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

histology; even if nonbulbar forebrain connections did contribute to the biochemical results, however, their function would be in doubt if not all bulbar connections had been eliminated.

Two further problems not adequately addressed in the report are the possibility of contributions by nonolfactory chemoreceptors and the lack of controls in the principal behavior experiments.

1) Aqueous dilutions of amyl acetate such as those used by Wright and Harding can produce vapor concentrations much above the equivalent-ratio air dilution (*3*) and well above threshold for intranasal trigeminal chemoreceptors (*4*).

2) The authors concluded that a learned odor aversion is temporarily lost after bilateral bulbectomy and subsequently recovered when connections between primary olfactory neurons and the brain are reestablished. This conclusion is untenable unless control and sham-operated groups are used to show that odor aversion learning occurs, that a temporary loss of response to the odor is related to bulbectomy, and that the reappearance of avoidance depends on the treatment before bulbectomy.

Our criticisms do not discount the possibility of some functional recovery, but we think the available evidence is inadequate.

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Meredith *et al.* (*1*) have made two major proposals to explain our earlier results. The first relates to the possible existence of bulb remnants and the fact that histologies were not performed on all animals tested behaviorally. Of the 50 animals, 6 underwent autoradiographic and histological examination by a colleague (C. Camara), and 8 more were intranasally irrigated with zinc sulfate and subsequently (425 days after surgery) examined for tritiated carnosine content of the epithelium and forebrain. None of these animals displayed remnants of bulb. Several additional animals were periodically selected at random during the course of behavioral testing and inspected for incomplete bulbectomy. Of the bulbectomized mice used specifically for biochemical evaluation, three were discarded because of the presence of bulb remnants. We agree that visual inspection cannot ensure that every cell of the olfactory bulb has been removed; it is possible, however, to detect as little as 5 percent of the bulb if it should remain. Even if a very small portion of the bulb does remain, we feel this offers no explanation for the apparent recovery of a previously learned olfactory behavior.

The second issue raised by Meredith *et al.* concerns a possible influence of other sensory information in the performance of the behavioral tasks. They suggested that the trigeminal system may take part in the chemical detection. Several pieces of information weigh against this possibility. In the odor aversion task, amyl acetate was used as one of the primary test odorants specifically because it is a poor activator of the trigeminal system as evidenced by electrophysiologically derived thresholds in rabbit and turtle (namely, 0.017 part per million) (*2*) and in isolated rat trigeminal nerve (260 to 520 parts per million) (*3*).

This lack of trigeminal activation is also supported by the nontransferance of the task between the two bulbectomized groups with aversions to either amyl acetate or 1-butanol.

The inability of amyl acetate to stimulate the trigeminal system can also be inferred from preliminary results of additional primary olfactory neurectomy studies (*4*). After nerve section, mice that had been trained to find buried sugar cubes scented with amyl acetate could no longer perform the task, whereas mice trained to find cubes scented with acetonitrile (a trigeminal stimulant) exhibited no deficit. Both groups had effective neurectomies based on [^{3}H]carnosine transport between the neuroepithelium and the olfactory bulbs.

We also subjected a group of mice to identical bulbectomy, but implanted embryonic mouse occipital cortex in the space vacated by the bulbs according to the procedures of Das *et al.* and Graziadei and Kaplan (*5*). Members of this group were unable to perform the pellet-finding task (*6*) at either 125 to 160 or 220 to 225 days after surgery. We suspect that the regenerating fibers required for behavioral recovery have been "short-circuited" by innervation of the implant. Since these animals had intact trigeminal systems, successful pellet location would be expected if trigeminal information were being contributed.

We have also improved control of odor stimulus presentation in order to address the issue of "whether the regenerated olfactory system has the same sensitivity and range of responsiveness to odor stimuli as the nondamaged system" (*6*, p. 323). A new Y maze allows gas chromatograph sampling in each odor stimulus arm. Preliminary data indicate that food-deprived normal mice can discriminate between as little as 2 parts per billion of amyl acetate and filtered air for a food reward. Once these animals were subjected to bilaterally bulbectomy, their performance dropped to chance level and remained impaired for as long as 300 days. We do not yet have complete behavioral data or histological information. We are also testing these bulbectomized animals on the earlier food-pellet task. The animals can find the buried pellet, but seem to be making some use of tactile sensory information. We have not yet determined the magnitude of tactile contribution to the successful performance of the pellet-finding task.

We agree with Meredith *et al.* regarding the importance of removing other sources of sensory information that may confound interpretation of behavioral recovery. Nevertheless, we remain convinced that some portion of the behavioral recovery depended on the newly regenerated olfactory neurons, and we hope to specify the sensitivity of the recovered system soon.

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