centage 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.

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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

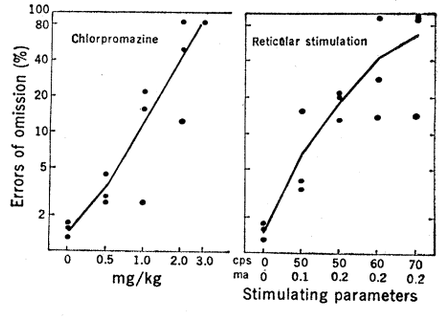

Fig. 1. The mean percentage of errors of omission as a function of dose (left) and parameters of electrical stimulation (right). Points indicate performance for each animal.

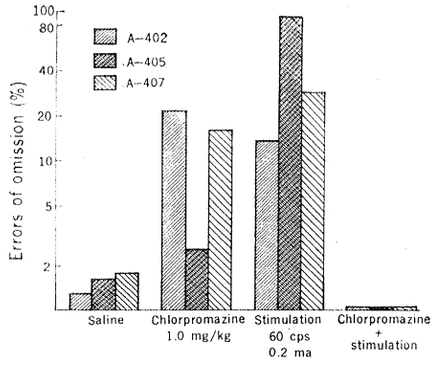

Fig. 2. The percentage of errors of omission for the three animals after administration of chlorpromazine (1.0 mg/kg) or during 60 hz, 0.2 ma of stimulation, and the effect of this dose and this amount of stimulation combined. Although errors are indicated for the combined treatment, none of the animals made errors of omission when chlorpromazine and stimulation were given together.

lever press to the noncritical stimulus was scored as an error of commission which postponed the presentation of the next stimulus for 15 seconds.

Six male albino Holtzman rats, 3 months old at the start of the experiment, were maintained at approximately 80 percent of their normal weight throughout the experiment. Only three animals completed all treatments. We have found this type of "go, no-go" task to be a difficult one for rats, and the training was not completed until the animals had reached an age of 8 months. The testing session lasted for an hour and occurred three to five times a week. At the completion of training the animals were surgically prepared with stereotaxically implanted, bipolar, stainless steel electrodes (0.10 inches in diameter) aimed for the mesencephalic brainstem reticular formation (*6*). Although no histology was done on these particular animals we have verified placement in other animals similarly prepared and have found no difficulty in placing the tips of the electrodes in the reticular formation. Only three of the animals survived beyond the period after surgery and were able to complete all experimental procedures. As soon as the animals recovered from surgery, retraining on the attention task was started. All surviving animals relearned the task without difficulty, and experimentation started 4 weeks after surgery. Stimuli, applied by means of a constant current stimulator, consisted of trains of 500-msec duration. Pulses were bidirectional, 0.1 ma intensity at 50 pulses per second and 0.2 ma at both 60 and 70 pulses per second. Electrical stimulation was presented at random within the 5-second silent period between tone presentations, and only during 40 percent of these intervals did stimulation occur. Although intraperitoneal doses of chlorpromazine from 0.5 to 2.0 mg/kg were used and the previously mentioned amounts of electrical stimulation were employed, chlorpromazine and electrical stimulation were given together only at a dose of chlorpromazine of 1.0 mg/kg and electrical stimulation of 0.2 ma, 60 pulses per second. When an animal was stimulated at this level outside of the testing situation, the stimulation caused him to open his eyes and turn his head in an orienting type of reaction. On test days the procedure lasted 30 minutes. Electrical stimulation, if it occurred, was delivered only during the last 15 minutes of the 30-minute period. Injection of the drug, when present, was given at the start of the 30-minute session, and the datum for analysis consisted of the second 15-minute interval.

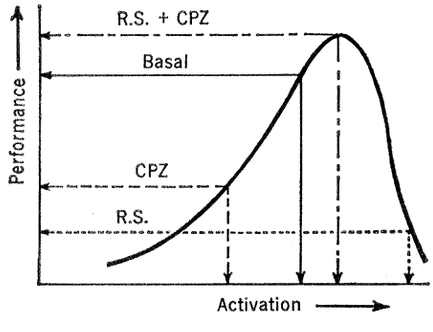

Fig. 3. A hypothetical "inverted U" indicating the postulated relationship between activation and performance. The figure indicates that chlorpromazine (*CPZ*) reduces activation from basal amount causing impairment in performance and that reticular stimulation (*R.S.*) by moving the subjects to the descending leg of the continuum also impairs performances. However, when chlorpromazine is combined with stimulation the subject is moved closer to basal activation amounts.

Performance was impaired by chlorpromazine or reticular stimulation (Fig. 1). Both chlorpromazine and reticular stimulation caused an increase in errors of omission, and these errors were related to dose in the case of the former and related to the magnitude of the parameters of stimulation in the latter. There was no relation between dose of drug or intensity of stimulation and errors of commission on the attention task. The results of combining reticular stimulation and chlorpromazine (Fig. 2) clearly point to an antagonism between the effects of reticular stimulation and drug (*7*) and may be interpreted in terms of the "inverted U" (Fig. 3).

Our results agree with those of Wilson and Radloff (*8*) who found a curvilinear relation between the intensity of reticular stimulation and performance. Slight stimulation improved performance of rats trained in a variable ratio conditioning procedure while intense stimulation impaired the performance. We found no evidence of improvement in the performance of our animals; however, the amount of stimulation we used was not as low as that used by Wilson and Radloff. Also, the behavioral procedure we used required the animals to make an auditory discrimination between two tones.

Our results indicate that electrical stimulation of the reticular formation to a moderately aroused rat (food deprived) interferes with attention as do effective doses of chlorpromazine. The effects of the stimulation are antagonized by chlorpromazine. This observed antagonism fits the model of the "inverted U" and supports the hypothesis that the impaired performance of certain schizophrenic patients on a similar task and their improved performance after chlorpromazine may be a function of a heightened basal level of central nervous system activation.

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