(1 khertz in these cases), and not the expectancies. Thus it was surmised that expectancy of reward rather than response to the tones per se accounted for the differing rates of firing in midbrain unit activity.

To find whether it was the motivational aspect of the expectancies, that is, the relative preference for the two rewards, or some factor more specifically linked to food or water, a procedure was used to bias the relative strength of motivation in all animals. For this purpose, animals showing the highest firing rates to food tones were given free food in addition to their food reward, but water was available only by means of the operant response. Ten of the animals were used in this test. After 1 day of this "water-deprivation" the water tone caused an augmentation of firing rates in *all* cases; the average increment was 29.1 percent of the response to the control tone. The food tone still caused an increment in eight of the units recorded, the average increment being 1.5 percent of control. In nine of the cases, however, the increment induced by the water tone was now larger than the increment induced by the food tone. Thirst was accelerated in four of the animals by intraperitoneal injection of 2 ml of 0.1M NaCl. Four of the animals were tested for 2 additional days under the same "drive-reversal" conditions; by the 3rd day, the average increment during the water tone amounted to 81.2 percent and that during the food tone was only 2.6 percent above the control tone response. From these data it was concluded that the motivational interest of the animal directed toward the expected goal object very likely determined the firing rate of these midbrain neurons.

When subliminal overt movements were detected and analyzed alongside the midbrain unit firing patterns, there were certain similarities and important differences between the rates of occurrence of these behavioral responses and the neuronal firing rates. Differences between the two sets of patterns, however, revealed that neither set was directly dependent on the other. First, the midbrain unitary firing rate changes appeared with shorter latencies than the behavioral response changes. Second, with respect to each individual instance of stimulus application there were often behaviorally quiet trials during which highly motivational stimuli were applied and accompanied by the large increments in midbrain neuronal firing. Our conclusion, therefore, was that descending influences of the highly motivational expectancies often influenced gross activity, but that the unitary changes in the midbrain which were observed were prior to and probably independent of these behavioral changes.

Besides these midbrain units, 31 other neurons were recorded from different parts of the brain. Of these, 17 were in the hippocampus and dentate gyrus, 9 in the hypothalamus, 2 in the septum, and 3 in the inferior colliculus. The hippocampal units did not regularly exhibit large differences in firing rates favoring the main-reward tone, and when such differences appeared in the early part of the experiment, they did not quickly reappear after tone reversal. In the case of two of the hypothalamic units there was a pattern quite similar to those observed in the cases of the midbrain units, but the other units in the hypothalamic group did not show such differences. One hypothalamic unit appeared to fire only to the water signal, irrespective of the drive state.

The results of these tests lead us to conclude that there are single cells in the midbrain which can make discriminatory responses to the significance of different sensory signals. These responses reflect an integration of sensory input with the internal state, where the response to tones which signified a reward appropriate to the motivational state of the organism was amplified by the degree of that motivation. The data did not indicate at what level the integration of the stimuli input with the drive occurred. It appeared that units in the auditory pathway were at a preintegrated level because they fired to the stimulus rather than to its significance, whereas the units in the midbrain group were apparently at a postintegrative level because they fired as a function of the relevance of the stimulus input to the actual drive. While these data did not point directly to the "integrative area," they depicted pre- and postintegrative levels, and therefore the method should be useful in the search for the actual integrative level.

M. Ian Phillips
James Olds

Division of Biology,
California Institute of Technology,
Pasadena 91109

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3. The data were analyzed as the probability of a unit firing in a given interval. In Fig. 1, the actual firing rate is given in order to make the ordinates readily comprehensible.
4. The experiment was carried out while we were at the Brain Research Laboratory, Department of Psychology, University of Michigan. Supported by grants from PHS. We thank P. J. Best and J. Rosenberg for computer programming and W. Allan, G. Baldrighi, W. Wetzel, and J. Frey for their technical assistance.

3 June 1969

Retention of Delayed-Alternation: Effect of Selective Lesions of Sulcus Principalis

Abstract. *Monkeys with bilateral lesions of the anterior, middle, or posterior thirds of the principal sulcus, of the periarcuate prefrontal region, or of the inferior parietal lobule were tested for retention of spatial delayed-alternation. Lesions limited to the middle third of sulcus principalis resulted in failure to relearn delayed-alternation within 1000 trials; lesions elsewhere had little effect.*

Since the discovery that ablation of the frontal lobes in monkeys results in severe behavioral deficits on delayed-response and delayed-alternation tasks (*1*), many investigations have assessed the minimum lesion that would produce such deficits. Two behavioral studies (*2*), whose purpose was to localize delayed-alternation deficits within the prefrontal cortex, have focused upon dorsal-ventral comparisons. Lesions involving the entire extent of sulcus principalis result in the severest spatial delayed-alternation (DA) impairments in comparison to lesions dorsal or ventral (or both) to this sulcus. Whereas it is evident that principalis is a focal area for DA performance, the possibility of further localization of function along the anterior-posterior axis of the sulcus and prefrontal region has not been explored. In this study monkeys with bilateral lesions of the anterior, middle, or posterior sectors of

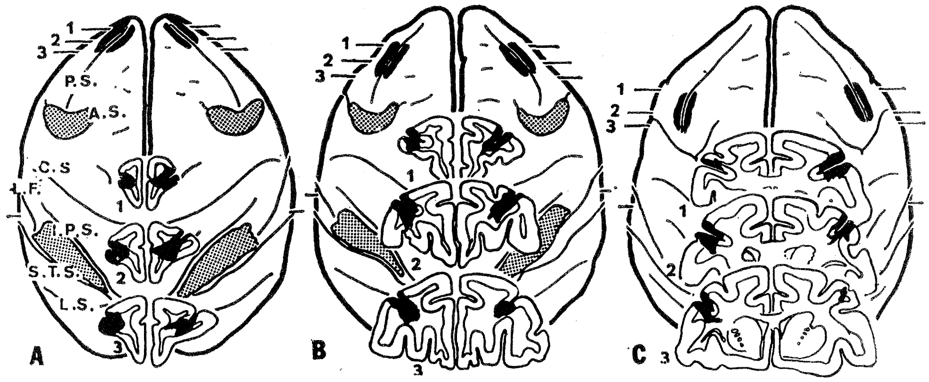

Fig. 1. Reconstructions of three brains with anterior (A), mid- (B), or posterior (C) principalis lesions. Three cross sections through different levels of the lesions are shown for each brain. Area in black represents dorsolateral extent of principalis damage; stippled area in brains (A) and (B) indicates the periarcuate and inferior parietal lesions made in the first two operations. A.S., arcuate sulcus; C.S., central sulcus; I.P.S., intraparietal sulcus; L.F., lateral fissure; L.S., lunate sulcus; P.S., principalis sulcus; S.T.S., superior temporal sulcus.

principalis, as well as lesions of the periarcuate prefrontal region, are compared in DA retention. Lesions limited to the middle sector of the principal sulcus result in a total failure to relearn DA within 1000 trials, but lesions in the anterior or posterior sectors of principalis or in the periarcuate region have little, if any, effect upon DA retention.

Twelve rhesus monkeys (3 to 4 kg) were the subjects for this experiment. All monkeys learned DA in a modified Wisconsin General Test Apparatus with black wooden plaques covering the two food wells on the tray. This test requires that the animal alternate his responses to the right and left plaques on succeeding trials in order to receive a reward. If the monkey makes an error on a given trial (that is, fails to alternate), the reward remains on the same side until the monkey responds to the correct plaque on some succeeding trial. A 5-second interval between trials was employed. The monkeys were given 30 trials, including correction trials, each day to a criterion of 90 correct responses in 100 consecutive trials (including the correction trials).

After reaching learning criterion, nine of the twelve animals received bilateral cortical lesions by subpial aspiration under aseptic conditions; three monkeys served as unoperated controls. Three monkeys received lesions of the periarcuate region including both banks and limbs of the arcuate sulcus but sparing the most superior 5 mm of the superior limb and the most inferior 8 mm of the inferior limb. Care was taken not to involve the posterior sector of sulcus principalis although the tissue surrounding the sulcus was included in this lesion.

For three animals cortical removal was limited to the middle third (9 mm) of sulcus principalis. Both the superior and inferior banks were removed; care was taken to spare the anterior and posterior thirds of the sulcus.

Three monkeys had bilateral removal of the inferior parietal lobe (operated controls). This lesion included the caudal third of the lower bank of the intraparietal sulcus and the adjacent part of the inferior parietal lobule, and it extended ventrally to the caudal tip of the Sylvian fissure and the dorsal bank of the superior temporal sulcus.

All subjects were tested for retention of DA 10 to 14 days after surgery.

Table 1. Mean number of trials and errors to relearn 5-second spatial delayed-alternation. Midprincipalis (MP), periarcuate (PA), inferior parietal (IP), anterior principalis (AP), unoperated control (UC), posterior principalis (PP). For all groups, $N = 3$ except operation III MP where $N = 2$.

Group	Trials	Errors
	*Operation (retention) I**	
MP	1000	408
PA	343	61
IP	30	8
UC	83	16
	Operation (retention) II†	
PA	260	76
IP	227	45
UC	57	9
	Operation (retention) III‡	
MP	1000	359
AP	243	44
PP	570	131

* The difference in trials and errors between MP and other groups is significant (Mann-Whitney U test). † The difference between PA and UC is significant ($P = .05$; Mann-Whitney U test). ‡ The difference between MP and others is significant ($P < .05$; Mann-Whitney U test).

Again, they received 30 trials a day until they reached a criterion of 90 correct responses in 100 consecutive trials. If an animal failed to relearn within 1000 trials, testing was terminated at this point. The unoperated controls and the monkeys with either periarcuate or inferior parietal lesions all relearned DA whereas the three monkeys with lesions in midprincipalis did not.

After this first retention test the six monkeys with lesions that had relearned DA were operated on a second time. Monkeys that had received periarcuate lesions in the first operation received bilateral inferior parietal lesions in the second; monkeys that had had inferior parietal removals in the first operation now received periarcuate lesions. A second test of DA retention was conducted with the six animals with new lesions and the three controls 10 to 14 days after surgery. All monkeys relearned DA within 1000 trials (Table 1).

To ascertain whether the midprincipalis area represented a focal point for DA deficits, five of the six monkeys (one died after the second DA retention) with periarcuate and parietal lesions received a third operation. For two subjects, the middle third of sulcus principalis was removed; for three others, the lesion was confined to the anterior third of principalis. The three controls underwent their first operation, receiving lesions in the most posterior third of principalis. Again, the subjects were allowed 2 weeks of rest before the third test of DA retention.

As indicated by the results of the first operation, the two monkeys with midprincipalis lesions failed to relearn DA within 1000 trials (Table 1). However, the six monkeys with anterior or posterior principalis lesions all relearned. Despite the large discrepancy between the means of the anterior and posterior groups, the differences are not statistically significant largely because of the poor retention of one anterior monkey (114 errors, 590 trials).

At the conclusion of testing all monkeys were killed, and their brains were prepared for histological examination. The lesions were placed as intended. Figure 1 shows the reconstructions of three brains with anterior, mid-, or posterior principalis lesions. For two of the brains the dorsolateral extent of periarcuate and inferior parietal damage is also presented. To assess the percentage of principalis damage, we projected the lesions on standard graph paper and computed the percentage of squares included in the lesion. In this manner, we determined that the principalis lesions involved from 30 to 42 percent of the total sulcus with only slight differences among the three principalis groups. In Fig. 1 the anterior principalis lesion in brain A involves 35 percent of the sulcus, the midprincipalis lesion in brain B 39 percent, and the posterior principalis lesion in brain C 32 percent. In the area of the lesions the gray matter was almost completely ablated with only slight involvement of underlying white matter. No damage to the caudate nucleus or other subcortical structures was noted after any of the lesions. However, slight damage to the orbital surface was noted in all three anterior principalis lesions.

As in previous reports (2), this study demonstrates the importance of sulcus principalis for DA performance but, unlike the earlier studies, suggests that this sulcus is not homogeneous with regard to DA. Lesions 9 mm in extent and limited to the middle third of sulcus principalis resulted in DA deficits at least as large as those reported after total ablation of the sulcus, while lesions in other sectors of principalis or in the periarcuate frontal region had only mild-to-moderate behavioral effects. The finding that all five monkeys with midprincipalis lesions failed to relearn, whereas all six with anterior or posterior principalis lesions did so, suggests that these differences are highly reliable. Thus, the midprincipalis region may be the focal area for DA performance, but other regions within principalis and prefrontal cortex have only slight involvement in this task. This finding is consistent with that of Stamm (3) in which electrical stimulation of the midprincipalis, but not anterior principalis, significantly impaired delayed-response performance.

Finally, recent anatomical findings (4) have demonstrated that the midprincipalis region differs from other prefrontal regions in terms of corticocortical projections. While the periarcuate, posterior principalis, and anterior principalis regions receive projections from various sensory association areas, the midprincipalis sector does not appear to have such corticocortical projections.

NELSON BUTTERS
DEEPAK PANDYA*

Veterans Administration Hospital and Boston University School of Medicine, Boston, Massachusetts 02130

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* Present address: Boston City Hospital, Boston, Mass.

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Reticular Stimulation and Chlorpromazine: An Animal Model for Schizophrenic Overarousal

Abstract. *It has been postulated that certain schizophrenic patients are in a state of continual central excitation and that improvement in these patients after treatment with chlorpromazine is a result of the action of the drug in reducing this excitation. A model was developed to test this postulated state of central excitation. Rats were electrically stimulated in the mesencephalic reticular formation while performing a simple attention task. Stimulation or treatment with chlorpromazine impaired the performance of the animals; however, the two treatments together resulted in performance indistinguishable from that seen after injections of saline alone.*

The theoretical formulation leading to our experiment is based upon the hypothesis that certain schizophrenic patients are in a continuous state of central excitation or overarousal (1). We have attempted to develop a model for this overarousal by means of electrical stimulation of the brainstem reticular formation in the rat.

We used the "inverted U" model (2) to explain the improvement seen in the schizophrenic patient after daily doses of chlorpromazine, the attenuated effect of single doses of chlorpromazine, and the poor performance of these patients on most psychological tests, especially those that require sustained attention (3). This model states that increasing the state of central arousal results in improvement of performance to some hypothetical optimum. Increasing arousal beyond this point results in impaired functioning. We believe that the schizophrenic patient is beyond this hypothetical optimal point (1). Chlorpromazine, either by means of increasing the filtering properties of the reticular formation or by interfering with the afferent input to the same locus, reduces this overarousal resulting in clinical improvement (4).

Support for the hypothesis of central overarousal in the schizophrenic person calls for the following in our model. Electrical stimulation at appropriate intensities of the reticular formation in the rat should result in impairment on a task requiring sustained attention; stimulation in the presence of chlorpromazine, which by itself impairs performance on this task, should result in an improvement in the performance of the stimulated animal.

The specific test of attention that was used was similar to the continuous performance test modified for animal use (5). We used auditory rather than visual stimuli. Animals were trained in a standard operant conditioning chamber to discriminate between two tones of equal loudness but differing in pitch. Tones were presented for 0.2 second with a presentation of a single tone every 5.0 seconds. The frequencies of the tones were 1200 or 1900 hz. The critical stimulus (1200 hz) was randomly presented on the average every 6.7 tone presentations. A lever press to the critical stimulus was reinforced by a food pellet. Failure to respond to the critical tone was scored as an error of omission and, except for the animal failing to receive a reinforcement, had no other immediate consequences. A

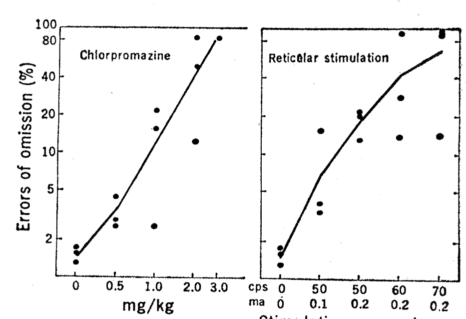

Fig. 1. The mean percentage of errors of omission as a function of dose (left) and parameters of electrical stimulation (right). Points indicate performance for each animal.