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Time Course of α-Flupenthixol Action Explains "Response Artifacts" of Neuroleptic Action on Brain Stimulation Reward

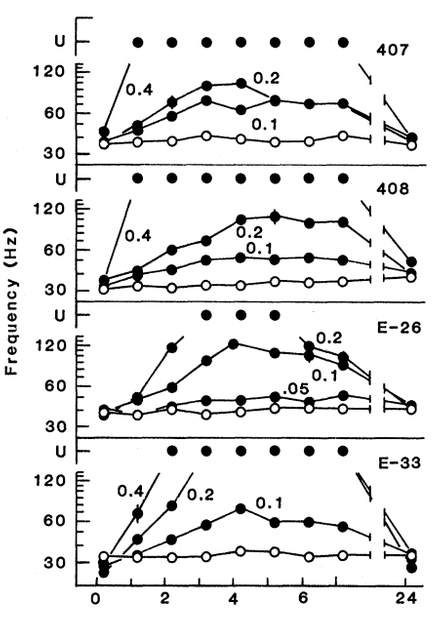
Ettenberg *et al.* (*1*) reported that doses of the neuroleptic α-flupenthixol that spared nose poking for lateral hypothalamic self-stimulation markedly suppressed bar pressing for the same reward. Central to their interpretations of this apparently task-dependent drug effect was the notion that the task used to earn brain stimulation somehow modulates the degree to which dopamine cells participate in reward.

We do not consider the viability of their interpretations because the experiment itself suffers a serious design error. The drug effect on nose poking was assessed 2.5 hours after injection, and bar-pressing tests were held about 50 minutes afterward. The task order was not counterbalanced: "The effects of each dose were tested on nose poking for brain stimulation and then on lever pressing" (*1*, p. 358). If these tests were held over the rising phase of receptor concentration, then for any particular dose the effective antagonism would be consistently lower in the nose-poke trials than in the bar-press tests. It thus would come as no surprise that nose-poking behavior survived at a dose that completely eliminated bar pressing.

To see whether α-flupenthixol's behavioral effect attains asymptote at 2 or even 3 hours after injection, we ran a time-course study of its action on lateral hypothalamic self-stimulation. Required frequencies (*2*) needed to sustain criterion bar-press rates were determined at hourly intervals beginning immediately after injection. This measure is equivalent to "threshold" determination; the sole difference is that reward summation functions (*3*) are cut at moderate levels of performance instead of at just noticeable departures from zero responding. Often, high doses suppressed responding altogether. Required frequencies could not be measured and these undetermined points are shown as unconnected dots against "U" of Fig. 1. Lower doses caused required frequencies to climb, on average, through to the 4-hour test. The implication is that Ettenberg *et al.* conducted their tests too soon after drug administration; by failing to counterbalance task order, they effectively assessed the two tasks with different pharmacological populations.

We then attempted to replicate their result with tests that (i) began after a longer postinjection interval (3 hours, 45 minutes) and (ii) included both orders of task presentation. Each behavior was tested daily for 20 minutes and the two sessions were separated by 20 minutes. Doses of α-flupenthixol were given every other day (*4*). The dose of 0.4 mg/kg completely abolished bar pressing and nose poking (Fig. 2), a result that is at odds with the spared nose poking reported at this dose and twice this dose by Ettenberg *et al.* Our failure to replicate fits with a report (*5*) that haloperidol reduces performance of these two operants to the same degree. Bar-pressing performance was more reduced than nose poking at our lower doses; we agree with Ettenberg *et al.* that this latter result cannot be taken as a task-dependent difference in substrate sensitivity.

Our first experiment demonstrates



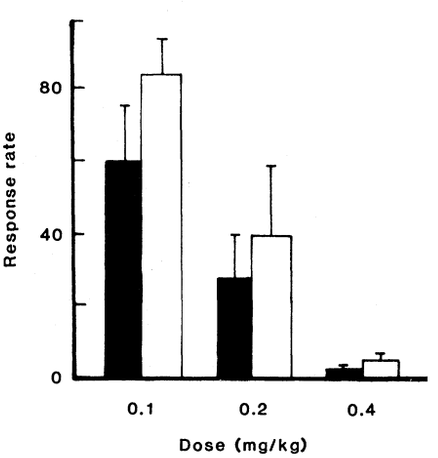


Fig. 1 (left). Time-course data. Frequency of stimulation pulses required to obtain criterion responding after administration of α-flupenthixol. Open circles represent saline tests and closed circles depict drug tests. Doses, in milligrams per kilogram, are shown beside the curves. Each symbol indicates the geometric mean and standard error of four measurements. Points at the "U" level are undetermined. Fig. 2 (right). Effects of α-flupenthixol on lever pressing (closed bar) and nose poking (open bar) for lateral hypothalamic stimulation. The mean response rate is expressed as a percentage of the saline control. These data illustrate that α-flupenthixol has equally disruptive effects on both tasks.

that the attenuation of reward by α-flupenthixol attains asymptotic levels about 4 hours after injection in bar-pressing tests submitted to psychophysical assessment (3). The second experiment shows that neither bar-pressing nor nose-poking behavior resists neuroleptic challenge when counterbalanced tests are conducted at about this time. We believe that if Ettenberg *et al.* had employed a counterbalanced design, or if they had tested the two tasks after the same postinjection interval on different days, then they too would have failed to detect a task-dependent neuroleptic effect.

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2. Fixed stimulation values were 0.1-msec cathodal pulses, current intensity (range, 320 to 500 μA across rats), and 0.3-second train duration. Pulse frequency was varied along a descending, 0.1 log unit progression beginning at 100 or 200 Hz. Dose sequences were randomly generated for each rat and the tests were separated by 3 or 4 days.
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4. Fixed stimulation values were 0.1-msec cathodal pulses, 100-Hz pulse frequency, and 0.5-second train duration. Current intensities were held constant throughout testing; they were individually selected (range, 150 to 500 μA) to produce rates matching those of Ettenberg *et al.* Dose sequences were randomly generated. Saline control tests were held on the day between drug tests; response rates were stable and not different from predrug baseline rates.
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6. Experiment 1 was supported by an Ontario Mental Health Foundation grant (808) to G.F and experiment 2 by a Harvard Bio-Medical Fund award to D.C.
7. Dr. O. Svendson of H. Lundbeck and Company A/S, Denmark, generously supplied α-flupenthixol.

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Ettenberg *et al.* (*1*) reported that the effect of neuroleptic treatment on brain-stimulation reward depends on the task employed in the experimental paradigm. They claim that, whereas several doses of α-flupenthixol attenuated bar-press responding for lateral hypothalamic brain stimulation in a dose-related fashion, the same doses disrupted nose-poke responding relatively less. Two points are raised.

First, Ettenberg *et al.* represent their data in the form of reward summation curves, and they conclude a dose-dependent reward reduction when bar pressing is tested, despite the fact that the curves have the same locus of rise. Reward summation functions are generally employed in order to distinguish between the reward versus performance characteristics following, for example, a pharmacological treatment (*2*). Lateral displacements of curves similar in slope are interpreted as reflecting changes in the reward value; vertical displacements that begin to rise at the same locus suggest only changes due to performance factors. In practice, a reward deficit is often accompanied by a decrease in performance. An assessment of Ettenberg *et al.*'s bar-press data, determined by computing the current required to elicit a half-maximum rate of responding (assuming that the highest current tested very nearly corresponds to maximum performance), yields the following: compared to the saline condition, a 0.1 mg/kg dose requires a 16 percent increase in current, while a dose of 0.2 mg/kg requires a 5 percent increase in current (*3*). This procedure cannot be applied to the nose-poke data because of the design error discussed by Corbett *et al.*

The second point explains why Ettenberg *et al.*'s bar-press data may fail to demonstrate a true reward deficit, a finding that is inconsistent with the results of Corbett *et al.*'s time-course study. In studies of this nature, a rate-intensity, or preferably rate-frequency function (*4*), is obtained for each subject and the required current or threshold computed per individual. The shift along the abscissa (the shift in required threshold) is then averaged across animals for each condition (for example, dose). By averaging the rate at each intensity first, Ettenberg *et al.* may have inadvertently concealed the effects of α-flupenthixol on reward. To illustrate this point, consider the theoretical data shown in Fig. 1A. The four curves (α to δ) represent results from individual subjects following a single-dose drug treatment; the curve at the extreme left (broken line) represents the no-drug condition in which all subjects had similar current thresholds, derived from rate-intensity curves that span the same intensity range. The magnitude of the drug effect was set up to range from 0 to 38 percent (*3*) to reflect individual differences in drug sensitivity, a common occurrence in pharmacological studies (*5*). However, when the averaged rate-intensity function is plotted (Fig. 1B, solid line), one concludes that there was no reward deficit. Whereas the individual reactions had been constructed as unambiguous reward effects with performance problems, the rate-averaging procedure yielded a final curve that reflects only a performance problem (asymptotic rates are reduced) with no reward effect (locus of rise is anchored at the foot of the control curve). In order to reveal a genuine reward change the practice of averaging rates first and then determining the current shift should be avoided in favor of computing individual current shifts first and then averaging these values.

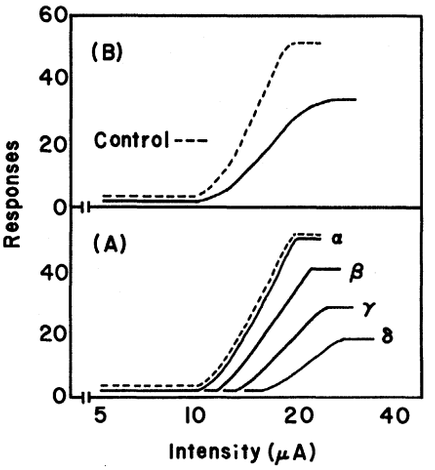

Fig. 1. Theoretical effects of a drug on the rate-intensity function of four subjects: α, β, γ, and δ. (A) represents the individual curves following drug treatment (solid lines); (B) represents the averaged rate-intensity function (solid line). In both cases, the same averaged control condition (broken line) is used to assess the magnitude of the reward deficit.

While I agree with Ettenberg *et al.* that they have failed to demonstrate that the neuroleptic α-flupenthixol blocks the rewarding effects of brain stimulation, methodological, interpretative, and analytical procedures contribute to that failure, not differences in the neural substrate of the two behaviors.

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Ettenberg *et al.* (*1*) reported that a dose of neuroleptic that attenuates lever pressing for brain stimulation reward causes relatively little attenuation of nose poking for the same reward. They argue two things from their data: (i) that the rewarding impact of stimulation must not be totally blocked by doses of a neuroleptic, α-flupenthixol, or by comparable doses of other neuroleptics, including the doses of pimozide that we have tested (*2–4*), and (ii) that the impairment of lever pressing must reflect a drug-induced response difficulty since the disruption is task-specific. On these grounds Ettenberg *et al.* assert that our anhedonia hypothesis of neuroleptic action (*2*, *4*, *5*) and similar hypotheses of others (*6*), which hold that neuroleptics reduce the hedonic or rewarding impact of a variety of rewards, are based at least in part on a "response artifact." The Ettenberg *et al.* report may be flawed methodologically, as suggested by Corbett *et al.* above, but even if it were not flawed, the conclusions would not be compelling.

On their first point, Ettenberg *et al.* set up a straw man. The anhedonia hypothesis does not hold that the reliable low-dose effect of neuroleptics is a total blockade of the rewarding impact of brain stimulation or other rewards; the literature, including the recent statements of the anhedonia hypothesis (*4*, *5*), has long ago established that it is not (*4–7*).

Several points should be made regarding their second conclusion. If one response is spared by a neuroleptic dose that disrupts another response, does this mean that the drug must disrupt a motor component of the second response? It does not. In this case nose poking was sustained by stimulation currents of 5 μA, where currents of 15 μA were required to sustain lever pressing. Thus the lever-pressing response required a stronger motivational payoff than the nose-poking response. In such a case lever pressing should be more easily disrupted by a purely motivational challenge (*5*); this interpretation of differential dose-effectiveness in different tasks is also well established in the specialist literature (*8*).

Further, even if the nose-poke response (*5*) (see Corbett *et al.*) were less responsive to neuroleptics than are other responses, this motor act is ill chosen for this type of study. Forward locomotion is an unconditioned response to rewarding brain stimulation (*9*); perhaps this explains why it has such a low threshold. Once a series of nose pokes is initiated (*10*), it may be sustained not by the rewarding property but rather by the motoric side effects of stimulation. Neuroleptics are not expected to block the motoric side effects of stimulation and may thus fail to block nose poking even when they cause major reward attenuation. Finally, α-flupenthixol may be a poor choice of neuroleptic for these studies. This agent appears to have relative selectivity for the D_1 dopamine receptor, whereas the neuroleptics that have been argued to be relatively free of motoric side effects (pimozide, butaclamol, haloperidol, and spiroperidol) are relatively selective for the D_2 receptor (*11*).

Ettenberg *et al.* ignore most of the empirical base for the anhedonia hypothesis when they argue that it may be based on a response artifact. It is now widely accepted that neuroleptics do cause major and primary attenuation of the impact of a number of positive rewards, as Ettenberg now concedes (*12*). The report of Ettenberg *et al.* may merely reflect findings that are artifacts of procedural errors; if not, the conclusion is likely based on an artifact of (i) the relative thresholds of the two tested tasks, (ii) the motoric side effects elicited by rewarding stimulation, or (iii) motoric side effects associated with blockade of the D_1 rather than the D_2 receptor.

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We have considered the comments of Wise and his present [Bielajew] and former [Corbett and Fouriezos] colleagues and find no compelling reasons to alter our original conclusions. The most serious criticism raised is the alleged "design error" described by Corbett *et al.* However, no such methodological error actually occurred. Contrary to the inference of Corbett *et al.*, our animals were tested at the same time after injections in experiments with both nose-poking and lever-pressing behaviors. The rats initially were trained to nose poke for ascending series of rewarding brain stimulation on a daily basis for several weeks. After this, α-flupenthixol trials were completed at every dose level during the next several weeks. We then retrained all these same animals to press a lever for brain stimulation and again repeated the entire test procedure with the drug in the identical manner as for nose poke. Hence we wrote: "The effects of each dose [of α-flupenthixol] were tested on nose poking for brain stimulation and then on lever pressing." The differential effects of neuroleptic challenge on nose poke and lever press that we reported cannot, therefore, be explained by the time course of α-flupenthixol action, as Corbett *et al.* suggest. Although our test methods may not have been adequately described, there was not any "serious design error" (*1*).

Shortly after the publication of our manuscript, we discussed with Corbett the imprecise manner with which we described our methodology and explained then the actual procedures that we used. We appreciate this opportunity to clarify our experimental procedures as well.

The time-course data presented by Corbett *et al.* suggest that the effects of α-flupenthixol on self-stimulation appear to become asymptotic at approximately 4 hours after injections. Since all our drug data were collected at the same time (2.5 hours) after injections with both behavioral tests, this does not affect the interpretation of our results. If the drug's peak action was not in fact reached at the time that we tested our subjects, then we were essentially testing lower doses than the corresponding doses employed by Corbett *et al.* Therefore, it is of interest to note that at smaller doses even these investigators observed that "Bar-pressing performance was more reduced than nose poking at our lower doses. . . ."

Finally, for their replication experiment Corbett *et al.* used 20-minute sessions during which a single-current intensity (ranging between 150 and 500 μA) of 0.5-second square-wave stimulation was delivered. In contrast, we tested our animals during eight consecutive 5-minute trials with 15-second time outs

between trials. The brain stimulation consisted of 300-msec pulses of sine-wave current at intensities from 0 to 40 μA, raised in 5-μA increments. The distinction between ascending current and constant current appears to be particularly important; we have observed far greater disruptive effects of α-flupenthixol when current was held constant for short test sessions, a result (*2*) consistent with those reported by others (*3*).

Bielajew suggests that our rate-intensity functions might have concealed a drug-induced reward deficit. However, as noted above, we found that ascending-series tests yielded more information than the more traditional approach with a single-current intensity held constant. In any event, we are not suggesting that no reward attenuation occurred in the presence of neuroleptic, only that a performance deficit was also evident. As a consequence, the behavioral disruption produced by neuroleptic treatment is an interaction between both variables (reward and performance deficits). When performance factors are reduced, as by reducing the kinetic requirements of the operant response, we observed a smaller reward deficit than others in the literature would probably have expected (*4*). We have little problem with Bielajew's comments since she herself admits the presence of drug-induced "performance deficits" in addition to "reward deficits."

Contrary to Wise's comment, although the brain stimulation reward thresholds for nose poking are undoubtedly lower than those for pressing levers, this does not alter the interpretation of our data since one would still expect to observe a dose-dependent reduction in both behaviors during neuroleptic challenge (that is, if the drug selectively attenuates reward, then increasing doses should do so with increasing effectiveness, independent of the response employed in the experimental design). Instead, doses of 0.2 to 0.8 mg per kilogram of body weight produced essentially the same behavioral disruption in nose-poking behavior. Wise, however, suggests that nose poking is a poor choice of response since it may be maintained "not by the rewarding property but rather by the motoric side effects of stimulation." In fact, all of our animals readily reinitiated responding during each 5-minute trial and efficiently followed the stimulation by seeking out and responding only on the positive of the two holes for nose poking (randomly alternated for each trial). We are unaware of evidence indicating that nose poking is an inappropriate operant response for studies of brain stimulation reward. In our view, much of the reinforcing properties of the stimulation survived the α-flupenthixol challenge. The pharmacological profile of α-flupenthixol is similar to many other neuroleptic agents used in behavioral work, and testing in our laboratory with a wide variety of behavioral assays does not support Wise's statement that α-flupenthixol has more motoric side effects than other drugs of its type.

The so-called anhedonia hypothesis (*4*) suggests (i) that neuroleptic drugs attenuate the positive properties of reinforcers and (ii) that this effect is produced by a disruption in the neurotransmission of central dopamine pathways. Contrary to what Wise suggests, we have not proposed that the anhedonia hypothesis "may be based on a response artifact." Many of our findings have been consistent with aspects of the anhedonia hypothesis (*5*). We do not question whether dopamine neurons may be involved in the biological basis of reinforcement, only the extent of involvement. Our position remains unchanged—that dopamine substrates represent neither a critical link nor a final common pathway in the neural mediation of reward.

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References and Notes

1. Counterbalancing the order of testing may have reduced the likelihood that repeated α-flupenthixol exposure would lead to the development of some tolerance to the drug effects. However, to avoid this, 1 week was left between drug trials and 3 weeks separated the conclusion of nose-poking tests from the commencement of drug trials on lever-press responding. Had some tolerance occurred to repeated drug administration, we would have expected a weaker, not greater, suppressive effect of the drug on behavior.
2. We observed that dose-dependent reductions in nose-poking behavior do occur during neuroleptic challenge when no reward is presented (that is, under conditions of extinction) [A. Ettenberg, S. A. Cinsavich, N. White, *Pharmacol. Biochem. Behav.* **11**, 557 (1979)]. Similarly, when the current intensity of the brain stimulation is held constant at some positive value, the disruptive effects of α-flupenthixol are far greater than when the current intensity is increased in 5-μA steps during each successive 5-minute trial. For example, we (A. Ettenberg, G. F. Koob, F. E. Bloom, unpublished data) trained animals (N = 10) to alternate every 5 minutes between nose poking and lever pressing for rewarding brain stimulation (held at constant currents). In that situation, α-flupenthixol administered 2.5 hours before testing, resulted in nose-poking rates of 102, 61, and 13 percent of drug-free performance for doses of 0.1, 0.2, and 0.4 mg/kg respectively. However, even in this situation, lever pressing was far more disrupted by α-flupenthixol with response rates of 69, 44, and 6 percent of drug-free performance for the same doses. This differential effect occurred in the same rats at essentially the same time with the same dose. One-tailed t-tests for correlated samples confirmed that the different effects of neuroleptic in the two tasks was statistically reliable at all but the highest dose [$t(9) = 2.04$ and 1.98 for the low and intermediate doses, respectively, $P < 0.04$].
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Olfactory Function After Bulbectomy

Wright and Harding (*1*) have suggested that a previously learned olfactory discrimination can reappear after all second-order olfactory neurons are surgically removed by bilateral bulbectomy. Primary olfactory axons do regenerate, and, in addition to reconnecting with the olfactory bulb, can make anatomical connections within the forebrain after bulbectomy (*2*). Wright and Harding do not demonstrate that these unusual connections are responsible for the behavioral recovery reported because they do not show (i) that such connections were formed in their behavioral animals, (ii) that all normal connections were removed, and (iii) that all other sources of information were inoperative.

Complete bulbectomy cannot be assured without histological verification, (i) because the ventromedial part of the olfactory bulb extends caudally under the forebrain and could be left intact, especially if "[c]are was taken to avoid forebrain damage . . ." (*1*, p. 322) and (ii) because the distortions of the forebrain, after cranial closure following partial or complete bulbectomy, make the recognition of remaining bulbar tissue uncertain. Furthermore, it seems that the animals surviving to the end of the behavioral experiment—that is, the animals showing the greatest recovery—were never examined for intact bulb tissue. In short, all the behavioral results reported could be accounted for by the presence of remaining olfactory bulb tissue and the reconnection of primary axons to this tissue. The biochemical results could be accounted for in the same way. Because of the distortions mentioned above, the nature of the intracranial tissue assayed in these experiments could not be accurately judged without