There is conspicuous coherence between the piriform cortex and the motor cortex in both cases. This evidence suggests that the electrical activity of the piriform cortex and the motor cortex are interdependent in some way that is independent of the influence of the motor cortex. Similarly, Fig. 3 indicates that there is significant coherence (interdependence) between the piriform cortex and the septal area, which is independent of the electrical activity of the motor cortex.

There is also significant coherence between the septal area and motor cortex (Fig. 4); however, between 4 to 10 hz, the partial coherence between these sites when the piriform cortex data is taken into account, is approximately zero. Therefore, essentially all of the coherent energy in both the septal area and the motor cortex in the interval between 4 to 10 hz (the concentration of energy is greatest for the six data channels in this interval) is a result of the energy imparted to it by that in the piriform cortex. From Fig. 2 to 4, we conclude that the piriform cortex supplies the energy or "drives" the activity in the septal area and the motor cortex.

Systematic examination of pairwise coherence and partial coherence in each of the 20 distinct triples of data sets taken from the six simultaneous recordings leads to the conclusion that the piriform cortex exclusively was also diriving the putamen, the reticular formation, and the nucleus lateralis posterior of the thalamus. In this sense, we say that we have identified the piriform cortex as the driving site of the epileptic focus.

The foregoing results were obtained on day 19 of the daily repetition of the piriform electrical stimulation. This was when the direct "driving" reached a maximum. Later, as the cat developed generalized tonic-clonic behavioral convulsions, the coherences diminished, suggesting that the various separate areas of the brain developed a degree of autonomous epileptic activity that did not depend on the piriform for direct driving.

The spectral computations were performed by the autoregressive representation method of spectral analysis (*4*). The spectral coherence and partial spectral coherence in Figs. 2 to 4 were computed with 89 degrees of freedom and have a maximum standard deviation of .094 at each point of zero coherence and considerably less variation for increasing values of coherence (*5*). Evidence of the validity and statistical stability of the results was obtained by observing apparently similar computational results from records that were adjacent, overlapping, and of longer duration (16 seconds, 160 degrees of freedom, maximum standard deviation .023).

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5. The analysis was performed on an 8-second record of data sampled every 10 msec. The number of degrees of freedom n for the autoregressive representation spectral analysis is $n = N/p$, where p is in the order of the autoregressive fit to the observed data and N is the number of observed data points (*4*). For the results of Figs. 2 to 4, $N = 800$, $p = 9$, so that $n = 89$. The standard deviation of the coherence estimate was computed from D. E. Amos and L. H. Koopmans, *Tables of the Distribution of the Coefficient of Coherence for Stationary Bivariate Gaussian Processes* (Sandia Corp. Monograph SCR-483, Albuquerque, N.M., 1963), for a coherence value of zero. Since the poorest estimate of sampling coherence occurs at zero coherence this is a conservative estimate. The same numerical results and justifications hold for the partial coherence estimate. The tables are computed with the assumption that the time series are jointly Gaussian. V. A. Benningus [*I.E.E.E. Inst. Elec. Electron Eng. Trans. Audio Electroacoust.* **AU-17**, 198 (1969)] demonstrated that this assumption is not critical.
6. The experiments were performed while we were visiting fellows in the laboratory of Dr. F. Morrell, Stanford University Medical School, Division of Neurology. All of the computations were performed at and supported by the ACME facility of the Stanford University Medical School. W.G. (on leave from Purdue University, School of Aeronautics, Astronautics, and Engineering Sciences, Center of Applied Stochastics, Lafayette, Ind.) was supported by NIH special training and research fellowship 1F 10NB 1686-C1A at Stanford University, Division of Neurology. G.V.G. was supported by a traveling fellowship from the Ontario Mental Health Foundation.

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Drinking and Eating Elicited by Cortical Spreading Depression

Abstract. *Single waves of unilateral and bilateral cortical spreading depression were administered to rats by electrophoretic injection of potassium ions into the occipital cortices. Aggressive and stereotyped eating, drinking, and exploratory behavior were elicited by unilateral and bilateral spreading depression. Onset of the elicited behaviors varied among rats from 4 to 8 minutes after injection of the ions. Direct activation of, or rebound from, inhibition of subcortical motivational mechanisms may be responsible for the effects.*

Functional decortication by spreading depression has been commonly found to attenuate or inhibit the performance of various behaviors including feeding and drinking (*1*). We now report an additional opposite effect—namely, that single waves of cortical spreading depression (CSD) induced in one or both hemispheres can, after the inhibitory effect is over, elicit drinking, eating, grooming, and exploratory behavior.

Hooded male rats, about 3 months old, were prepared for electrophoretic injection of K^+ ions into the cortex and for recording of slow potential changes in both hemispheres. For injection of K^+ ions, refillable glass cannulas were implanted over each hemisphere with the tip placed about 1 mm below the occipital surface. The cannulas contained 25 percent KCl solution, a coiled silver wire, and a mandrel attached to a sealing screw. About 2 μg of K^+ ions were injected into the cortex by passing 1-ma anodal current for 10 seconds between the silver wire and an indifferent silver-wire electrode attached to the back of the skull. The injected amount of K^+ triggered a single wave of spreading depression. To monitor the slow potential changes accompanying the wave of depolarization, two Ag-AgCl screw electrodes were implanted bilaterally at the level of the bregma, and an indifferent electrode was screwed about 10 mm anterior to the bregma at the midline. Electrodes and cannulas were anchored with dental acrylate. This preparation was useful for as long as 6 weeks.

The rats were tested for elicitation of behavior in a box 35 cm high, 24 cm long, and 13 cm wide with a transparent wall and a hole at one end for a water spout. Drinking activity was measured by a meter which recorded licks and cumulatively recorded in one channel of a recording millivoltmeter (Fig. 1). The other two channels were used to record passage of the SPC in both hemispheres (Fig. 1). Eating behavior was monitored visually by the experimenter.

For several days preceding the testing sessions, the animals had access to water only in the experimental chamber. Initial studies had shown that such training was essential for the later elicitation of drinking by CSD and also, that the effect was enhanced when the rats had an opportunity to drink in the chamber on the day of the testing session. Hence, the animals were tested after being deprived of water for 0 to 48 hours. During testing sessions, the rats were placed in the chamber with free access to water or food, or both. Testing for CSD-elicited behavior began from ½ to 3 hours later when the animals could be considered to be satiated. Potassium ions were injected during periods of acute satiation; that is, the criterion for administering a CSD was that the animal refrain from eating and drinking for at least 5 minutes. In practice, the period of no drinking or eating which preceded a wave of CSD was frequently extended up to 1 hour.

It was possible to elicit drinking by unilateral CSD in 7 out of the 12 animals tested. Three of these were also tested for elicited drinking under bilateral CSD, with positive results in each case.

Figure 2 summarizes the distribution of onset times of 159 cases of elicited drinking for five representative animals. The histogram shows the probability that drinking will start in any of the ten 1-minute intervals following the electrophoretic injection of K+. All the measurements were taken from the point of maximal depolarization at the anterior recording electrode, an arbitrary synchronization point corresponding to the spread of depolarization into the frontal cortex. Whenever drinking followed a wave of CSD it was most likely to occur (55 percent of the time) between 4.5 and 6.5 minutes after initiation of the CSD in the occipital cortex. The duration of the elicited drinking varied from a few seconds to several minutes.

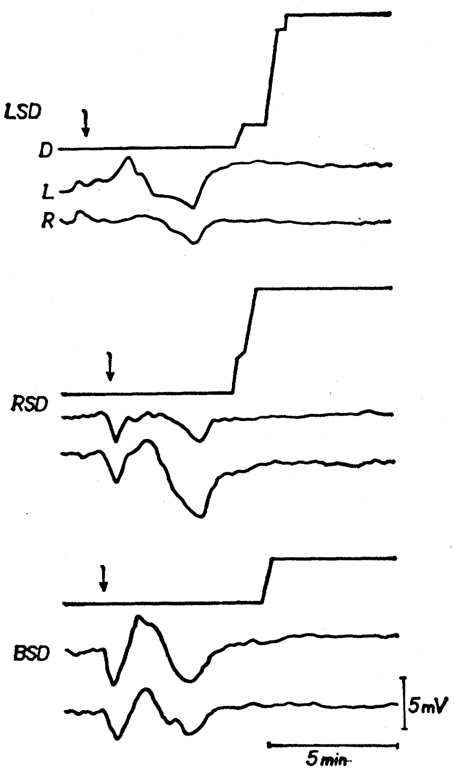

Fig. 1. Examples of cumulative records of licking (*D*) correlated with slow potential changes, in the left (*L*) or right (*R*) hemispheres, accompanying unilateral (*LSD* and *RSD*) and bilateral (*BSD*) waves of cortical spreading depression. The arrows indicate electrophoretic injection of K$^+$ into occipital cortex.

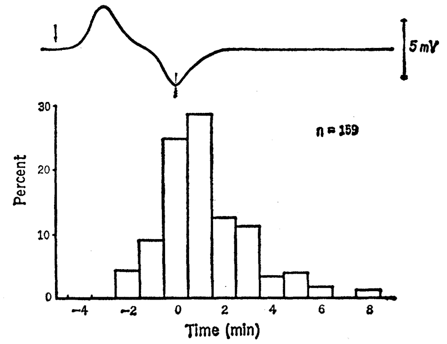

Fig. 2. Probability distribution of onset times of drinking (below) measured from the peak of the wave of slow potential change (above) corresponding to the penetration of the waves of cortical spreading depression into the frontal pole. The histogram represents 159 cases of elicited drinking in five rats. In about 55 percent of all cases of elicited drinking, onset occurred within a 2-minute period.

Eating could be consistently elicited by unilateral CSD in five animals, all of whom also exhibited elicited drinking. Figure 3 shows the distribution of onset times of 44 representative cases of elicited eating in four of the rats. All cases are for unilateral CSD, although eating could also be elicited by bilateral CSD in the two animals tested. The distribution is quite similar to that of elicited drinking, with onset of eating being most probable about 5 minutes after initiation of the wave of depression; about 75 percent of the time eating began within about 4.5 to 8.5 minutes of K+ injection. Whenever eating followed a CSD it was accompanied by drinking in 82 percent of the cases.

Within sessions of 10 to 15 CSD's the reliability with which a wave of CSD elicited drinking or eating was quite high, frequently approximating 100 percent. With additional CSD's, however, it often decreased to zero, probably due to a cumulative effect of CSD waves which have reportedly lead to metabolic exhaustion due to depletion of cortical glucose and glycogen and to inhibition of protein synthesis (*2*). Other behavioral signs which accompanied the deterioration of elicited behavior with repeated CSD's were locomotor deficit, decrement in placing reflexes, and general lack of reactivity. Usually, when the animals were allowed to recover from CSD for several hours, drinking and eating could be elicited again. Metabolic deficit due to cumulative effects of CSD could explain why the energizing effect of CSD has not been observed in the more common preparations where multiple waves of CSD are induced by the application of concentrated KCl solutions directly to the cortical surface.

The elicited drinking and eating was usually aggressive and stereotyped. In most rats the induced drinking or eating was consistently preceded or accompanied by a period of frantic exploratory activity, especially by wall climbing, and often by excited grooming. Some animals, including two in which neither eating nor drinking could be elicited, exhibited chewing movements in response to CSD. In two of these rats CSD triggered chewing movements and teeth gnashing which

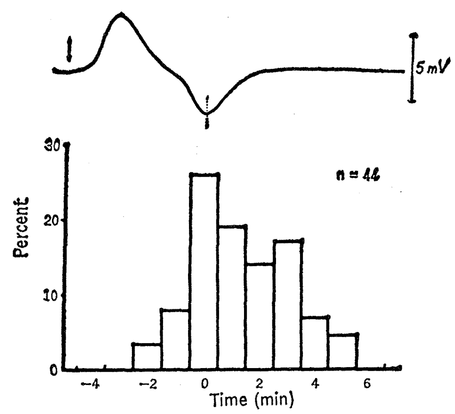

Fig. 3. Probability distribution of onset times of 44 cases of elicited eating in four rats (below). Onset of drinking was measured from the peak of the wave of slow potential change (above) corresponding to spread of waves of cortical spreading depression into the frontal pole.

were curiously followed at regular intervals of about 15 seconds by wide mouth opening (yawning?). In two other animals drinking was consistently preceded by stereotyped air-licking and licking of the walls of the box.

The variety of behaviors elicited by single waves of CSD suggests that a general release of motivating systems is involved; however, the fact that when tested with both food and water in the box some animals exhibited a preference for one prior to the other indicates some specificity of the energizing effect. For example, one animal voraciously ate after a CSD wave, and began to drink only after several minutes of eating. When food was withdrawn from the box, he began to drink with a shorter latency, however, only after frantic exploratory activity and biting of the floor and edges of the box. After a CSD wave the same animal vigorously approached the experimenter's hand, which he normally avoided, and attempted to seize food from it. Another rat only drank and never ate, even when the water was withdrawn.

In one animal unilateral CSD waves became ineffective in eliciting drinking after drinking was elicited five times consecutively with bilateral waves of CSD. This suggests that the motivating effect is prone to adaptation and that the effect is stronger when simultaneously induced in both hemispheres.

A number of studies have demonstrated that CSD attenuates activity in the hypothalamus. Single waves of unilateral CSD depress the electroencephalogram, evoked responses (*3*), and single unit activity (*4, 5*) in the lateral hypothalamus, especially on the side ipsilateral to the hemisphere depressed. Lateral hypothalamic self-stimulation is suppressed more by ipsilateral than by homolateral CSD (*4, 6*). Repeated waves of CSD decrease hypothalamic noradrenaline (*7*), and reinstate aphagia in animals recovered from lateral hypothalamic lesions (*8*). These results, in conjunction with the data showing impairment of alimentary responses by repeated waves of CSD (*1*), strongly suggest that the cerebral cortex exerts tonic control over some hypothalamic motivational systems. Withdrawal of cortico-hypothalamic facilitation presumably results in motivational decrement for certain behaviors.

It is tempting to interpret the energizing effects of CSD as being an aftereffect of such motivational inhibition, for example, as a result of rebound activity of the subcortical areas depressed during the CSD. Our studies show that when drinking is disrupted by single waves of unilateral or bilateral CSD, the recovery of drinking corresponds in time to the peak of the onset distribution of Fig. 2 (*9*). Hence, the elicited drinking corresponds temporally to recovery from motivational depression, in accord with the hypothesis of subcortical rebound from depression.

Alternatively, the motivation may be induced by direct activation of subcortical areas, possibly as a result of spreading depression entering the entorhinal cortex, amygdala, or caudate nucleus (*10*), or by accompanying increase of extracellular potassium. For example, eating and drinking have been induced in goats by the injection of KCl into the third ventricle, and have been interpreted as a result of nonspecific stimulation of hypothalamus by spread of extracellular K^+ via the vascular system (*11*).

Whatever the mechanism involved, it is clear that waves of CSD have an energizing effect in additon to their well-known inhibitory properties, which preponderate with short intervals between individual CSD waves and obscure the excitatory components.

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Hyperbaric Oxygen

The report by Joanny *et al.* (*1*) provides further evidence for the involvement of lipid peroxides and the inhibition of the production of adenosine triphosphate by hyperbarbric oxygen. However, their results as presented suffer from several serious uncertainties. First, no control data is presented showing the relative conversion of the different substrates to $^{14}CO_2$ in an atmosphere of air or under nitrogen at the different pressures used for oxygen (3, 6, and 10 atmospheres).

Second, it is not likely that the stirring rate (shaking the chamber at 120 times per minute) was adequate to rapidly mix the gas phase, the turbulence of which depends on the oscillating surface of the medium. My own experience with a small chamber of almost exactly the same volume and shape (*2*) suggests that adequate gas transfer is best achieved by direct mechanical mixing of the gas phase. The higher the pressure—and thus the viscosity—of the gas, the slower will be both diffusive and convective transfer of $^{14}CO_2$. In the absence of quantitative information (CO_2 transfer times between medium and trap), the degree to which the oxygen pressures of 3, 6, and 10 atm actually inhibited the oxidation of the various substrates used remains uncertain because decreases in the amount of