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The Slow Therapeutic Action of Antipsychotic Drugs

A Possible Mechanism Involving the Role of Dopamine in Incentive Learning

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There has been great interest in the function of the brain's dopaminergic systems since they were first described about 25 years ago [Lindvall and Bjorklund, 1983]. A factor contributing to this interest was the discovery that dopaminergic cells were lost in Parkinson's disease [Hornykiewicz, 1979] and may, in some way, hyperfunction in schizophrenia [Matthysse, 1974]. At the basic research level, experimental results have shown that dopamine (DA) may be involved in incentive learning, a form of learning that occurs when rewarding stimuli are encountered by an animal and results in an enhanced ability of reward-related stimuli to elicit responses (e.g. approach) in the future [Beninger, 1983, 1987]. Using dopamine as the link, it may be possible to understand some of the symptoms of schizophrenia as the consequence of excessive incentive learning. The present paper explores this possibility and, in particular, suggests that the delayed therapeutic action of antipsychotic drugs may be understood within this context.

Dopamine and Schizophrenia

A large number of antipsychotic drugs are now in use for the treatment of schizophrenia. These drugs have the effect of gradually reducing positive symptoms, including thought disorder and delusions, over several weeks of treatment and of maintaining this improved state, preventing relapse, with continued medication [Davis et al., 1983]. Antipsychotics are less effective in alleviating negative symptoms such as affective flattening and apathy [Johnstone et al., 1978]. They also have a number of nonessential or

undesirable neurological effects often termed extrapyramidal or parkinsonian; these include bradykinesia, mild rigidity, tremor and akathesia. The term, neuroleptic, originally used to refer to all of these actions of antipsychotic drugs, and often used as a synonym for antipsychotic, now is suggested for more restricted use to refer just to the neurological effects [Baldessarini, 1980]. For this reason, the term antipsychotic will be used in this paper.

Antipsychotic drugs have been found to block receptors for the neurotransmitter DA. Supporting data came from a wide variety of experimental approaches including neurochemical observations of increased production of DA and its metabolites in the striatum, a major DA terminal site, following treatment with antipsychotics, electrophysiological observations of enhanced activity in putative DA cells of the mesencephalon following antipsychotics and behavioural evidence that antipsychotics antagonized the motor effects of DA agonists [Baldessarini, 1980]. Furthermore, it has been shown that there is a highly significant positive correlation between the ability of antipsychotic drugs to inhibit by 50% the binding of [^{3}H]-haloperidol to homogenates of calf brain caudate nucleus and the average clinical dose used for controlling schizophrenia. [^{3}H]-Haloperidol binding is used as an index of binding to a subclass of DA receptors, the D2 DA receptor [Seeman, 1981]. These observations, along with the general finding that treatment with DA agonists led to schizophrenic symptoms in non-psychotic patients [Angrist et al., 1977] or to an exacerbation of symptoms in psychotic patients [Angrist et al., 1980; Janowsky et al., 1973] and the discovery of significantly enhanced D1 DA receptor function [Memo et al., 1983] or increased numbers of D2 DA receptors in postmortem brain tissue from schizophrenics [Cross et al., 1981; Lee and Seeman, 1980; Seeman et al., 1984] contributed to the DA hypothesis of schizophrenia. This hypothesis states that DA may, in some way, hyperfunction in the brains of persons who develop schizophrenia [see reviews by Carlton and Manowitz, 1984; Crow, 1978, 1979; Lipton and Nemeroff, 1978; Mackay, 1980; Matthysse, 1974; Miller, 1984; Pearlson and Coyle, 1983; Rupniak et al., 1983; Sayed and Garrison, 1983; Snyder, 1976, 1981]. One difficulty with this hypothesis is the observation that antipsychotic drugs have a gradual therapeutic effect that may not reach maximum for up to 6 weeks (fig. 1). Antipsychotic drugs are known to have their maximal blocking effect at DA receptors within a few hours of administration. If schizophrenia results simply from hyperfunctioning of DA in the brain, then the therapeutic response should be seen when DA receptor blockade is maximal.

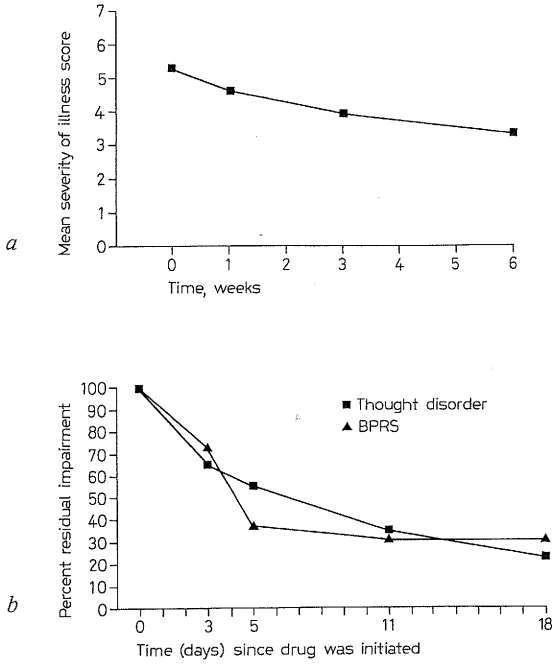

Fig. 1. The delayed onset of action of antipsychotic drugs. *a* Severity of illness over time (weeks) in patients treated with chlorpromazine. Severity ratings range from normal (1), through mild illness (3), marked illness (5), to the most severely ill patients (7). *b* Improvement in thought disorder (■) and score on the Brief Psychiatric Rating Scale (▲) over time (days) for patients treated with haloperidol. Adapted from Davis et al. [1983], with the permission of J. M. Davis.

The slow therapeutic action of antipsychotic drugs may not require the rejection of the DA hypothesis if it can be shown that DA is involved in learning. Accordingly, hyperfunctioning of DA systems may lead to inappropriate learning (see below). Although antipsychotic therapy leads to an almost immediate decrease in DA synaptic transmission, the previous inappropriate learning, now stored in memory, may remain intact and may continue to lead to various symptoms such as delusions. However, with continued drug therapy, perhaps no further inappropriate learning will occur allowing the information stored during the period of DA hyperfunctioning to eventually be overridden by the accumulation of new, appropriate learning [Miller, 1984, pp. 783–784]. There exists an extensive literature, involving research with nonhuman species, reporting the possible role of

DA in various types of learning and results suggest that DA may be involved in incentive learning. Using DA as the link, it may be possible to understand the symptoms of schizophrenia as resulting from inappropriate incentive learning. The slow therapeutic action of antipsychotic drugs may then be seen as consistent with the hypothesis that schizophrenia results from hyperfunctioning of DA.

Dopamine and Incentive Learning

The term incentive learning is an abbreviated form of the term incentive motivational learning. Although this type of learning was referred to over 50 years ago, it did not figure strongly in psychological learning theory until perhaps the last 25 years [Bindra, 1974]. Incentive learning refers to one aspect of the learning that takes place when an animal encounters a biologically important (rewarding) stimulus such as food. Theoretically, as a consequence of this learning, the incentive motivational properties of the rewarding stimulus are transferred to previously neutral environmental stimuli that are associated with the rewarding stimulus and act as signals for it. These previously neutral stimuli are now conditioned incentive stimuli that have the ability to produce appetitive reactions that include instrumental responses that serve to bring the animal close to the reward. Put simply, rewarding stimuli have the unconditioned ability to attract the animal and stimuli associated with them acquire this ability. This process is defined as incentive learning [cf. Beninger, 1983].

Examples of incentive learning abound in everyday life. Anyone who regularly feeds a pet dog or cat will be familiar with the activating effects that prefeeding signals such as opening a can or a particular cupboard have on the animal. These signals would be termed conditioned incentive stimuli, having acquired the ability to produce approach responses like those produced by the reward itself. In the laboratory, when a rat learns to press a lever for food, according to incentive theory, the food-related stimuli (e.g. the wall around the lever and the lever itself) have become conditioned incentive stimuli, having an enhanced ability to elicit approach and transactional responses. If rats are fed in one side of a long narrow box and not in the other they will subsequently be seen to show a preference for the place associated with food [Spyraki et al., 1982]; the stimuli from this side would be said to be conditioned incentive stimuli having an enhanced ability to attract. It has also been shown that animals are more active when simply

exposed to environmental stimuli previously associated with reward [Bindra and Campbell, 1967; Zamble, 1967]. Furthermore, in each of these examples, repeated exposure to the conditioned incentive stimuli in the absence of the usual reward will lead to a gradual diminution of the response until eventually the conditioned incentive stimulus will again appear neutral, eliciting minimal reaction from the animal. This process is termed extinction.

Psychopharmacological studies evaluating the effects of antipsychotic drugs (DA receptor blockers) on the *acquisition* of incentive learning have repeatedly shown that these compounds impair this type of learning [see reviews by Beninger, 1983; Wise, 1982]. Thus, it was found that animals treated with the DA receptor blocker, pimozide, were impaired in a dose-related fashion in learning to approach and press a lever for food reward even though they ate experimenter-delivered food [Tombaugh et al., 1979; Wise and Schwartz, 1981]. Similarly, the antipsychotic, haloperidol, blocked the acquisition of a place preference based on food even though it did not impair eating [Spyraki et al., 1982].

As already mentioned, animals are seen to be more active when exposed to environmental stimuli previously associated with reward [Bindra and Campbell, 1967; Zamble, 1967]. According to incentive theory, this occurs because the reward-related stimuli have become conditioned incentive stimuli with an enhanced ability to elicit responses. One way to examine the possibility that DA is involved in this effect would be to pair injections of a known DA agonist with a particular environment over a number of trials and then examine the ability of those environmental stimuli to elicit activity. A typical experimental protocol might be as follows. Two groups of rats individually receive one 30-min exposure to an experimental environment each day for several days. The experimental environment is a standard plexiglass cubicle. One group, immediately prior to each exposure, receives a systemic injection of the DA agonist, amphetamine, and the other receives saline. Following each exposure, the rats of the amphetamine group receive a saline injection upon return to their home cages and rats of the saline group receive amphetamine. This is an important control procedure that equates the groups for drug history and number of injections. The only difference is the particular set of environmental stimuli that was associated with enhanced DA transmission for each group. On the test day, both groups are tested for activity in the experimental environment while in the drug-free state. Prior to this test, each animal is injected with saline to maintain the routine of an injection prior to each exposure to the experimental environ-

ment. Results of experiments employing this basic protocol have repeatedly shown that the animals previously receiving amphetamine in the experimental environment were significantly more active on the test day than animals previously receiving saline in the experimental environment [Beninger and Hahn, 1983; Hayashi et al., 1980; Herz and Beninger, 1987; Pickens and Crowder, 1967; Pihl and Altman, 1971; Tilson and Rech, 1973]. Similar results have been reported following treatment with another DA agonist, cocaine [Barr et al., 1983; Beninger and Herz, 1986; Post et al., 1981]. To confirm that this apparent incentive learning was mediated by the actions of amphetamine and cocaine on DA synaptic transmission, the ability of pimozide to antagonize conditioning was evaluated. Animals treated with pimozide prior to injections of amphetamine or cocaine and exposure to the experimental environment showed no conditioned activity effect on the test day [Beninger and Hahn, 1983; Beninger and Herz, 1986].

The preceding discussion has focused on the role of DA in the *acquisition* of incentive learning. It can also be shown that DA is important for the *maintenance* of already-established incentive learning. Thus, if animals that are trained to press a lever for food are treated with a DA receptor blocker they will show an extinction-like gradual decline in responding (fig. 2). This was first shown by Wise et al. [1978a] in what is now a classic paper and has often been replicated [Gray and Wise, 1980; Mason et al., 1980; Tombaugh et al., 1979, 1980, 1982; Wise et al., 1978b]. Of particular interest is the gradual decline; in spite of treatment with the same dose of antipsychotic drug each test day, significantly more responding was seen on the first than on the second or third day (control studies have ruled out the possibility of drug accumulation). To what can this initial resistance of conditioned responding to the effects of DA receptor blockade be attributed?

One possibility is that when incentive learning occurs, it may happen that conditioned incentive stimuli acquire the ability themselves to activate DA neurons. As activation of DA neurons is well-known to lead to increased motor activity [this is presumably a function of DA in addition to its role in learning, see Beninger, 1983], this might explain the response-eliciting ability of conditioned incentive stimuli. Support for this possibility is provided by studies demonstrating that conditioned incentive stimuli signalling injections of the DA agonists amphetamine or apomorphine [Schiff, 1982] or food [Blackburn et al., 1986] can lead to increased turnover or levels of DA or its metabolites in the DA terminal region, nucleus accumbens. Thus, it might be suggested that the initial resistance of conditioned

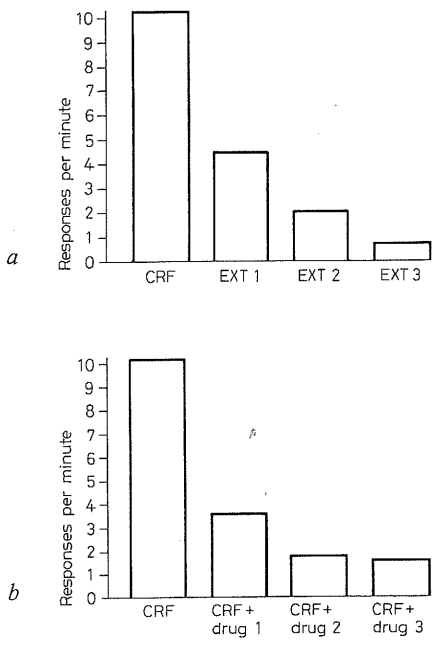

Fig. 2. Mean responses per min during the final session (15 min) of responding for groups of 10 rats on a continuous reinforcement schedule (CRF) and *a* during 3 sessions of nonreinforcement (extinction: EXT 1–3) or *b* during 3 CRF sessions (36 min) where animals were treated with a 1.0-mg/kg dose of pimozide (CRF + drug 1–3). Response rates of animals treated with pimozide showed an extinction-like decline. Adapted from Mason et al. [1980].

responding to the effects of DA receptor blockers results from this conditioned release of DA. With repeated testing of animals treated with antipsychotics, as incentive learning is blocked, the conditioned effect may weaken and a gradual decline in responding is seen. One difficulty with this position is that the gradual decline in responding following DA receptor blockers is seen even after treatment with large doses that might be expected to block the effect of conditioned DA release.

Another possibility is that incentive learning involves DA-mediated changes in nondopaminergic systems. This hypothesis was tested using the amphetamine-produced environment-specific conditioned activity paradigm already described [Beninger and Hahn, 1983]. Results are reproduced in figure 3. In experiment 1, on conditioning days, animals were injected with amphetamine (2.5 mg/kg) or saline prior to 30-min exposures to the

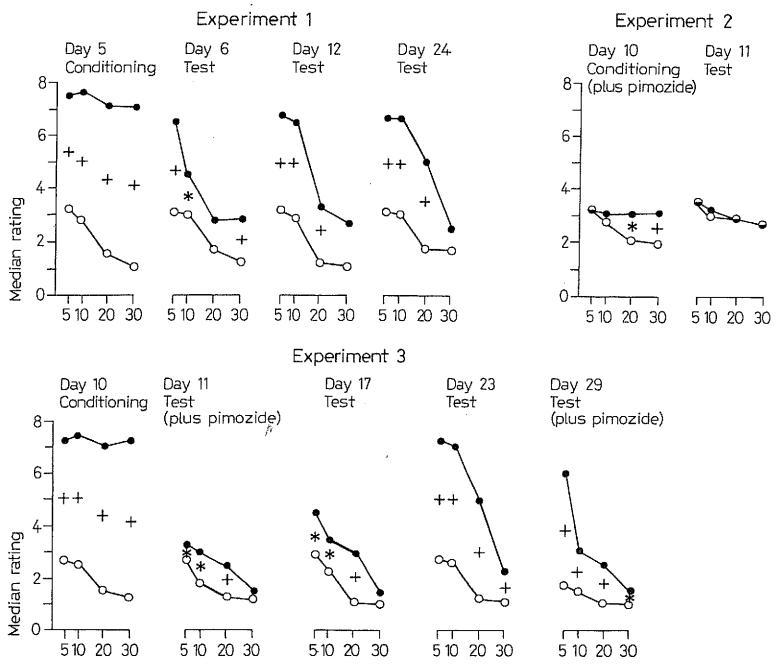

Fig. 3. Median activity rating for the experimental (●) and control (○) groups. In experiment 1, the experimental group received amphetamine and the control group saline before conditioning session 5. Both groups received saline before test sessions. In experiment 2, both groups received pimozide (0.4 mg/kg) 4 h before conditioning session 10, and the experimental group received amphetamine and the control group saline immediately before that session. Both groups were injected with saline before the test on day 11. In experiment 3, the experimental and control groups received amphetamine and saline, respectively, before conditioning session 10. Both groups received saline before test sessions: however, both groups were also injected with pimozide (0.4 mg/kg) 4 h before test sessions on days 11 and 29. Statistical comparisons were made with Mann-Whitney U tests: *$p<0.05$; +$p<0.01$. From Beninger and Hahn [1983].

experimental environment. Figure 3 shows activity ratings at 5, 10, 20 and 30 min into conditioning session 5; the unconditioned stimulant effects of amphetamine are clearly seen. On day 6 animals were tested with saline and the significantly greater activity of the group previously receiving amphetamine in the experimental environment can be seen. Days 7–11 and 13–23 were conditioning days and additional tests were carried out on days 12 and 24 with similar results. Experiment 2 was like experiment 1 except that the

DA receptor blocker, pimozide (0.4 mg/kg), was injected prior to each conditioning session. Only conditioning day 10 is shown and the almost total antagonism of amphetamine's unconditioned activity effects by this low dose of pimozide can be seen. On day 11 both groups received saline prior to the test session. Results show that pimozide blocked the *acquisition* of incentive learning. Experiment 3 also was similar to experiment 1. There were 4 saline test days. In addition, prior to 2 of these test days (day 11 and 29), pimozide (0.4 mg/kg) was injected. As can be seen, pimozide failed to block the *expression* of incentive conditioning. This result is particularly noteworthy because pimozide blocked the larger and longer-acting unconditioned effect of amphetamine but not the smaller conditioned effect. This result has been replicated recently using cocaine as the DA agonist in my laboratory [Beninger and Herz, 1986] and by Post and his colleagues in his laboratory [personal communication]. Results suggest that the response-eliciting influence of conditioned incentive stimuli may not require DA for its initial expression. Of course, repeated exposure to these conditioned incentive stimuli in the absence of a DA agonist will lead to an eventual extinction of the conditioned response. It should also be noted that the observation of conditioned activity of DA neurons following the presentation of conditioned incentive stimuli (see above) is not inconsistent with the conclusion that conditioned incentive stimuli can influence responding even when DA receptors are blocked. It simply means that the conditioned release of DA is not necessary for the expression of incentive conditioning.

In summary, previously neutral environmental stimuli associated with reward may become conditioned incentive stimuli, acquiring the ability to produce approach responses or, in other words, to attract the animal. DA appears to be critically involved in the establishment and maintenance of this type of learning. However, once incentive learning has occurred, conditioned incentive stimuli appear to retain their ability to attract, at least transiently, even when DA neurotransmission is significantly reduced by treatment with an antipsychotic drug.

Incentive Learning and Schizophrenia

As already discussed, there is now a substantial body of evidence from diverse areas of neuroscience to support the hypothesis that DA may, in

some way, hyperfunction in the brains of persons who develop schizophrenia. There also is good evidence that DA may mediate the acquisition and maintenance of incentive learning that occurs when rewarding stimuli are encountered. Using DA as the link, it may follow that schizophrenia is an impairment of incentive learning. As DA may hyperfunction in the brains of schizophrenics, it may be that schizophrenics undergo excessive incentive learning and that this learning leads to the behavioural changes seen in the disease.

To speculate about those changes in behavior that might be expected in persons undergoing excessive incentive learning, it may be useful first to consider the normal function of incentive learning. Incentive learning occurs when reward is encountered. Animals foraging about their environment for food, for example, find food in some places but not others. Presumably, when an animal finds and eats food the DA system is activated [Heffner et al., 1980, 1981; Heffner and Seiden, 1980; Keller et al., 1983] leading to incentive learning. As a result, food-associated stimuli acquire an enhanced ability to attract the animal in the future. It should be noted that incentive learning is certainly not the only type of learning and a number of studies have shown that animals with DA neurotransmission blocked can still learn associations between stimuli [cf. Beninger, 1983, 1987]. DA seems to be involved in altering the attractiveness of stimuli associated with reward but not forming the associations between stimuli. As the anatomical and biochemical organization of the central nervous systems of nonhumans and humans is remarkably similar, it is possible that DA might mediate the same functions in the animal species typically studied in the laboratory and humans. Incentive learning in humans, therefore, may also involve the enhanced ability of reward-related stimuli to attract. In rich Western cultures where food, water and thermal comfort are readily and widely available to most people, it is difficult to describe incentive learning with reference to these rewards. However, when people are hungry, they are probably more attracted by certain odors (those olfactory stimuli previously associated with food) than others and to certain places than others. Although I know of no direct experimental evidence of support this speculation, perhaps DA-mediated incentive learning is also normally involved in enhancing the ability of certain other individuals to attract, for example, those who provide rewards related to needs for contact. A person might recognize many other individuals through work, recreation, shopping, etc., but may find only a small subgroup of them attractive in the sense of being more likely to respond to them.

If the normal function of DA-mediated incentive learning is to enhance the attractiveness of reward-related environmental stimuli, then persons with hyperfunctioning DA systems (schizophrenics) might be expected to be inappropriately attracted to stimuli to which they would not normally respond. For example, other individuals who normally would be viewed as relatively neutral might come to be conditioned incentive stimuli for schizophrenics, having inappropriately acquired the ability to attract. This conclusion is consistent with the results of a large number of psychological studies of schizophrenic patients as reviewed by McGhie [1977]. He concluded that schizophrenics experience a widening of attention. This has been seen in observational studies where schizophrenics frequently reported difficulty in ignoring sounds or other irrelevant environmental stimuli and in empirical studies of attention. For example, schizophrenics recognized tachistoscopically presented pictures faster than control subjects and were more easily distracted by extraneous stimuli in the performance of vigilance tasks. This apparent widening of attention in schizophrenics may be associated with inappropriate incentive learning, possibly resulting from overactive DA neurotransmission.

In an effort to more directly assess the possible effects of DA hyperfunctioning on the responses of animals to others of their own species, some researchers have examined the effects of DA agonists on the social behavior of monkeys. In general, results showed that social behavior was disrupted. For example, status-characteristic responses of dominant squirrel monkeys were no longer observed when they were given amphetamine [Miczek and Gold, 1983] and the typical pattern of care of mother vervet monkeys towards their infants was disrupted by amphetamine [Schiorring and Hecht, 1979]. Although these studies did not show a specific increase in responding to inappropriate stimuli when DA neurotransmission was enhanced, they do suggest that DA may be involved in the mechanisms underlying the maintenance of social status-characteristic behavior. Further support for this suggestion is provided by the results of Schlemmer et al. [1980]. They assessed the effects of apomorphine on the social behavior of individual stumptail macaques in a colony and found that the drug produced hypervigilance and an increase in submissive gestures. They concluded that the apomorphine-treated monkeys '... apparently perceived seemingly normal, nonthreatening situations as threatening' [p. 288]. Although these were acute studies and any generalizations to humans must be made with caution, results can be seen as consistent with the present thesis that hyperfunctioning of DA may lead to inappropriate incentive learning.

Many of the characteristic symptoms of schizophrenic disorders listed in the DSM-III [American Psychiatric Association, 1980] also can be understood with reference to inappropriate incentive learning leading to the enhanced attractiveness of stimuli that would normally remain neutral. For example, in discussing the content of thought, the DSM-III describes:

> ...Simple persecutory delusions involving the belief that others are spying on, spreading false rumors about, or planning harm to the individual are common. Delusions of reference, in which events, objects, or other people are given particular or unusual significance, usually of a negative or pejorative nature, are also common. For example, the individual may be convinced that a television commentator is mocking him (or her) [p. 182].

The consequence of inappropriate incentive learning might be that persons or objects that normally would be ignored acquire the ability to attract. For the schizophrenic, these stimuli really would have an enhanced ability to attract. The delusions of persecution or reference may reflect relatively normal cognitive processing of the information as it is represented in the brain of the schizophrenic.

Finally, if schizophrenia does result from inappropriate incentive learning, the slow therapeutic action of antipsychotic drugs can be understood. As discussed in the previous section, during incentive learning DA appears to mediate a change in the brain that is nondopaminergic. When the DA system is blocked with an antipsychotic drug, the effects of conditioned incentive stimuli can still be seen at least transiently until the DA-mediated change weakens and incentive conditioning is lost. It is particularly noteworthy that until conditioned incentive stimuli are encountered in the absence of enhanced DA neurotransmission, they may not lose their ability to attract. This might suggest that the most effective use of antipsychotic drugs would be to administer them in the presence of the environmental stimuli originally associated with the disease.

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