the initial latency in the runway was not significantly different from that of controls, no motor defect was apparent, and the animals showed the same levels of exploratory activity as did the controls. In other experiments we have shown that these animals are not impaired in ability to discriminate sucrose solution from water. We therefore interpret our data as evidence of defective learning capacity, and our results are in obvious contrast with those of Lashley (*10*), who found that even large lesions of the cerebral cortex itself had relatively little effect on the animal's ability to learn simple tasks.

Previous experiments suggest that coerulocortical norepinephrine-containing neurons are one of two catecholamine systems supporting electrical self-stimulation behavior (*5*, *6*). The earlier data, taken together with the present results, suggest that this pathway may function as a "reinforcement" system. This concept would be consistent with hypotheses that the noradrenergic terminals in the cerebral cortex mediate the synaptic changes assumed to take place during learning (*11*, *12*).

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References and Notes

1. K. Fuxe, B. Hamberger, T. Hökfelt, *Brain Res.* **8**, 125 (1968).
2. U. Ungerstedt, *Acta Physiol. Scand.* (Suppl. 367), 1 (1971); G. W. Arbuthnott, J. E. Christie, T. J. Crow, D. Eccleston, D. S. Walter, *Experientia* **29**, 52 (1973).
3. G. W. Arbuthnott, T. J. Crow, K. Fuxe, L. Olson, U. Ungerstedt, *Brain Res.* **24**, 471 (1970); G. M. Anlezark, G. W. Arbuthnott, T. J. Crow, D. Eccleston, D. S. Walter, *Brit. J. Pharmacol.* **47**, 645P (1973).
4. T. J. Crow, P. J. Spear, G. W. Arbuthnott, *Brain Res.* **36**, 265 (1972).
5. T. J. Crow and G. W. Arbuthnott, *Nature New Biol.* **238**, 245 (1972).
6. T. J. Crow, *Psychol. Med.* **2**, 414 (1972).
6a. T. J. Crow, *ibid.* **3**, 66 (1973).
7. E. Fifkova and J. Marsala, in *Electrophysiological Methods in Biological Research*, J. Bures, M. Petran, J. Zachar, Eds. (Academic Press, New York, 1967), pp. 653–695. Coordinates were measured from the skull surface with lambda-bregma horizontal.
8. H. Klüver and E. Barrera, *J. Neuropathol. Exp. Neurol.* **12**, 400 (1953).
9. The method used was a modification [J. Hughes, *Brit. J. Pharmacol.* **44**, 472 (1972)] of the method of U. S. von Euler and F. Lishajko [*Acta Physiol. Scand.* **51**, 348 (1961)].
10. K. S. Lashley, *Brain Mechanisms and Intelligence* (Chicago Univ. Press, Chicago, 1929).
11. T. J. Crow, *Nature* **219**, 736 (1968); S. S. Kety, in *The Neurosciences*, F. O. Schmitt, Ed. (Rockefeller Univ. Press, New York, 1970), pp. 324–336.
12. These experiments were first reported to the Physiological Society Meeting in February 1973 [G. M. Anlezark, T. J. Crow, A. P. Greenway, *J. Physiol. London* **231**, 119P (1973)].
13. Supported by grants from the United Kingdom Medical Research Council (No. G968/301/B) and the Mental Health Research Fund. We thank J. L. Malcolm for providing facilities; J. Hughes for assistance and advice concerning the chemical estimations; and H. Anderson, L. Porter, L. Sutherland, A. Ewing, and A. Simpson for technical assistance. Address reprint requests to T.J.C.

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Memory Mechanisms in Instrumental Responding

John's main discovery (*1*) is that when the occurrence of an instrumental response (for example, lever pressing to obtain food or to avoid an electric shock) has been brought under the control of a positive discriminative conditioned stimulus (CS+), each presentation of the CS+ releases a neural "readout component," which is recordable as a set of uniform high-amplitude evoked potentials in diverse brain structures. Such a readout component—the particular evoked-potential waveform—is not produced by a negative discriminative conditioned stimulus (CS–); the waveform produced by a CS– is quite different. The further observation that the readout component is not produced by a generalization test stimulus (CS^G) on occasions when it fails to instigate the instrumental response, but is produced by the same CS^G on occasions when it instigates the instrumental response, indicates that the release of the readout component may be a necessary link in the sequence of neural events that results in response occurrence. The interpretation that John places on his findings is essentially that the effective stimuli (CS+ or CS^G) are successful in instigating the response because they activate a unique, specific memory that has become organized during training with CS+. He equates the activation of a memory with the release of the readout component. This interpretation is disputable on two points: Does the readout component represent memory? How is it produced?

It is unlikely that the readout component represents memory per se. A memory presumably is a neural correlational organization representing the correlation (or contingency) that an animal has observed to exist between two environmental events. Thus the memory CS+ : US^I represents the correlation that CS+ is followed (with or without an intervening response) by an unconditioned stimulus with incentive (or "reinforcing") properties (US^I), and the memory CS– : $\overline{US^I}$ represents the correlation that CS– is followed by the absence of the incentive stimulus ($\overline{US^I}$). It is known that behaviorally the presentation of a CS– is not equivalent to either the absence of CS+ or to the presentation of a familiar neutral test stimulus (CS^0)—one which is not correlated, positively or negatively, with any incentive stimulus and to which the animal has been habituated. In general, compared to the presentation of a CS^0, CS+ facilitates instrumental responding while CS– suppresses responding (*2*). Clearly, a memory is organized not only in the case of positive learning (CS+ : US^I), but also in the cases of negative learning (CS– : $\overline{US^I}$) and habituation learning (CS^0 : no important consequence). Thus, if a readout component represents a memory, it (the component) ought to be produced not only in the case of the response-facilitative CS+ but also in the cases of the response-suppressive CS– and the habituated CS^0.

John, however, uses the label "readout component" to describe only the waveform produced by CS+, not that produced by CS– (or CS^0). But if a waveform represents a memory per se, each training stimulus (CS+, CS–, or CS^0) should produce some characteristic readout component. Any difference between the waveform produced by CS+ and the waveform produced by CS– (or CS^0) could then be attributed to the contents of the two memories. But, alternatively, the difference in waveforms could also be attributed to some other process affecting response output. This could be a motivational process; response-facilitative in the case of CS+ which is linked to the presentation of the incentive stimulus (US^I), and response-suppressive in the case of CS– which is linked to the nonpresentation of the incentive stimulus ($\overline{US^I}$). Such an alternative interpretation could be tested by determining whether variations in motivational arousal (produced, say, by varying degrees of hunger or palatability of a food incentive) would result in systematic changes in the amplitude or other features of what John identifies as the readout component (CS+ waveform). If this happens, it would suggest that the readout component represents a motivational process rather than a mnemonic one. Such an experiment appears not to have been done so far.

John's data (his figure 9, read vertically) show that the CS+ readout component may not appear until the CS+ (a flickering light of, say, 3 hz) has been repeated for several seconds. This finding appears inconsistent with John's hypothesis because, at least subjectively, memories appear to be activated instantaneously by appropriate environmental cues; it is motivational processes that tend to be slow. Further, the fact that the instrumental response may not occur for a few additional seconds after the onset of the CS+ readout component would suggest that the readout component is not a critical correlate even of the instrumental response. Indeed, the actual occurrence of a response involves several factors other than the memory of a contingency (*3*). The occurrence or nonoccurrence of a response would thus appear to be an insufficient basis for isolating the mnemonic from the other processes controlling instrumental responding.

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References

1. E. R. John, *Science* **177**, 850 (1972).
2. R. A. Rescorla and R. L. Soloman, *Psychol. Rev.* **74**, 151 (1967); R. A. Rescorla and V. M. LoLordo, *J. Comp. Physiol. Psychol.* **59**, 406 (1965); R. C. Bolles, N. E. Grossen, G. E. Hargrave, P. M. Duncan, *J. Exp. Psychol.* **85**, 138 (1970); S. Siegel, *J. Comp. Physiol. Psychol.* **68**, 245 (1968).
3. D. Bindra, in *Classical Conditiong II*, A. H. Black and W. F. Prokasy, Eds. (Appleton-Century-Crofts, New York, 1972), p. 453; also see *Nebraska Symposium on Motivation* (1969), vol. 17.

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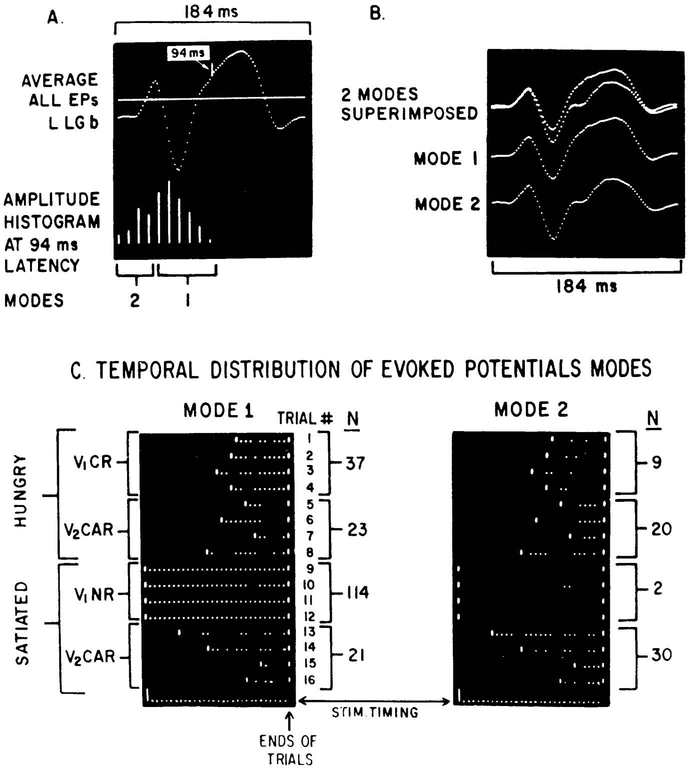

Fig. 1. Computer evaluation of the effects of satiation on the readout waveshape from a trained cat. Data were obtained from a bipolar electrode in the left lateral geniculate (*L LG b*). (A) Upper waveshape is the average of all 256 evoked potentials (*EPs*) obtained in four sets of behavioral trials: (i) four trials in which presentations of a 5-hz flicker (V_1) elicited correct pressing of the left lever on a work panel to obtain food (V_1CR); (ii) four trials in which a 2-hz flicker (V_2) resulted in correct right lever response to avoid shock (V_2CAR); (iii) four trials in which V_1 failed to elicit lever press after the animal had been satiated with food (V_1NR); and (iv) four trials in which V_2 resulted in correct performances of the CAR by the satiated animal (V_2CAR). The histogram below the average response waveshape shows the distribution of amplitudes of all the 256 evoked potentials at a latency of 94 milliseconds. Note that this distribution appears to be bimodal. The brackets below the histogram show that the lower portion of the amplitude distribution was classified as mode 2 and the upper portion as mode 1. (B) The results of averaging together all the waveshapes classified as mode 1 and all those classified as mode 2. Waveforms for the two modes are superimposed at the top and are then displayed separately. (C) The distribution of mode 1 and mode 2 evoked potentials in the 16 different trials. Each row of white dots represents a behavioral trial, beginning at the left vertical mark and ending at the right vertical mark. For each of the 16 trials evoked potentials classified as mode 1 are represented by white dots in the left rectangle; those classified as mode 2 are represented by white dots in the right rectangle. Both V_1CR and V_1NR trials were dominated by mode 1 potentials. Mode 1 potentials were less frequent in V_2CAR trials, tending to appear toward the beginning of the trials. In contrast, mode 2 potentials were very sparsely scattered throughout V_1CR or V_1NR trials, while mode 2 dominated the ends of all V_2CAR trials. Thus the distribution of evoked potentials of modes 1 and 2 was the same whether the anim 1 was hungry or satiated. These data also demonstrate the great differences in distribution of these two modes between CR and CAR trials.

The phenomenon upon which Bindra's comment focuses, described in my article (*1*), is that the waveshape of the evoked potential reflects two processes: one, which I term "exogenous," is determined by the physical stimulus, and another, termed "endogenous" or "readout," reflects the release of a memory activated by that stimulus. The readout process develops as a new late component that is first elicited after several presentations of an initially unfamiliar stimulus. It is inaccurate to say, as Bindra does in his first paragraph, that each presentation of the conditioned stimulus (CS) releases the readout component. Figures 9, 10, and 11 in my article clearly show that the CS usually elicits a variety of waveshapes with the readout process becoming more probable as the stimulus train continues.

The readout process remains essentially dynamic. Once formed, it can be changed by altering the stimulus-response contingencies which it represents. A close relationship thus exists not only between the readout process and the stimulus that initiates its formation and elicits its appearance, but also between the readout process and the response that follows its apearance. The same readout process is elicited in an animal that presses a particular bar on a work panel in a correct response to a learned cue, as is elicited when the same animal presses that bar in an incorrect response to a different cue or during generalization to a novel cue. This stability of readout should not be surprising. As an animal learns a particular stimulus-response contingency, it must develop a process that represents the relationship between the stimulus and the required response. Any decision relevant to that behavior that the animal makes must involve the process representing those relations. If, after differential training, an animal is presented with an unfamiliar cue and performs a response appropriate for a cue with which it is familiar, one might assume that it has "remembered" the familiar cue and its associated response: the readout process representing that association has been elicited. One might also assume that there would be instances when the cue and its associated response would be "remembered," yet the response would not actually be performed. Contrary to Bindra's assumption, this is exactly what we have found. I pointed out in my article that the readout process is a necessary but not sufficient correlate of the actual instrumental response.

I agree with Bindra that an inhibitory stimulus, CS–, requiring response suppression, should produce some characteristic readout waveshape, analogous to that produced by a positive stimulus, CS+, albeit different in form. Bindra errs, however, in assuming that this is not the case, although I was at fault for not explicitly stating this fact (*2*). Apparently he was misled by my figures 6 and 7, comparing waveshapes obtained to the same stimulus in go and no-go outcomes. Further examination of the data presented in figures 8, 9, 10, and 11, as well as a careful reading of the text, ought to clarify this point (*1*).

Bindra suggests that the differences between readout waveshapes which we reported primarily reflect motivational processes. It was precisely because of the obvious motivational differences between go and no-go contingencies that we trained some animals in approach-approach (CR$_1$ and CR$_2$) discriminations and some in avoidance-avoidance (CAR$_1$ and CAR$_2$) discriminations. Clear differences between readout waveshapes elicited by the same stimulus during trials resulting in performance of CR$_1$ compared with trials resulting in CR$_2$, and in CAR$_1$ compared with CAR$_2$, are documented in figures 10 and 11 and for cats 9, 16, and 21 in table 1 of my article (*1*).

Bindra suggests that a decisive test of his alternative interpretation, that the difference in waveforms reflects a motivational process, could be accomplished by determining whether variations in motivational level produced systematic changes in the amplitude of the readout waveform to CS+. In control studies conducted previously but not reported in my article, the waveshapes elicited by an appetitive CS in hungry and satiated cats were compared. In the satiated condition, not only was the cat fed to satiety but a dish of food was placed beside the response lever on the work panel in the apparatus. These studies showed that neither readout processes associated with the approach CS nor those associated with the avoidance CS were altered by satiation (see Fig. 1). Numerous other control experiments (*1*, *3*) for unspecific processes including motivation support the interpretation that the phenomena defined as the readout process do in fact reflect mnemonic processes. These further experiments show that processes related to a variety of unspecific features, probably including motivational processes, can indeed influence the evoked potential waveshape. Differences in the stimuli themselves also are reflected in the waveshapes. These influences, undoubtedly of intrinsic interest, have explicitly been excluded from contribution to the readout process as we have identified it.

Bindra, in his last contention that memories are instantaneously activated by appropriate cues whereas motivational processes are slow, fails to consider an essential point. The cats in our experiments are put in decision-making situations that are difficult and important. The decision requires identification of the stimulus repetition rate, that is, the length of the time interval *between* identical flashes or clicks. Obviously, it would be impossible for the appropriate memory to be instantaneously activated under these conditions. The time intervals must be sampled enough for the animal to estimate their length, *before* the memory appropriate to a particular repetition rate can be activated. In differential generalization, when the stimulus repetition rate is itself novel, the sample of intervals required for this time estimation must be even larger. Response latencies are prolonged and the animals appear stressed.

Finally, although I believe that I have adequately answered Bindra's questions, I find it necessary to challenge a basic assumption in his comments. I fail to understand how one can separate "motivational" processes from mnemonic ones. Motivational processes reflect the valence attached to an event, and such valences are not intrinsic to a CS but derive from experience. Were the readout processes which we have discovered to reflect the valence attached to a stimulus because of past experience, rather than the broader implications of meaning which I believe to be the case, readout would nonetheless reflect the activation of memory.

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References and Notes

1. E. R. John, *Science* **177**, 850 (1972).
2. Studies (E. Grastyan, E. R. John, F. Bartlett, in preparation) confirm that in cats trained to a CS+ and a CS–, the waveshape elicited by the CS– does acquire a readout component as an inhibitory response is established.
3. E. R. John, F. Bartlett, M. Shimokochi, D. Kleinman, *J. Neurophysiol.*, in press.
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Role of the Skin in Amphibian Sodium Metabolism

McAfee's (*1*) rebuttal of a statement by Kalckar (*2*), and the latter's concurring reply, raises and helps clarify some interesting questions about the role of the skin, and its active Na^+ transport mechanism, in maintaining the sodium balance of amphibians. McAfee's (*1*) measurements of a frog's (*Rana pipiens*) ability to survive, and to maintain body Na^+, when bathed in deionized water helps to resolve the problem of the relative importance of the skin in amphibian osmoregulation. I have been seeking an answer to the same problem but using a different procedure. Instead of preventing Na^+ uptake by excluding it from the bathing media, I have attempted to bring about the same effect by inhibiting its active uptake by soaking amphibians in dilute solutions of amiloride. The conclusions on three species of anurans are in general accord with those of McAfee.

Amiloride (*3*) is a diuretic drug which is a potent (but its action is reversible) inhibitor of active transmural Na^+ influx, although it does not change Na^+ outflux, across several amphibian epithelial membranes. These include