent of the time. During performance of the arithmetic task, the portion of Gaussian electroencephalogram decreases to 32 percent. The probability function characterizing gross electroencephalographic activity is determined by the degree of mutual interaction of individual cellular generators of wave activity in the tissue underneath the recording electrode. The data imply an increase in the cooperative activity of cortical neuronal elements during performance of a mental task.*

After three decades of intensive investigation, the spontaneous electrical activity recorded from the brain [electroencephalogram (EEG)] still remains one of the most elusive aspects of cerebral function. It is best characterized as continuous wave activity of variable amplitude and frequency, with inconstant phase relations; its overall character is quite similar to random noise.