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Disruption of Autoshaped Responding to a Signal of Brain-Stimulation Reward by Neuroleptic Drugs

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PHILLIPS, A G., A C. McDONALD AND D M WILKIE. *Disruption of autoshaped responding to a signal of brain-stimulation reward by neuroleptic drugs* PHARMAC. BIOCHEM BEHAV. **14**(4) 543–548, 1981 —Repeated pairing of the onset of a stationary light (CS) that signalled electrical stimulation of brain-stimulation reward sites in the mesencephalon (US) resulted in autoshaped approach behavior to the CS. After acquisition of approach to the CS two groups of rats were injected with either pimozide (0.15, 0.50, or 1 0 mg/kg) or haloperidol (0 05, 0 10, or 0.15 mg/kg) prior to test sessions consisting of 30 CS-US pairings Both neuroleptic drugs caused a significant dose-related attenuation of the autoshaped CS-approach. A within-session analysis of responding after treatment with the high dose of each drug indicated that most responses occurred in the first 10 trials, a result that appears to rule out a direct effect of the drugs on sensory processes and orientation. The effect of repeated testing with pimozide (1.0 mg/kg) or haloperidol (0 15 mg/kg) was compared to three sessions with CS alone (extinction) Autoshaped CS-approaches declined gradually over the three extinction sessions, in contrast to the immediate and sustained disruption of approaching during the three drug sessions These data suggest that neuroleptic-induced suppression of autoshaped CS-approach with brain-stimulation reward cannot be attributed solely to a block of reward processes. It is suggested that neuroleptic drugs disrupt neural mechanisms by which signals of impending reward release pre-organized response patterns.

Brain-stimulation reward Autoshaping Pimozide Haloperidol Extinction Pavlovian conditioning

NEUROLEPTIC drugs such as haloperidol, pimozide and spiroperidol cause a dose-related attenuation of intracranial self-stimulation [12, 13, 16, 22, 23, 24, 38]. These effects are observed with doses that produce a selective blockade of brain dopamine (DA) receptors [1]. Accordingly, the data provide correlative evidence for the involvement of DA in brain-stimulation reward [9].

These empirical findings have been confirmed on numerous occasions over the past decade, but there has been considerable discussion as to the exact means by which neuroleptics disrupt self-stimulation behavior. General disruption of operant responding has been shown to be an important factor, especially in those studies employing continuous reinforcement schedules [8,28]. Subsequent attempts to link neuroleptic drugs with the blockade of a neural substrate of reinforcement have compared the temporal pattern of responding for brain-stimulation reward in a drugged state to that seen when reinforcement is withheld (i.e., extinction) [36]. The progressive disruption of self-stimulation behavior by neuroleptics resembles extinction [10,11] but other factors are involved as neuroleptics have been shown to summate with non-reward to produce very rapid extinction [24]. Despite difficulties in interpreting the extinction like effects of neuroleptics, several other procedures have provided convincing evidence for the blockade of a neural substrate of reward by neuroleptics. Franklin [10] has reported a reduction in the rewarding effect of brain-stimulation as revealed by a shift in the reward summation function which relates running speed to number of electrical pulses received as reward. Pimozide did not produce a proportional depression in maximum running speed, thus confirming that this procedure can be used to dissociate reward and performance effects. The temporary reinstatement of self-stimulation on presentation of a discriminative stimulus also confirms that pimozide does not prevent responding for a stimulus signalling the availability of reward [11] Further confirmation of the blockade of brain-stimulation reward by neuroleptics comes from studies that have controlled for activity changes by employing rate-free test paradigms [16,38]. Zarevik and Settler [38] have reported significant increases in current intensity thresholds for brain-stimulation reward after pimozide; but concurrent monitoring of barpress rates failed to confirm a performance effect.

Another paradigm that may provide further insight into the effect of neuroleptics on brain-stimulation reward is autoshaping. Autoshaping refers to the emergence and maintenance of a sequence of skeletal responses following repeated pairing of a conditioned stimulus (CS) such as a light, with reinforcers such as food (unconditioned stimulus, US) [6]. The skeletal responses typically are directed at the CS.

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Thus, pigeons approach and peck an illuminated key paired with food, while rats approach and press an illuminated lever paired with food. It is important to emphasize that the delivery of the reward is not contingent upon the skeletal response as is the case in operant conditioning procedures. Rather, the important element is the association of the CS with the US, as is typical in Pavlovian conditioning.

Autoshaped responding has been observed when a light was paired with brain-stimulatin at a variety of subcortical loci [19, 20, 35]. The response topography can be described as "orient-locomote towards-sniff or explore the CS" [35]. Thus a rat's autoshaped response with brain-stimulation reward differs from the more traditional operant bar press response in that there is (a) a well-defined associative element (CS–US pairing), (b) lack of response-reinforcer contingency, and (c) a different response topography.

Given these important differences, it was of interest to examine the effects of haloperidol and pimozide on autoshaped responding to a signal of brain-stimulation reward obtained from electrodes located in the DA cell groups of the ventral tegmentum and adjacent substantia nigra [9].

METHOD

Subjects

Sixteen male Wistar rats weighing 280–320 g at the time of surgery were housed individually in stainless steel cages located in a climatically controlled colony room with a 12 hr light/dark cycle Food and water were available ad lib.

Surgery and Histology

Each animal was anaesthetized with sodium pentobarbital (50 mg/kg), placed into a stereotaxic apparatus, and a small diameter (0.005 in., Plastic Products Co.) nichrome bipolar electrode was implanted chronically. The uninsulated electrode tips were aimed at DA containing cell bodies in the ventral tegmental area and substantia nigra pars compacta. The stereotaxic co-ordinates with the mouthbar located 4.2 mm below the interaural line were: anterior from stereotaxic zero = +1.3 mm; lateral = +0.8 − 2.1 mm; dorsal = +1.8 − 2.1 mm. At the completion of the experiment all subjects were sacrificed, their brains removed rapidly and stored in 10% buffered Formalin. For histological confirmation of electrode placements, each brain was frozen, sectioned at 30μ and the sections containing electrode tracts were mounted and stained with cresyl violet.

Procedure

The autoshaping procedure employed with brain-stimulation reward as the US followed the methodology of Wilkie and McDonald [35] with only slight variation. Briefly, rats were first observed in a Plexiglas chamber as they received brain-stimulation (0.5 sec 60 Hz sine wave AC) at various current intensities. The current intensity was increased gradually until the subject displayed forward locomotion and sniffing. These behaviors have been shown to correlate highly with the reinforcing effect of brain-stimulation [9] and the lowest intensity that reliably elicited these behaviors was employed throughout the experiment ($\bar{X}$ current intensity = 25 μA).

Autoshaping. Autoshaping sessions were conducted in a box (25×25×45 cm) constructed from sheet aluminum painted flat black (three sides) and Plexiglas (fourth, viewing side). A No. 313 28 V DC lamp, mounted inside a metal 35 mm film canister pierced numerous times (1 mm holes), was suspended 7.5 cm above the floor, touching one side of the box. This box was housed in a dimly illuminated, ventilated outer chamber with a viewing port in the door.

An autoshaped CS-approach response was defined as orienting to and locomotion towards the light CS. Inter-observer agreement on this measure was 100% when tested by viewing films of a session for three animals [35]. Autoshaping trials occurred during daily test sessions, consisting of 30 CS–US pairings, separated by an intertrial interval averaging 60 sec. On each trial, the CS was illuminated 5 sec prior to the US and terminated with US offset 5 sec later. Brain-stimulation was delivered 5 sec before the offset of the 10 sec CS, and consisted of five 0.5 sec trains with 0.5 sec intertrain interval. During the acquisition phase, each rat received 300 trials. All 16 subjects displayed reliable autoshaping (i.e., approached CS on a high percentage of trials) and subsequently acquired a nose poke response for brain-stimulation reward (see [35]) following pharmacological tests.

Effect of pimozide and haloperidol Seven animals were employed in the experiment with pimozide and the remaining nine subjects were assigned to the haloperidol study Each rat received 30 autoshaping trials five days each week. The subjects received one vehicle and one drug test each week. Pimozide was prepared by dissolving the drug in hot tartaric acid (1:6) which was then cooled and each of three doses (0.15, 0.5, 1.0 mg/kg) was injected intraperitoneally (IP) 3 hours prior to the 30 standard CS–US presentations Three doses of haloperidol (0.05, 0.1, 0.15 mg/kg) were injected IP, 45 min before each test session. These post-injection intervals were selected to ensure near maximal pharmacological effects during the behavioral tests [15]. The sequence in which each dose was presented was randomized across subjects. Each dose was prepared fresh and given once to each rat.

Comparison of extinction and repeated drug treatment. Following the initial treatments with pimozide or haloperidol, each group received several additional daily sessions to ensure stable autoshaped responding prior to 3 consecutive days of 30 trials of CS alone (extinction) or 3 days (30 trials per day) of repeated drug injections (1.0 mg/kg pimozide (N=7); 0.15 mg/kg haloperidol (N=5)). The intervals between injections and testing were the same as those described above. Half of the subjects in each drug condition received extinction tests first, the converse sequence was used for the remaining subjects. Additional tests with CS-US pairing were imposed between the two experimental treatments to ensure stable baseline performance

RESULTS

Acquisition of Autoshaped Responding

Each of the 16 subjects readily acquired an autoshaped approach response to the canister which was illuminated for the 5 sec preceding US onset. Sniffing often was observed during the orienting and approach response. As may be seen in Fig. 1, the group displayed approach behavior on an average of 72.8% of the first 30 trials and approached the CS on 91% of trials 120–150. When tested subsequently with CS alone for 3 consecutive days, the mean number of approach responses fell to 63% on the first day, 49.6% on day 2, and had reached 35% by the third extinction session. The mean

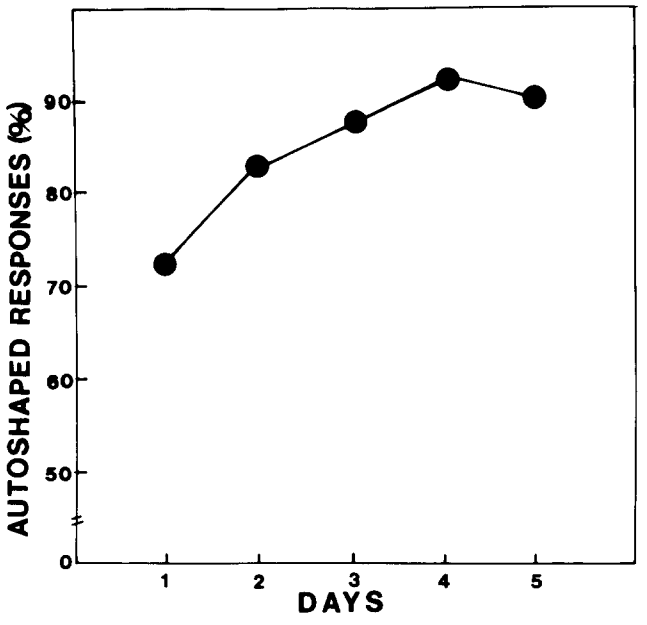

FIG. 1 Acquisition of autoshaped 'orient-approach-sniff' response to a light-onset CS paired with electrical stimulation (US) of sites in the ventral tegmentum and substantia nigra

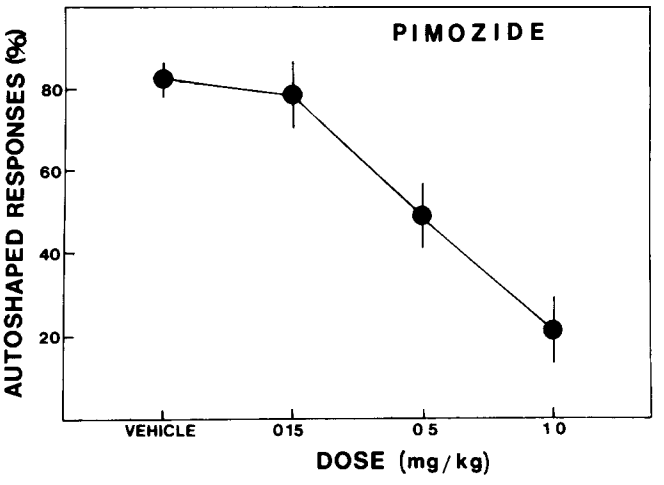

FIG. 2. Effect of pimozide (0 15, 0.5, 1.0 mg/kg) on autoshaped responding to a light-onset CS paired with electrical stimulation of sites in the ventral tegmentum and substantia nigra

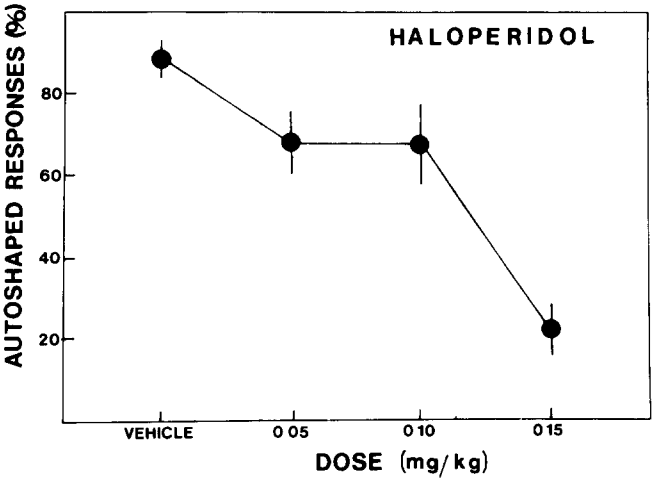

FIG. 3. Effect of haloperidol (0.05, 0 10, 0.15 mg/kg) on autoshaped responding to a light-onset CS paired with electrical stimulation of sites in the ventral tegmentum and substantia nigra.

number of autoshaped responses after vehicle injections did not differ significantly from no-drug control scores.

Pimozide Test

As may be seen in Fig. 2, pimozide injections caused a dose-related attenuation of autoshaped approach to signals of brain-stimulation reward. This was confirmed statistically by a repeated measures ANOVA, $F(3,18)=47.02$, $p<0.001$. Post-hoc t-tests indicated significant differences ($p<0.01$) between vehicle, 0.5 mg/kg and 1.0 mg/kg. The two higher doses differed significantly from each other and from the lower dose (0.15 mg/kg).

Haloperidol Tests

Treatment with haloperidol also produced a significant reduction in approach responses to a light CS paired with electrical brain-stimulation, $F(3,24)=39.45$, $p<0.01$. Post-hoc tests revealed significant differences ($p<0.02$) between vehicle and each dose of haloperidol. The scores obtained after 0.05 mg/kg and 0.10 mg/kg haloperidol did not differ significantly but both were significantly higher than those recorded after 0.15 mg/kg (see Fig. 3).

Comparison of Extinction and Repeated Drug Treatment

Presentation of the CS alone to each group was accompanied by a significant reduction in CS-approach responses across the daily test sessions, $F(3,18)=21.95$, $p<0.01$; $F(3,12)=87.75$, $p<0.01$, for the pimozide and haloperidol groups, respectively. A significant reduction in CS approaches also was recorded after 3 consecutive daily treatments with a dose of 1.0 mg/kg pimozide, $F(3,12)=76.34$, $p<0.01$, or 0.15 mg/kg haloperidol, $F(3,18)=100.10$, $p<0.01$. A 2-way ANOVA also revealed a significant interaction between treatment (extinction or drug) and days, for each drug groups, $F(3,18)=9.80$, $p<0.01$; $F(3,12)=6.84$, $p<0.01$, for pimozide and haloperidol groups, respectively. These data reflect the rapid decline to stable but low approach scores following the repeated drug tests, as compared to the more gradual attenuation across extinction sessions (see Fig. 4).

In order to determine whether the drug-induced disruption of autoshaped responding reflected a general and immediate disruption of sensory-motor function or a more gradual process, the data from the first of the 3 sessions with pimozide (1.0 mg/kg) or haloperidol (0.15 mg/kg) were analyzed across blocks of 5 trials. As shown in Fig. 5, both groups responded at the highest levels during the first or second block

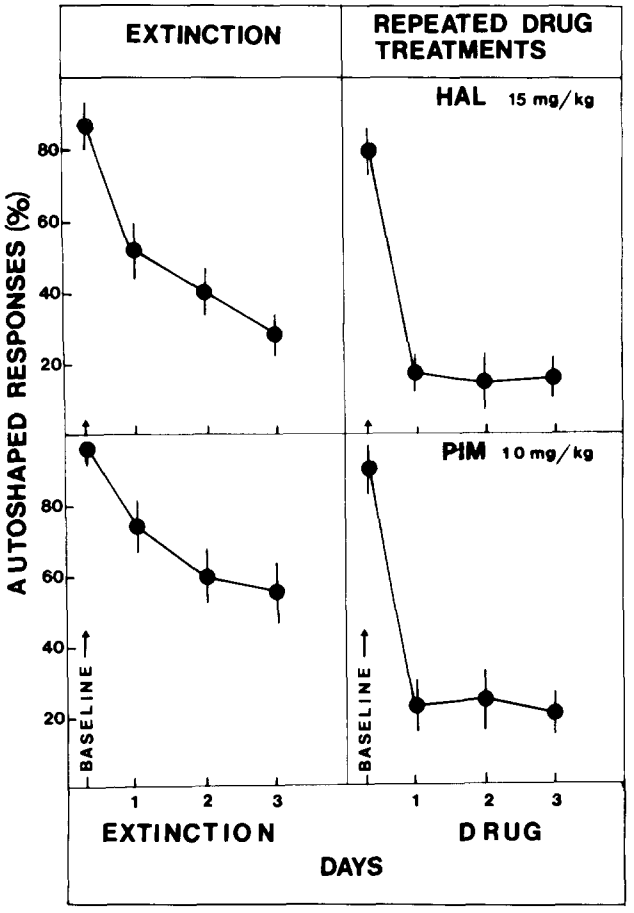

FIG 4 Comparison of decline in autoshaped responses over three sessions with CS alone (extinction) or three sessions of CS–US pairing after treatment with haloperidol (0 15 mg/kg) or pimozide (1 0 mg/kg)

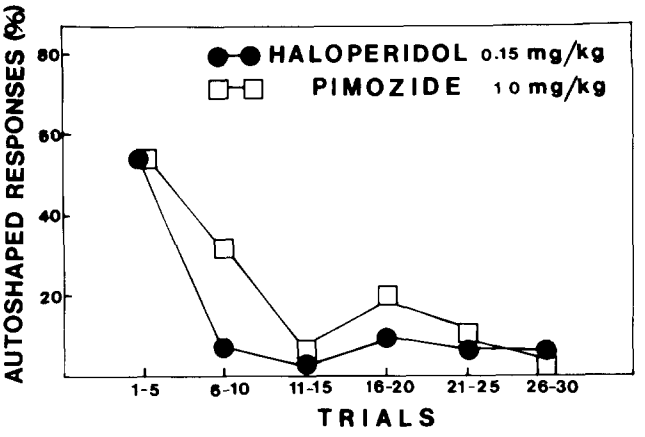

FIG. 5 Disruption of autoshaped responding over blocks of 5 trials in a 30 trial test session after treatment with 0.15 mg/kg haloperidol

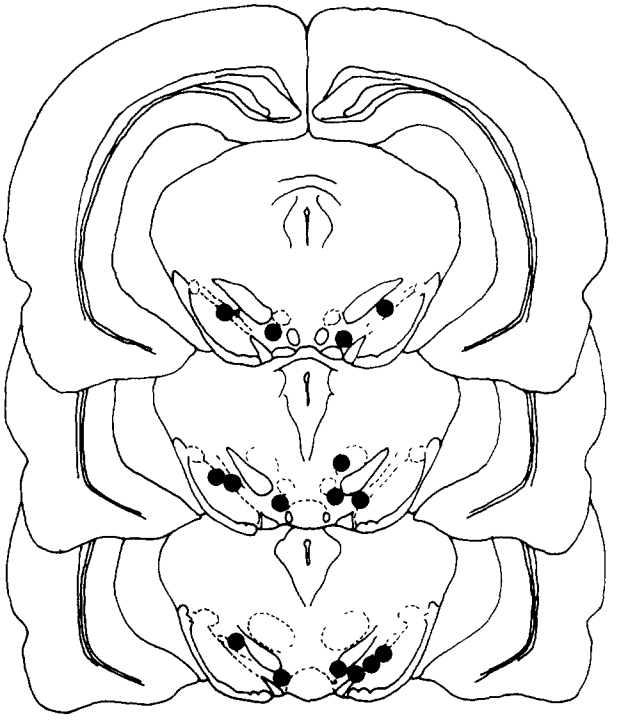

FIG 6 Location of electrode tips in the ventral tegmental area and substantia nigra

Histology

The electrode placements as depicted in Fig. 6 were all located within or immediately adjacent to the dopamine cell layer in the ventral tegmentum and adjacent substantia nigra.

DISCUSSION

The present results confirm previous reports of autoshaped responding in the rat with brain-stimulation reward as the US [19, 20, 35] and furthermore provide a clear demonstration of the disruption of this type of responding by pretreatment with the neuroleptic drugs pimozide and haloperidol. These drugs are known to disrupt operant responding for brain-stimulation reward [12, 13, 16, 22, 23, 27] and to increase current intensity thresholds [38]. The latter finding is particularly important as it provides evidence for drug-induced attenuation of brain-stimulation reward in a paradigm that is relatively independent of changes in performance. In this context, the present results take on added significance by showing that neuroleptics also disrupt a relatively simple 'orient and approach' response to a CS paired with brain-stimulation reward.

Dopamine systems have been implicated in sensory-motor neglect [16] and therefore the disruption of an autoshaped response by a neuroleptic drug may simply reflect a disturbance in the orienting response to a brief light CS. This explanation would appear to be ruled out by the fact that all subjects displayed CS-approach during the early trials of a drug session (see Fig. 5), despite the fact that a sufficient post-injection interval had elapsed to ensure maximal pharmacological effects of both pimozide and haloperidol [15]. Previous experiments also have confirmed, in a wide variety

of tests, that neuroleptic drugs do not interfere with sensory-sensory associations [1, 4, 5, 26]. The possibility remains, however, that the drug produced a slight sensory-motor impairment which in turn interacted with a reduction in reinforcement to produce suppression of the approach response.

The most parsimonious explanation for the observed dose-related attenuation of autoshaped responding by pimozide and haloperidol is the blockade of dopaminergic substrates of brain-stimulation reward. It has been suggested that neuroleptic drugs block the reward value of a variety of incentive stimuli including food and electrical brain-stimulation and that the ensuing decline in responding resembles an extinction curve [36]. However, several recent studies have shown that the disruption of reinforced responding by neuroleptics bears only a superficial resemblance to extinction [18, 24, 30, 31]. A similar discrepancy between these two processes was observed in the present study. When undrugged animals were presented with the CS alone, approach responses to the CS declined gradually In contrast, drugged animals presented with regular pairing of CS-brain-stimulation reward displayed a rapid attenuation of CS-approach behavior. These data do not rule out blockade of a dopaminergic substrate of brain-stimulation reward as one effect of neuroleptic drugs, but they do serve to emphasize the involvement of other important factors.

Theoretical Implications

It remains a distinct possibility that the pharmacological blockade of brain DA receptors interferes with a neural process that underlies autoshaped responding. Given the well established relationship between DA neurons and brain-stimulation reward [9], a more complete understanding of the origin of autoshaped responses may provide further insight into the nature of brain-stimulation reward. Woodruff and Williams [37] have presented a convincing argument for a "learned-release" hypothesis of autoshaping. The main tenet of this hypothesis is the release of pre-patterned species-specific responses by signals of impending reinforcers. These species-specific responses are described as "preparatory" because they are organized to ensure effective contact with the reinforcer. Also, these responses are released by incentive stimuli that precede contact with the reinforcing stimulus. A careful analysis of the topography of autoshaped responses has confirmed a close resemblance to biologically pre-organized behavior patterns that prepare the organism to obtain a specific reinforcer [33,37]. Consequently, it is suggested that "the origin of autoshaped 'preparatory' responses lies in the selection and instigation of components of the organism's species-specific behavior repertoire by associative learning factors" ([37], p. 13).

Several lines of evidence point to an important role for DA in the initiation of preorganized patterns of species-specific behavior Neurotoxic lesions of the ascending DA pathways disrupt consumatory behavior elicited by electrical brain-stimulation [23,29] and tail-pinch [3,29]. Similar effects are observed after treatment with neuroleptic drugs [3,25]. Conceivably, the integrity of one or more of these DA pathways also is essential for the release of species-specific autoshaped responses by conditioned stimuli. In this context, it has been suggested that the reward produced by electrical stimulation of DA neurons is related to activation of a motivation system whose normal function is to serve as an interface between incentive stimuli and appropriate patterns of motor behavior [21]. This formulation stresses the relation between dopaminergic activity and the anticipation of reward and therefore stands in contrast to hypotheses that emphasize a role for DA neurons in ascribing hedonic value to primary reinforcing stimuli (i.e., [36]). As such, the present proposal is compatible with those theories that claim reinforcement to be synonomous with the facilitation of patterns of motor activity essential for survival [14,32].

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