Nucleus accumbens dopamine and rate of responding: Neurochemical and behavioral studies

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It has been suggested that accumbens dopamine (DA) is involved in the process of enabling organisms to expend energy in various situations, including foraging, maze running, and leverpressing. Although accumbens DA depletions impair stimulant self-administration, the effects of these depletions on various food-reinforced operant schedules are highly variable. Accumbens DA depletions have little or no effect on total response output in rats responding on the simplest schedule of food reinforcement (i.e., the fixed ratio 1). In addition, it has been shown clearly that the effects of accumbens DA depletions do not resemble the effects of extinction or prefeeding to reduce food motivation. Over the last several years, our laboratory has investigated the effects of accumbens DA depletions on several schedules, including fixed ratio 1, variable interval 30 sec, fixed interval 30 sec, progressive ratio, and fixed ratio 4, 5, 16, and 64. These schedules generate very different rates of responding, ranging from 300 to 3,000 responses per 30 min. Regression analyses of all these studies indicates a significant linear relation between control rates of responding and the degree of suppression of responding produced by accumbens DA depletions. Schedules that generate relatively low response rates, such as fixed ratio 1 or variable interval 30 sec, are little affected by accumbens DA depletions, yet schedules that generate high response rates (e.g., fixed ratio 64) are severely disrupted. Prefeeding shows different patterns of suppression as a function of response rate. Microanalysis of the temporal characteristics of leverpressing has shown that accumbens DA depletions produce a response slowing, as measured by the interresponse time; extinction and prefeeding produce a different pattern of effects. These results indicate that accumbens DA depletions do not blunt the reinforcing effects of food, but do suppress responding in a rate-dependent manner. In addition, microdialysis studies have shown that accumbens DA release is positively correlated with leverpressing response rate. Accumbens DA appears to be involved in energy expenditure, behavioral activation, or maintenance of high local rates of responding, which are functions that represent an area of overlap between motor and motivational processes.

For the last several years, research into the behavioral functions of the nucleus accumbens has been one of the most intense and hotly debated areas in behavioral neuroscience. Although neuroscience has not generally been a theoretically rich area since its inception, research into the functions of the nucleus accumbens has been an exception. The nucleus accumbens has been referred to as a crucial part of the reward circuit, as a limbic-motor interface, as part of the brain's energy regulating mechanism, and as a cognitive pattern generator. This structure has been considered to be involved in aspects of motor function, motivation, emotion, and cognition. Reports on the nucleus accumbens will often mention some of the terms and concepts from psychological learning theory, perhaps more commonly than behavioral psychology itself. The large number of studies, and the varied theoretical landscape, has made this a complex and fascinating area of research.

The purpose of this review is not to provide a broad survey of all areas of research on the nucleus accumbens; such a task would require a large monograph, and even then it would be incomplete. Rather, this article is intended to provide a summary of the research from our laboratory on the behavioral effect of accumbens dopamine (DA) depletions. Specifically, the pages that follow will focus on the effects of accumbens DA depletions on various food-related instrumental tasks. This work was undertaken partly because of the hypothesized involvement of accumbens DA in "reward" or "reinforcement" processes. Although the vast majority of studies on the purported "reward" functions of DA have focused on self-administration and the effects of drugs of abuse (e.g., Bozarth & Wise, 1981), it should be emphasized that a critical part of the DA/reward hypothesis is that accumbens DA mediates the reinforcing properties of natural stimuli, such as sex and food (Hernandez & Hoebel, 1988; Smith, 1995; Wise, 1982, 1985; Wise, Spindler, DeWit, & Gerber, 1978). Indeed, according to what has been described as the *general anhedonia model* (see Salamone, Cousins, & Snyder, 1997), a major tenet of the DA/reward hypothesis is that a natural reward system evolved to mediate reinforcement processes with regard to natural reinforcers, and that this same system is activated by drugs of abuse.

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The DA hypothesis of reward, though ubiquitous in textbooks and omnipresent in the popular press, has not achieved general assent. As described below, there are numerous empirical and conceptual difficulties with the DA hypothesis of reward. In fact, these problems are so many and varied that they are beyond the scope of this review, and the reader should consult other articles to obtain a more complete picture (Berridge, 1996; Salamone, 1987, 1991, 1992, 1994; Salamone et al., 1997). Thus, after a description of some of the research on accumbens DA depletions, and a critical evaluation of the hypothesis that accumbens DA depletions mediate food reward, the present review will focus on alternative hypotheses for the behavioral functions of accumbens DA generated from work conducted by our laboratory.

Effects of Accumbens DA Depletions on Instrumental Leverpressing

Perhaps the most salient feature of the literature on the effects of accumbens DA depletions on leverpressing is that the results of the depletion depend greatly on the particular schedule of reinforcement being used. In fact, for many schedules, the most obvious thing to report is that substantial DA depletions have little effect on operant responding at all. In two studies, the effects of accumbens DA depletions on continuously reinforced responding were assessed. The major effect of accumbens DA depletions was an initial slowing of responding during the first few minutes of the test session, which was only evident for a few days of postsurgical testing (McCullough, Cousins, & Salamone, 1993; Salamone, Kurth, McCullough, & Sokolowski, 1995). Another result of the DA depletions was a slowing of the distribution of inter-response times (IRTs; Salamone et al., 1995); this particular result will be discussed in greater detail below. Yet despite the effects on response patterning that were observed, it should be emphasized that global measures of response output on the continuous schedule were basically unaffected by accumbens DA depletions (see also Aberman & Salamone, 1999). These findings are important in view of the fact that this schedule represents the most fundamental schedule of primary, positive reinforcement.

Interval schedules also have been investigated. Sokolowski and Salamone (1998) injected 6-hydroxydopamine (6-OHDA) into either the core or the shell of the nucleus accumbens in animals trained to respond on a variable interval 30-sec (VI 30) schedule. Neither core nor shell DA depletions had any significant effect on VI 30 leverpressing. Another recent study compared the effects of nucleus accumbens DA depletions with those of DA depletions in ventrolateral striatum (VLS). In that study, responding on a fixed interval 30-sec (FI 30) schedule was substantially affected by VLS DA depletions, whereas accumbens DA depletions had only a modest suppressive effect on leverpressing (Cousins, Trevitt, Atherton, & Salamone, 1999). Although rats with accumbens DA depletions exhibited leverpressing levels that were signifi-

cantly lower than those shown by control animals, rats with accumbens DA depletions demonstrated significantly higher levels of responding than did rats with VLS DA depletions.

Ratio schedules have been used in several recent experiments to investigate the effects of accumbens DA depletions. In another study, a fixed ratio 5 (FR 5) schedule was employed to compare the effects of accumbens and VLS DA depletions (Salamone, Kurth, McCullough, Sokolowski, & Cousins, 1993). As with the experiment reviewed above, VLS DA depletions produced severe impairments in FR 5 leverpressing. Accumbens DA depletions did significantly reduce FR 5 leverpressing compared to controls, although rats with accumbens depletions had significantly higher levels of responding than did rats with VLS depletions. In addition, the deficit in total number of responses shown by rats with accumbens DA depletions was only significant during the first week of postsurgical testing. Similar to what was shown with the continuous schedule, analysis of the IRT distributions showed that accumbens DA depletions produced a slowing of the local rate of responding (see below). Sokolowski and Salamone (1998) also used the FR 5 schedule to study the effects of core and shell injections of 6-OHDA. Although shell injections of 6-OHDA had no significant effects on FR 5 responding, injections into the accumbens core site suppressed FR 5 responding and altered the IRT distribution. In a recent study (Aberman & Salamone, 1999), the effects of accumbens DA depletions were assessed with the use of four schedules: FR 1, FR 4, FR 16, and FR 64. Rats with accumbens DA depletions showed behavioral deficits that were highly dependent on the FR value; there were no effects of DA depletions on FR 1 leverpressing, but with larger ratio values, the impairment was much greater. Accumbens DA depletions appear to be facilitating an effect known as "ratio strain." Normally, response rates are higher at larger FR values than at smaller FR values. At some point, the ratio value is too large, and rats decrease responding (Staddon & Ettinger, 1989). In the Aberman and Salamone (1999) study, accumbens DA depletions altered the functional relation between ratio value and response rate, effectively increasing the response-suppressing effects of large ratio values.

Another line of investigation has been to study the behavior of rats tested in choice procedures, in which there are alternative paths to reinforcement that involve different instrumental response requirements. The primary behavioral procedure that has been used was one in which rats have a choice of pressing a lever on an FR 5 schedule to receive a more preferred food (Bioserve pellets), or of simply feeding on a less preferred food (lab chow) that is freely available in the operant chamber (i.e., concurrent FR 5/feeding task; Salamone et al., 1991). Untreated rats will work for the preferred food by leverpressing and will consume very little of the freely available but less preferred lab chow. Systemic or intra-accumbens administration of the DA antagonist haloperidol decreased

leverpressing for food but increased lab chow consumption. Haloperidol was shown not to alter food preference in free-feeding choice tests, and the effects of haloperidol did not resemble the effects of prefeeding to reduce food motivation. Systemic administration of DA antagonists with different receptor subtype specificities (i.e., haloperidol, *cis*-flupenthixol, SCH 23390, SKF 83566) were all shown to decrease leverpressing and increase chow consumption substantially (Cousins, Wei, & Salamone, 1994; Salamone, unpublished observations). Considerable research indicated that the nucleus accumbens is the critical brain locus at which DA antagonism or DA depletions decrease leverpressing and increase chow consumption in the concurrent FR 5/feeding task (Cousins & Salamone, 1994; Cousins, Sokolowski, & Salamone, 1993; Salamone et al., 1991). Injections of 6-OHDA into the nucleus accumbens core significantly decreased leverpressing for food pellets, increased lab chow consumption, and decreased the relative amount of food obtained by leverpressing (Sokolowski & Salamone, 1998). Dorsomedial shell injections of 6-OHDA had no significant effects on either leverpressing or lab chow consumption. Accumbens DA depletions also produced similar effects in a T-maze version of the cost/benefit procedure. In this task, rats were given a choice between an arm with a 44-cm barrier that contained four food pellets and an arm with no barrier that contained two food pellets. Rats with accumbens DA depletions shifted their choice from the arm that had a high barrier and a high density of food reinforcement and instead chose the arm of the maze with no barrier but with a lower density of food reinforcement (Cousins, Atherton, Turner, & Salamone, 1996; Salamone, Cousins, & Bucher, 1994; for review see Salamone et al., 1997). Thus, rats with accumbens DA depletions showed dramatic shifts away from leverpressing or barrier crossing and instead selected less preferred or lower density food sources if they had a lower work requirement. The T-maze results also indicate that the DA antagonist- or DA-depletion-induced shift in responding away from FR 5 responding in the concurrent FR 5/feeding procedure is not merely an artifact of using leverpressing and does not simply involve a shift away from an "instrumental" response to a "consummatory" response.

It should be stressed that these deficits did not occur because of obvious, gross or debilitating motor impairments. In one study, we compared the effects of accumbens DA depletions on the FR 5/chow feeding task with effects on the FR 5 schedule alone, without chow present (Cousins & Salamone, 1994). On days when chow was not present, FR 5 responding was only mildly affected by accumbens DA depletions; there was no significant overall response deficit in DA-depleted rats, although the more severely depleted rats showed slight reductions in responding. Nevertheless, on alternate days, when chow was available in the chamber during the operant session, DA depleted rats showed a substantial decrease in FR 5 leverpressing and a concomitant increase in chow consumption. Similar results were obtained with

the T-maze task. Accumbens DA depletions did not affect the choice of the arm with the barrier if the other arm in the maze did not contain food; the shift in responding occurred only if the arm without the barrier contained food (Cousins et al., 1996). Thus, although accumbens DA depletions may have been producing subtle motor impairments that were not directly measured, it does appear as though DA depletions caused shifts in choice behavior on the concurrent FR 5/feeding and T-maze tasks that were not simply due to an absolute ceiling on response output.

Accumbens DA Depletions Do Not Produce "Anhedonia" or Block Primary Food Reward

As noted above, one of the most popular notions in behavioral neuroscience has been that DA, particularly in the nucleus accumbens, mediates the reinforcing impact of stimuli such as food, water, sex, and drugs of abuse. Indeed, in a recent review article, Smith (1995) claimed that the DA hypothesis of reward had been "proved." Yet despite the popularity of this hypothesis, there are enormous difficulties with the idea that accumbens DA mediates the primary reinforcing characteristics of natural stimuli such as food (see Salamone et al., 1997). A full review of this area is beyond the scope of the present work, but several lines of research should be discussed briefly. Although it is often stated that accumbens DA depletions affect "reward" because they blunt stimulant self-administration, it should be emphasized that depletions of accumbens DA that have severely affected cocaine self-administration had little effect on food-reinforced responding (Caine & Koob, 1994; Roberts, Corcoran, & Fibiger, 1977). Although Smith (1995; see also Schneider, Sikorsky, Rauhofer, Davis, & Smith, 1992; Schneider, Sikorsky, Rauhofer, & Smith, 1993) emphasized that sucrose consumption can be affected by intra-accumbens injections of DA antagonists, there are numerous problems with these studies. Very high doses (i.e., nearly systemic doses) of SCH 23390 and raclopride were injected directly into the accumbens, so the anatomical specificity of the drug injections is questionable. Although Smith argued that the fact that the local lick frequency is not affected by intracranial DA antagonists proves that there is no motor effect being produced, such an argument is extremely spurious. In fact, the local lick frequency is set by brainstem pattern generators rather than the basal ganglia, and this frequency is not affected by even cataleptogenic doses of DA antagonists (Fowler & Das, 1994). Other motor parameters are affected by systemic and intra-accumbens DA antagonists, including lick efficiency, lick duration, lick force, lap volume, and tongue extension (Fowler & Das, 1994; Fowler & Mortell, 1992; Gramling & Fowler, 1985; Hsiao & Smith, 1995; Jones & Mogenson, 1979).

Fundamental aspects of food reinforcement and food motivation are intact after interference with accumbens DA transmission. Appetitive taste reactivity to sucrose is unaffected by accumbens DA depletions (Berridge, 1996; Berridge & Robinson, 1998). As noted by Ber-

ridge and Robinson (1998, p. 309), "dopamine systems are not needed either to mediate the hedonic pleasure of reinforcers or to mediate predictive associations involved in hedonic reward learning." Accumbens DA depletions did not affect the discrimination of reinforcement magnitude, and failed to alter response selection based on reinforcement magnitude, in a food-reinforced T-maze task (Cousins et al., 1996; Salamone, Cousins, & Bucher, 1994). Several lines of evidence indicate that accumbens DA depletions do not generally suppress appetite. It has been reported that accumbens DA depletions or intra-accumbens injections of DA antagonists do not affect food intake (Bakshi & Kelley, 1991; Koob, Riley, Smith, & Robbins, 1978; Salamone, Mahan, & Rogers, 1993). Accumbens DA depletions have little or no effect upon the total amount of food obtained by FR 1 leverpressing (Aberman & Salamone, 1999; McCullough, Cousins, & Salamone, 1993; Salamone et al., 1995). Although accumbens DA depletions did produce effects on response patterning (i.e., initial reductions of response rate early in the session, and slowing of the interresponse time distribution), these effects did not resemble those of extinction (McCullough, Cousins, & Salamone, 1993; Salamone et al., 1995). Indeed, the presumed relation between extinction and interference with DA systems appears to be a gross oversimplification; as emphasized in a recent review (Salamone et al., 1997), several articles have shown that, on closer examination, DA antagonists and DA depletions produce effects that are distinct from those of extinction (Asin & Fibiger, 1984; Ettenberg & Carlisle, 1985; Evenden & Robbins, 1983; Faustman & Fowler, 1981, 1982; Gramling, Fowler, & Collins, 1984; Gramling, Fowler, & Tizzano, 1987; Mason, Beninger, Fibiger, & Phillips, 1980; McCullough, Cousins, & Salamone, 1993; Phillips & Fibiger, 1979; Salamone, 1986; Salamone et al., 1995; Spivak & Amit, 1986; Tombaugh, Anisman, & Tombaugh, 1980; Tombaugh, Szostak, & Mills, 1983; Tombaugh, Szostak, Voorneveld, & Tombaugh, 1982; Willner, Chawala, Sampson, Sophokleous, & Muscat, 1988; Wirtschafter & Asin, 1985).

As noted above, with rats on a concurrent FR 5/chow-feeding schedule, accumbens DA depletions or intra-accumbens injections of haloperidol decreased leverpressing but *increased* chow consumption (Cousins & Salamone, 1994; Cousins et al., 1993; Salamone et al., 1991; Sokolowski & Salamone, 1998). Thus, it seems untenable to maintain that accumbens DA depletions suppress leverpressing on some schedules because they produce a general reduction in food motivation. In fact, prefeeding to reduce food motivation was shown to suppress both leverpressing and chow consumption on the concurrent leverpressing/chow-feeding task (Salamone et al., 1991). As previously described, the effects of accumbens DA depletions do not closely resemble the effects of extinction. In this context, it is worth emphasizing that the effects of accumbens DA depletions also bear little resemblance to the effects of prefeeding. In a recent study, Aberman and Salamone (1999) employed

FR schedules with various ratio requirements (FR 1, FR 4, FR 16, FR 64) and observed that the effects of accumbens DA depletions were determined by the schedule; there was no significant effect of accumbens DA depletions on FR 1 responding, and as ratio value increased, accumbens DA depletions caused greater suppression of responding. In a second experiment, they studied the effects of prefeeding to reduce food motivation. Prefeeding for 24 h suppressed leverpressing on all four schedules tested, including the FR 1 schedule. Across all schedules, if data are expressed as a percent of control responding, prefeeding suppressed responding by approximately 50%–60%. Thus, it can hardly be argued that the effects of accumbens DA depletions closely resemble the effects of prefeeding (see also Figures 2 and 4, below).

In summary, several lines of evidence indicate that rats with accumbens DA depletions remain directed toward the acquisition and consumption of food, provided that the work requirement is relatively low. Several studies have shown that the effects of accumbens DA depletions do not resemble those of either extinction or prefeeding. Numerous papers have reported that fundamental aspects of food motivation are left intact after systemic DA antagonists or accumbens DA depletions (Berridge, 1996; Cousins, Sokolowski, & Salamone, 1993; Koob et al., 1978; McFarland & Ettenberg, 1998; Salamone, 1986, 1992, 1994; Salamone, Cousins, & Bucher, 1994; Salamone et al., 1997; Salamone et al., 1991). Although behavioral researchers disagree about the precise nature of the reinforcement process, an enormous body of behavioral research and theory emphasizes that motivation is a critical aspect of primary reinforcement (Bindra, 1978; Dickinson & Balleine, 1994; Nader, Bechara, & van der Kooy, 1997; Thorndike, 1911; Timberlake, 1993; Timberlake & Allison, 1974; see reviews by Salamone, 1992, and Salamone et al., 1997, for a much more detailed discussion of this issue). The fundamental property of reinforcers to elicit approach responses is sometimes referred to as the unconditioned rewarding or reinforcing property of a stimulus (see, e.g., Stefurak & van der Kooy, 1994). Thus, taking several lines of investigation into account, the preponderance of evidence indicates that accumbens DA depletions do not interfere with the primary or unconditioned reinforcing properties of food.

Effects of Accumbens DA Depletions: Importance of Baseline Response Rate

As described above, the effects of accumbens DA depletions on food-reinforced leverpressing depend markedly on the nature of the task being assessed. Leverpressing on some schedules (e.g., FR 1, VI 30) is relatively unaffected by accumbens DA depletions, whereas other schedules (e.g. FR 64) appear to be highly sensitive to the loss of accumbens DA. Studies with the concurrent FR 5/feeding procedure indicate that interference with accumbens DA, either by DA depletions or local injections of DA antagonists, affects the relative allocation of instrumental responses with different kinetic requirements.

For several reasons, which have been reviewed above, it does not appear that this pattern of effects is consistent with the DA hypothesis of reward. We have put forth an alternative hypothesis: Rats with accumbens DA depletions are very sensitive to the kinetic requirements of the instrumental response being performed. In particular, we, as well as others, have argued that accumbens DA depletions reduce the propensity for expending energy or exerting effort (Cousins & Salamone, 1994; Neill & Justice, 1981; Salamone, 1987, 1988, 1991, 1992; Salamone, Cousins, & Bucher, 1994; Salamone et al., 1997; Szechtman, Talangbayan, Ganaran, Dai, & Eilam, 1994; see also Hsiao & Chen, 1995).

An important manifestation of this hypothesis is that instrumental tasks characterized by a high work output should be more greatly affected by accumbens DA depletions than tasks with a low work output. Indeed, this idea can explain the variability in the effects of accumbens

DA depletions across different operant schedules. Schedules that generate only 300–600 responses per 30 min (e.g., CRF, fixed and variable interval 30 sec) show little or no effect after accumbens DA depletions (Cousins et al., 1999; McCullough, Cousins, & Salamone, 1993; Salamone et al., 1995; Sokolowski & Salamone, 1998). Schedules that generate moderately high rates (e.g. FR 5, FR 16, progressive ratio) are substantially impaired by accumbens DA depletions (Aberman, Ward, & Salamone, 1998; Hamill, Trevitt, Nowend, Carlson, & Salamone, 1999; Salamone, Kurth, et al., 1993), and schedules generating very high rates (e.g., FR 64) are severely impaired (Aberman & Salamone, 1999).

To illustrate this principle, we have constructed a figure relating the extent of impairment induced by accumbens DA depletions to the baseline rates of responding generated by each schedule (Figure 1). This figure includes data from several separate studies from this labo-

Figure 1. Scatterplot showing the relation between baseline response rate per 30 min (i.e., responding in the vehicle-treated control group) and suppression of responding shown in rats with accumbens DA depletions. Data in this figure are taken from several different studies (i.e., each point represents a separate study; schedule shown on the figure). Line represents least squares regression line, which significantly fits these data [$y = -0.03x + 98.385$; $r^2 = .892$; $F(1,7) = 57.6$, $p < .001$]. The data show a monotonic relation between response rate and the suppressive effects of DA depletions. For schedules in which the baseline response rate is higher, the suppressive effects of accumbens DA depletions are much greater. Although a linear relation is illustrated, it is not clear whether other mathematical relations would also fit the data.

ratory. The FR 1 data are from Aberman and Salamone (1999), and data on FI 30 performance are from Cousins et al. (1999), and the progressive ratio data are from Hamill et al. (1999). Aberman and Salamone (1999) studied FR 4, FR 16, and FR 64 schedules. As is shown in Figure 1, there is a linear relation between the baseline rate of responding generated by a schedule and the degree to which that schedule can be suppressed by accumbens DA depletions. Higher baseline rates are associated with greater suppression by accumbens DA depletions, whereas lower baseline rates are associated with little or no suppressive effects. To emphasize that this precise relation is specific to the effects of accumbens DA depletions, Figure 2 shows an additional line for the effects of prefeeding (data from Aberman & Salamone, 1999). Although prefeeding also suppresses responding, it does so in a manner substantially different from that of accumbens DA depletions. Examination of these two sets of data clearly demonstrates that accumbens DA depletions produce effects quite distinct from those produced by prefeeding, and also that the effects of accumbens DA depletions depend highly on the baseline rate generated by the schedule.

The relations depicted in Figures 1 and 2 also serve to rebut another point often raised by proponents of the an-

hedonia hypothesis. It is sometimes claimed that the motor effects of interfering with DA systems "mask" the hypothesized reward deficits, because these motor effects are added on top of the supposed reward effects of DA depletion. A detailed examination of Figures 1–2 would not support that. Accumbens DA depletions do not simply produce severe motor impairments that more greatly affect responding than the "subtle" motivational effects would do. Accumbens DA depletions produce *more* of a suppressive effect than prefeeding does on high-rate schedules, but actually produce *less* of an effect than prefeeding does on low-rate schedules. The FR 1 schedule, which is the most fundamental example of a simple, continuous, primary reinforced task, is greatly affected by prefeeding but is little altered by accumbens DA depletions.

Effects of Accumbens DA Depletions: Microstructure of Operant Responding

In presenting results of operant experiments, the most common datum depicted is typically the average rate of responding over large units of time. For example, in the discussion above, response rates were referred to in terms like "300 responses per 30 min." Over the last few years, it has become more common to analyze the temporal microstructure of operant responding. Parameters such as

Figure 2. Relation between baseline response rate per 30 min (i.e., responding in the control condition) and suppression of responding shown in rats that were prefed for 24 h (squares). Prefeeding data are from Aberman and Salamone (1999). Line represents least squares regression line. Data from Figure 1, for DA-depleted rats, also are shown (circles). It can be seen that the relation between baseline responding and suppression of responding is substantially different in prefed animals than in DA-depleted ones.

response duration and response initiation have been determined with detailed computerized analyses of leverpressing, and such analyses have been useful for characterizing the effects of various drugs and brain lesions, including DA depletions (Carriero et al., 1998; Carriero, Outslay, Mayorga, Gianutsos, & Salamone, 1997; Cousins & Salamone, 1996, 1997; Faustman & Fowler, 1981, 1982; Liao & Fowler, 1990; Salamone, Kurth, et al., 1993). One of the parameters useful for characterizing the effects of accumbens DA depletions has been the interresponse time (IRT). In our research, the IRT has been defined as the time interval between the onset of successive responses. Of course, because shorter IRTs mean that more responses can be emitted per unit time, the IRT is related to response rate; in fact, the average IRT for an entire session is the reciprocal of the average response rate. As such, the average IRT does not convey much more information than the number of responses per 30 min. Nevertheless, computer analyses of the IRT of each successive response allows a researcher to develop a detailed temporal thumbprint of leverpressing behavior. Each individual IRT is the reciprocal of the *local* response rate. Therefore, an IRT of 250 msec represents a local rate of 4 responses per second. Several analyses can be performed with these data, but one that has been employed commonly is the construction of IRT distributions. One can sort the IRT values into time bins, and thus determine the relative number of fast responses (i.e., short IRTs), slow responses, and pauses (i.e., IRTs longer than a particular criterion value). To correct for effects of a manipulation upon the total number of responses, the IRT bin distribution is typically calculated as a relative distribution (expressed as a percent of all IRTs) rather than an absolute distribution.

The general effect of accumbens DA depletions is a response slowing, which manifests itself as a relative increase in the proportion of pauses (i.e., long IRTs) and a relative decrease in the proportion of fast responses (i.e., short IRTs). In rats responding on a continuous (i.e., FR 1) schedule, accumbens DA depletions substantially decreased the proportion of IRTs in the range of 0.0–1.5 sec, which, for this schedule, is relatively fast (Salamone et al., 1995). Such an effect is not the inevitable outcome of any manipulation that suppresses responding; extinction decreases the total number of responses, but actually increases the relative number of fast IRTs (Salamone et al., 1995). Thus, analysis of IRT distributions can yield more information than simply the fact that responding has been reduced by DA depletions. This type of analysis can identify the specific pattern with which a drug or lesion alters the temporal organization of responding.

The FR 5 schedule has also been used to assess the effects of DA depletions on local rate of responding. DA depletions in VLS were shown to severely suppress the total number of responses, and also to profoundly alter the IRT distribution (Salamone, Kurth, et al., 1993). Al-

though nucleus accumbens DA depletions produced effects that were milder than VLS depletions, analysis of IRTs showed that accumbens DA depletions did substantially alter the local rate of responding. Accumbens DA depletions produced a 40% drop in the proportion of IRTs in the fastest time bin (0–250 msec). In addition, rats with accumbens DA depletions showed a three-fold increase in the proportion of IRTs in the slowest bin category (i.e., >5.0 sec). In a more recent study of FR 5 responding, injections of 6-OHDA into the core of the accumbens produced substantial alterations in the IRT distribution (Sokolowski & Salamone, 1998). As with the other experiments described above, the major effect of core injections of 6-OHDA was to decrease the proportion of fast IRTs and increase the proportion of slow IRTs (Figure 3). The baseline rate of leverpressing varies greatly across different schedules, and this is reflected in the IRT distribution. As the global rate of responding across large units of time gets higher, one generally sees a larger percentage of the IRTs in the fast time bins (e.g., Salamone et al., 1995; Salamone, Kurth, et al., 1993). A recent study of FR leverpressing, which was described above (Aberman & Salamone, 1999), reported that the FR 64 schedule was highly sensitive to the effects of accumbens DA depletions. The FR 64 schedule generates a very high baseline rate, and analysis of the IRT distributions shows that under control or baseline conditions the vast majority of IRTs are relatively fast in comparison with other schedules. As is shown in Figure 4A, accumbens DA depletions dramatically altered the distribution of IRTs in animals responding on the FR 64 schedule. Although prefeeding also reduced the total number of responses, it did not substantially alter the IRT distribution (Figure 4B).

In summary, another manifestation of the role of response rate as a mitigating factor in the expression of deficits after accumbens DA depletions is that accumbens DA depletions slow the local rate of responding. If one examines the faster end of the IRT distribution (i.e., the time bins with lower values), one sees that accumbens DA depletions reduce the proportion of IRTs that have relatively low time values. In addition, accumbens DA depletions increase the relative number of very long IRTs. One can interpret a long IRT (i.e., greater than 2.5 or 5.0 sec) as a break, or pause, in responding. Thus, accumbens DA depletions have two major effects; they increase the tendency to take pauses, and they decrease the relative number of fast IRTs. The reduction in the relative number of fast responses can have a powerful influence over the total number of responses, particularly on schedules such as FR 16 and FR 64, which normally are characterized by large “bursts” of responding at high local rates. In addition, increased pausing can substantially affect total response output by decreasing the time available for responding. According to Staddon and Ettenger (1989), one factor that contributes to ratio strain is the tendency to pause. Thus, the fact that accumbens DA de-

Figure 3. Relative distribution of interresponse times (IRTs) in vehicle-treated rats and in rats injected with 6-OHDA in either the core or the shell of nucleus accumbens. All rats are responding on an FR 5 schedule (Week 1 postsurgery; data from Sokolowski & Salamone, 1998). There were no significant effects of shell 6-OHDA. In rats with core injections of 6-OHDA, there was a suppression of the relative number of IRTs in the first time bin (i.e., short IRTs or fast responses), and an increase in the relative number of IRTs in the last time bin (i.e., the longest IRTs, which represent "pauses" or "breaks" in responding).

pletions increase the tendency to pause could make rats very sensitive to high-ratio schedules, which could facilitate ratio strain (Aberman & Salamone, 1999).

On the Relation Between Accumbens DA Release and Operant Response Rate

The studies reviewed above involved investigations in which the behavioral effects of accumbens DA depletions were assessed. The development of *in vivo* neurochemical methods has allowed for the possibility of studying behavior and neurotransmitter activity concomitantly (e.g., Salamone, Cousins, McCullough, Carriero, & Berkowitz, 1994; Salamone, Keller, Zigmond, & Stricker, 1989; Salamone, Lindsay, Neill, & Justice, 1982; see review by Salamone, 1996). Several microdialysis studies have demonstrated that accumbens DA release is positively correlated with leverpressing rate. Responding on either FR 1 or avoidance leverpressing schedules increased extracellular DA levels in the accumbens, and significant positive linear correlations between the number of responses and the increases in DA were reported (McCullough, Cousins, & Salamone, 1993; McCullough, Sokolowski, & Salamone, 1993). During FR 5 responding, there also were substantial increases in accumbens extracellular

DA over baseline, and a significant hyperbolic relation between responding and increases in DA (Salamone, Cousins, et al., 1994). The FI 30 schedule is characterized by a higher rate of responding than the FI 120 schedule, and it also is accompanied by greater increases in DA release (Cousins et al., 1999). A recent study (Sokolowski, Conlan, & Salamone, 1998) examined DA release in the accumbens core and shell during three operant tasks in the rat, in order to investigate in more detail the relation between DA release and leverpressing rate. Rats were trained to leverpress on an FR 5, a VI 30 sec, or a tandem variable time 30 sec/FR 5 schedule (referred to as a tandem VI/FR in the article); these three schedules were chosen because they generate a wide range of response and reinforcement rates. Attaching a ratio requirement to the variable time interval generated a very high response rate, but the density of food presentation was approximately the same as on the VI 30 sec schedule. After several weeks of training, dialysis probes were implanted into the nucleus accumbens core or shell subregions. A single 30-min behavioral test was conducted during the dialysis test session. Rats leverpressing on each of the three operant schedules showed a significant increase in extracellular DA relative to the food-deprived control group

Figure 4. (A) Relative distribution of interresponse times (IRTs) in vehicle-treated rats and in rats injected with 6-OHDA in the nucleus accumbens. These data are from rats responding on an FR 64 schedule (Aberman & Salamone, 1999), and data are taken from Day 5 postsurgery (i.e., middle of the first week of postsurgical testing) for both vehicle-treated and DA-depleted rats. Accumbens DA depletions significantly altered the IRT distribution, detected by a factorial analysis of variance with a significant bin $\times$ group interaction ($p < .01$). In rats with core injections of 6-OHDA, there was a suppression of the relative number of IRTs in the first time bin (i.e., short IRTs or fast responses), and an increase in the relative number of IRTs in the last time bin (i.e., the longest IRTs, which represent "pauses" or "breaks" in responding). The IRT bin dimensions are different in this figure than in Figure 3, because a different computer program was used. (B) Data from the prefeeding experiment of Aberman and Salamone (1999). Rats trained on the FR 64 schedule were either food deprived or removed from food deprivation and placed on ad-lib feeding for 24 h before testing (prefed). Although prefeeding substantially suppressed the absolute number of leverpresses relative to deprived controls, there was no significant alteration of the relative distribution of IRTs (bin $\times$ group interaction, $p > .3$). Rats with accumbens DA depletions show response slowing (panel A), yet prefed rats respond at normal local rates. Thus, the suppression of responding in prefed rats is due to an increase in the length of pauses, rather than an alteration in the relative number of pauses or the relative distribution of IRTs. Data shown in panels A and B are additional analyses performed on data reported in Aberman and Salamone (1999).

during the behavioral session. In addition, increases in extracellular DA were found to be significantly greater in the accumbens shell than in the core during the leverpressing period. Thus, the shell seems to show substantial increases in DA release during operant responding, despite the fact that accumbens DA depletions in the shell have very little effect on response rate (Sokolowski & Salamone, 1998). The significance of this increased DA release in the shell is unclear. It is possible that DA release in the shell during operant responding is not involved in response output, but is related to other processes that are not measured by response rate. Across all three schedules and both probe placements, extracellular DA in the nucleus accumbens was significantly correlated with the number of leverpresses performed, but was not correlated with the number of food pellets delivered (Sokolowski et al., 1998). Analysis of covariance, in which the amount of food consumed was the covariate, showed an overall group difference, indicating that DA levels increased in leverpressing animals even if one cor-

rected for the amount of food consumed. Therefore, increases in extracellular DA in the nucleus accumbens core and shell shown by well-trained animals leverpressing for food were related to response rate rather than reinforcement magnitude.

Conclusions: Involvement of Accumbens DA in the Regulation of Energy Expenditure

From an energetic standpoint, individual cells, as well as complex multicellular organisms, are nonequilibrium open systems. Complex organisms must obtain energy by ingesting substances from their environment. Of course, to acquire energy in the form of nutrients, animals must expend energy in contracting their muscles. The acquisition of food involves more than just consummatory behaviors; it also involves instrumental actions that increase the proximity and availability of food. Because organisms are separated from significant stimuli such as food by environmental constraints or obstacles (i.e., response or procurement "costs"), these instrumental behaviors are

often characterized by a high degree of vigor, persistence, and work output. The notion that motivated behaviors have an energetic or activational component is old, and there are numerous examples of this idea in the literatures of psychology (e.g., Cofer & Appley, 1964; E. Duffy, 1963; Killeen, Hanson, & Osbourne, 1978) and ethology (e.g. Hinde, 1970; Marler & Hamilton, 1966). In addition, this view is consistent with more recent "economic" models of operant conditioning, and with the idea that response procurement "costs" affect operant responding (Allison, 1981; Collier & Jennings, 1969; Collier, Johnson, Hill, & Kaufman, 1986; Gannon, Smith, & Tierney, 1983; Hursh, Raslear, Shurtleff, Bauman, & Simmons, 1988; Kaufman, 1980; Lea, 1978; Rashotte & Henderson, 1988; Staddon, 1979, 1983). In mammals, the brain is a critical structure for the regulation of complex behavior, and thus it is important to investigate the brain mechanisms involved in activational aspects of instrumental behavior. Several lines of evidence indicate that accumbens DA is involved generally in behavioral activation (Koob et al., 1978; McCullough & Salamone, 1992; Salamone, 1988, 1992). A specific manifestation of the involvement of accumbens DA in behavioral activation is that release of DA in the nucleus accumbens may be an important part of the neural process that enables organisms to overcome work-related response costs. In economic terms, nucleus accumbens DA appears to be involved in the elasticity of demand for food.

As described above, studies involving response choice tasks or various schedules of reinforcement have demonstrated that the effects of accumbens DA depletions interact strongly with the work output typically seen on that particular task. Rats with accumbens DA depletions are impaired on operant schedules characterized by high levels of work output, and, on choice procedures, accumbens DA depletions cause animals to shift their relative response allocation in the direction of the task with lower work requirements. In addition, release of DA in the nucleus accumbens is correlated with operant response output. Although it is difficult to identify precisely the behavioral functions of nucleus accumbens DA, it does appear that depletions of DA reduce the propensity for expending energy or effort, and that accumbens DA release could be one of the mechanisms through which response output is regulated. The regulation of global aspects of work output can be conceived of as a higher order sensorimotor process, but also as an aspect of motivation (for reviews, see Salamone, 1987, 1992; Salamone et al., 1997). This view of nucleus accumbens function is consistent with the notion that this structure serves as an interface between limbic areas and the motor system (Mogenson, Jones, & Yim, 1980; Salamone, 1991). Moreover, it is possible that the nucleus accumbens, through its anatomical connections, participates in frontal cortical control of behavioral regulation. Although the nucleus accumbens may not directly assess reward value, or perform cost/benefit analyses, it is possible that accu-

bens DA transmission sets constraints on energy expenditure that profoundly influence the relative allocation of instrumental responses toward various alternatives. As well as shedding light on the neural control of motivated behavior, research into the functions of nucleus accumbens DA could also have important implications for clinical studies of energy-related disorders, such as anergia or apathy (Campbell & J. D. Duffy, 1997; J. D. Duffy & Kant, 1997).

REFERENCES

- ABERMAN, J. E., & SALAMONE, J. D. (1999). Nucleus accumbens dopamine depletions affect the behavioral economics of demand for food but do not affect primary food reinforcement. *Neuroscience*, **92**, 545-552.
- ABERMAN, J. E., WARD, S. J., & SALAMONE, J. D. (1998). Effects of dopamine antagonists and accumbens dopamine depletions on time-constrained progressive ratio performance. *Pharmacology, Biochemistry & Behavior*, **61**, 341-348.
- ALLISON, J. (1981). Economics and operant conditioning. In P. Harzem & M. D. Zeiler (Eds.), *Predictability, correlation and contiguity* (pp. 321-353). New York: Wiley.
- ASIN, K. E., & FIBIGER, H. C. (1984). Force requirements in lever-pressing and responding after haloperidol. *Pharmacology, Biochemistry & Behavior*, **20**, 323-326.
- BAKSHI, V. P., & KELLEY, A. E. (1991). Dopaminergic regulation of feeding behavior: I. Differential effects of haloperidol microinjection into three striatal subregions. *Psychobiology*, **19**, 223-232.
- BERRIDGE, K. C. (1996). Food reward: Brain substrates for wanting and liking. *Neuroscience & Biobehavioral Reviews*, **20**, 1-25.
- BERRIDGE, K. C., & ROBINSON, T. E. (1998). What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Research Review*, **28**, 309-369.
- BINDRA, D. (1978). How adaptive behavior is produced: A perceptual-motivational alternative to response-reinforcement. *Behavioral & Brain Sciences*, **1**, 41-91.
- BOZARTH, M. A., & WISE, R. A. (1981). Involvement of the ventral tegmental dopamine system in opioid and psychomotor stimulant reinforcement. *Life Sciences*, **28**, 551-555.
- CAINE, S. B., & KOOB, G. F. (1994). Effects of mesolimbic dopamine depletion on responding maintained by cocaine and food. *Journal of Experimental Analysis of Behavior*, **61**, 213-221.
- CAMPBELL, J. J., & DUFFY, J. D. (1997). Treatment strategies in amotivated patients. *Psychiatric Annals*, **27**, 44-49.
- CARRIERO, D. [L.], ABERMAN, J., LIN, S. Y., HILL, A., MAKRIYANNIS, A., & SALAMONE, J. D. (1998). A detailed characterization of the effects of four cannabinoid agonists on operant lever pressing. *Psychopharmacology*, **137**, 147-156.
- CARRIERO, D. L., OUTSLAY, G., MAYORGA, A. J., GIANUTSOS, G., & SALAMONE, J. D. (1997). Motor dysfunction produced by tacrine administration in rats. *Pharmacology, Biochemistry & Behavior*, **58**, 851-858.
- COFER, C. N., & APPELY, M. H. (1964). *Motivation: Theory and research*. New York: Wiley.
- COLLIER, G. H., & JENNINGS, W. (1969). Work as a determinant of instrumental performance. *Journal of Comparative & Physiological Psychology*, **68**, 659-662.
- COLLIER, G. H., JOHNSON, D. F., HILL, W. L., & KAUFMAN, L. W. (1986). The economics of the law of effect. *Journal of the Experimental Analysis of Behavior*, **46**, 113-136.
- COUSINS, M. S., ATHERTON, A., TURNER, L., & SALAMONE, J. D. (1996). Nucleus accumbens dopamine depletions alter relative response allocation in a T-maze cost/benefit task. *Behavioural Brain Research*, **74**, 189-197.
- COUSINS, M. S., & SALAMONE, J. D. (1994). Nucleus accumbens dopamine depletions in rats affect relative response allocation in a novel cost/benefit procedure. *Pharmacology, Biochemistry & Behavior*, **49**, 85-91.

- COUSINS, M. S., & SALAMONE, J. D. (1996). Involvement of ventrolateral striatal dopamine in movement initiation and execution: A microdialysis and behavioral investigation. *Neuroscience*, **70**, 849-859.
- COUSINS, M. S., & SALAMONE, J. D. (1997). Skilled motor deficits in rats induced by ventrolateral striatal dopamine depletions: Behavioral and pharmacological characterization. *Brain Research*, **732**, 186-194.
- COUSINS, M. S., SOKOLOWSKI, J. D., & SALAMONE, J. D. (1993). Different effects of nucleus accumbens and ventrolateral striatal dopamine depletions on instrumental response selection in the rat. *Pharmacology, Biochemistry & Behavior*, **46**, 943-951.
- COUSINS, M. S., TREVITT, J., ATHERTON, A., & SALAMONE, J. D. (1999). Different behavioral functions of dopamine in nucleus accumbens and ventrolateral striatum: A microdialysis and behavioral investigation. *Neuroscience*, **91**, 925-934.
- COUSINS, M. S., WEI, W., & SALAMONE, J. D. (1994). Pharmacological characterization of performance on a concurrent leverpressing/feeding choice procedure: Effects of dopamine antagonist, cholinomimetic, sedative and stimulant drugs. *Psychopharmacology*, **116**, 529-537.
- DICKINSON, A., & BALLEINE, B. (1994). Motivational control of goal-directed action. *Animal Learning & Behavior*, **22**, 1-18.
- DUFFY, E. (1963). *Activation and behavior*. New York: Wiley.
- DUFFY, J. D., & KANT, R. (1997). Apathy secondary to neurologic disease. *Psychiatric Annals*, **27**, 39-43.
- ETTENBERG, A., & CARLISLE, H. J. (1985). Neuroleptic-induced deficits in operant responding for temperature reinforcement. *Pharmacology, Biochemistry & Behavior*, **22**, 761-767.
- EVENDEN, J. L., & ROBBINS, T. W. (1983). Dissociable effects of *d*-amphetamine, chlorthalidopoxide and alpha-flupenthixol on choice and rate measures of reinforcement in the rat. *Psychopharmacology*, **79**, 180-186.
- FAUSTMAN, W. O., & FOWLER, S. C. (1981). Use of operant response duration to distinguish effects of haloperidol from non-reward. *Pharmacology, Biochemistry & Behavior*, **15**, 327-329.
- FAUSTMAN, W. O., & FOWLER, S. C. (1982). An examination of methodological refinements, clozapine and fluphenazine in the anhedonia paradigm. *Pharmacology, Biochemistry & Behavior*, **17**, 987-993.
- FOWLER, S. C., & DAS, S. (1994). Haloperidol-induced decrements in force and duration of rats tongue movements during licking are attenuated by concomitant anticholinergic treatment. *Pharmacology, Biochemistry & Behavior*, **49**, 813-817.
- FOWLER, S. C., & MORTELL, C. (1992). Low doses of haloperidol interfere with rat tongue extensions during licking: A quantitative analysis. *Behavioral Neuroscience*, **106**, 1-9.
- GANNON, K. N., SMITH, H. V., & TIERNEY, K. J. (1983). Effects of procurement cost on food consumption in rats. *Physiology & Behavior*, **31**, 331-337.
- GRAMLING, S. E., & FOWLER, S. C. (1985). Effects of neuroleptics on rate and duration of operant versus reflexive licking in rats. *Pharmacology, Biochemistry & Behavior*, **22**, 541-545.
- GRAMLING, S. E., FOWLER, S. C., & COLLINS, K. R. (1984). Some effects of pimozide on nondeprived rats licking sucrose solutions in an anhedonia paradigm. *Pharmacology, Biochemistry & Behavior*, **21**, 617-624.
- GRAMLING, S. E., FOWLER, S. C., & TIZZANO, J. P. (1987). Some effects of pimozide on nondeprived rats' leverpressing maintained by a sucrose reward in an anhedonia paradigm. *Pharmacology, Biochemistry & Behavior*, **27**, 67-72.
- HAMILL, S., TREVITT, J. T., NOWEND, K., CARLSON, B., & SALAMONE, J. D. (1999). *Accumbens dopamine depletions and time-constrained progressive ratio performance: Effects of different ratio requirements*. Manuscript submitted for publication.
- HERNANDEZ, L., & HOEBEL, B. G. (1988). Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. *Life Sciences*, **42**, 1705-1712.
- HINDE, R. A. (1970). *Animal behavior: A Synthesis of ethology and comparative psychology*. New York: McGraw Hill.
- HSIAO, S., & CHEN, B. H. (1995). Complex response competition and dopamine blocking: Choosing of high cost sucrose solution vs. low cost water solution in rats. *Chinese Journal of Physiology*, **38**, 99-109.
- HSIAO, S., & SMITH, G. P. (1995). Risperidone reduces sucrose preference in rats. *Pharmacology, Biochemistry & Behavior*, **50**, 121-125.
- HURSH, S. R., RASLEAR, T. G., SHURTLEFF, D., BAUMAN, R., & SIMMONS, L. (1988). A cost-benefit analysis of demand for food. *Journal of the Experimental Analysis of Behavior*, **30**, 419-440.
- JONES, D. L., & MOGENSEN, G. L. (1979). Oral motor performance following central dopamine receptor blockade. *European Journal of Pharmacology*, **59**, 11-21.
- KAUFMAN, L. W. (1980). Foraging cost and meal patterns in ferrets. *Physiology & Behavior*, **25**, 139-141.
- KILLEEN, P., HANSON, S., & OSBOURNE, S. (1978). Arousal: Its genesis and manifestation as response rate. *Psychology Review*, **85**, 571-581.
- KOOB, G. F., RILEY, S. J., SMITH, S. C., & ROBBINS, T. W. (1978). Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat. *Journal of Comparative & Physiological Psychology*, **92**, 917-927.
- LEA, S. E. G. (1978). The psychology and economics of demand. *Psychological Bulletin*, **85**, 441-466.
- LIAO, R. M., & FOWLER, S. C. (1990). Haloperidol produces within-session increments in operant response duration in rats. *Pharmacology, Biochemistry & Behavior*, **36**, 199-201.
- MARLER, P., & HAMILTON, W. J. (1966). *Mechanisms of animal behavior*. New York: Wiley.
- MASON, S. T., BENINGER, R. J., FIBIGER, H. C., & PHILLIPS, A. G. (1980). Pimozide-induced suppression of responding: Evidence against a block of food reward. *Pharmacology, Biochemistry & Behavior*, **12**, 917-923.
- MCCULLOUGH, L. D., COUSINS, M. S., & SALAMONE, J. D. (1993). The role of nucleus accumbens dopamine in responding on a continuous reinforcement operant schedule: A neurochemical and Behavioral study. *Pharmacology, Biochemistry & Behavior*, **46**, 581-586.
- MCCULLOUGH, L. D., & SALAMONE, J. D. (1992). Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: A microdialysis and behavioral study. *Brain Research*, **592**, 29-36.
- MCCULLOUGH, L. D., SOKOLOWSKI, J. D., & SALAMONE, J. D. (1993). A neurochemical and behavioral investigation of the involvement of nucleus accumbens dopamine in instrumental avoidance. *Neuroscience*, **52**, 919-925.
- MCFARLAND, K., & ETTENBERG, A. (1998). Haloperidol does not affect motivational processes in an operant runway model of food-seeking behavior. *Behavioral Neuroscience*, **112**, 630-635.
- MOGENSEN, G., JONES, D., & YIM C. Y. (1980). From motivation to action: Functional interface between the limbic system and the motor system. *Progress in Neurobiology*, **14**, 69-97.
- NADER, K., BECHARA, A., & VAN DER KOY, D. (1997). Neurobiological constraints on behavioral models of motivation. *Annual Review of Psychology*, **48**, 85-114.
- NEILL, D. B., & JUSTICE, J. B. (1981). An hypothesis for a behavioral function of dopaminergic transmission in nucleus accumbens. In R. B. Chronister & J. F. Defrance (Eds.), *The neurobiology of the nucleus accumbens*. Brunswick, ME: Haer Institute for Electrophysiological Research.
- PHILLIPS, A. G., & FIBIGER, H. C. (1979). Decreased resistance to extinction after haloperidol: Implications for the role of dopamine in reinforcement. *Pharmacology, Biochemistry & Behavior*, **10**, 751-761.
- RASHOTTE, M. E., & HENDERSON, D. (1988). Coping with rising food costs in a closed economy: Feeding behavior and nocturnal hypothermia in pigeons. *Journal of the Experimental Analysis of Behavior*, **50**, 441-456.
- ROBERTS, D. C. S., CORCORAN, M. E., & FIBIGER, H. C. (1977). On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. *Pharmacology, Biochemistry & Behavior*, **6**, 615-620.
- SALAMONE, J. D. (1986). Different effects of haloperidol and extinction on instrumental behaviors. *Psychopharmacology*, **88**, 18-23.
- SALAMONE, J. D. (1987). The actions of neuroleptic drugs on appetitive instrumental behaviors. In L. L. Iversen, S. D. Iversen, & S. H. Snyder (Eds.), *Handbook of psychopharmacology* (pp. 575-608). New York: Plenum.
- SALAMONE, J. D. (1988). Dopaminergic involvement in motivational as-

- pects of motivation: Effects of haloperidol on schedule-induced activity, feeding and foraging in rats. *Psychobiology*, **16**, 196-202.
- SALAMONE, J. D. (1991). Behavioral pharmacology of dopamine systems: A new synthesis. In P. Willner & J. Scheel-Kruger (Eds.), *The mesolimbic dopamine system: From motivation to action* (pp. 599-613). Cambridge: Cambridge University Press.
- SALAMONE, J. D. (1992). Complex motor and sensorimotor functions of accumbens and striatal dopamine: Involvement in instrumental behavior processes. *Psychopharmacology*, **107**, 160-174.
- SALAMONE, J. D. (1994). The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. *Behavioural Brain Research*, **61**, 117-133.
- SALAMONE, J. D. (1996). The behavioral neurochemistry of motivation: Methodological and conceptual issues in studies of the dynamic activity of nucleus accumbens dopamine. *Journal of Neuroscience Methods*, **64**, 137-149.
- SALAMONE, J. D., COUSINS, M. S., & BUCHER, S. (1994). Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. *Behavioural Brain Research*, **65**, 221-229.
- SALAMONE, J. D., COUSINS, M. S., MCCULLOUGH, L. D., CARRIERO, D. L., & BERKOWITZ, R. L. (1994). Nucleus accumbens dopamine release increases during instrumental leverpressing for food but not food consumption. *Pharmacology, Biochemistry & Behavior*, **49**, 25-31.
- SALAMONE, J. D., COUSINS, M. S., & SNYDER, B. J. (1997). Behavioral functions of nucleus accumbens dopamine: Empirical and conceptual problems with the anhedonia hypothesis. *Neuroscience & Biobehavioral Review*, **21**, 341-359.
- SALAMONE, J. D., KELLER, R. W., ZIGMOND, M. J., & STRICKER, E. M. (1989). Behavioral activation in rats increases striatal dopamine metabolism measured by dialysis perfusion. *Brain Research*, **487**, 215-224.
- SALAMONE, J. D., KURTH, P. A., MCCULLOUGH, L. D., & SOKOLOWSKI, J. D. (1995). The effects of nucleus accumbens dopamine depletions on continuously reinforced operant responding: Contrasts with the effects of extinction. *Pharmacology, Biochemistry & Behavior*, **50**, 437-443.
- SALAMONE, J. D., KURTH, P. A., MCCULLOUGH, L. D., SOKOLOWSKI, J. D., & COUSINS, M. S. (1993). The role of brain dopamine in response initiation: Effects of haloperidol and regionally specific dopamine depletions on the local rate of instrumental responding. *Brain Research*, **628**, 218-226.
- SALAMONE, J. D., LINDSAY, W. S., NEILL, D. B., & JUSTICE, J. B. (1982). Behavioral observations and intracerebral electrochemical recording following administration of amphetamine in rats. *Pharmacology, Biochemistry & Behavior*, **17**, 445-450.
- SALAMONE, J. D., MAHAN, K., & ROGERS, S. (1993). Ventrolateral striatal dopamine depletions impair feeding and food handling in rats. *Pharmacology, Biochemistry & Behavior*, **44**, 605-610.
- SALAMONE, J. D., STEINPREIS, R. E., MCCULLOUGH, L. D., SMITH, P., GREBEL, D., & MAHAN, K. (1991). Haloperidol and nucleus accumbens dopamine depletion suppress leverpressing for food but increase free food consumption in a novel food-choice procedure. *Psychopharmacology*, **104**, 515-521.
- SCHNEIDER, L. H., SIKORSKY, C. A., RAUHOFFER, E. A., DAVIS, J. D., & SMITH, G. P. (1992). Risperidone microinjected into nucleus accumbens inhibits sucrose sham feeding. *Appetite*, **19**, 215.
- SCHNEIDER, L. H., SIKORSKY, C. A., RAUHOFFER, E. A., & SMITH, G. P. (1993). Accumbens D1 and D2 receptors support sham-fed sweet reward. *Society for Neuroscience Abstracts*, **19**, 1695.
- SMITH, G. P. (1995). Dopamine and food reward. *Progress in Psychobiology & Physiological Psychology*, **16**, 83-144.
- SOKOLOWSKI, J. D., CONLAN, A., & SALAMONE, J. D. (1998). A microdialysis study of nucleus accumbens core and shell dopamine during operant responding in the rat. *Neuroscience*, **86**, 1001-1009.
- SOKOLOWSKI, J. D., & SALAMONE, J. D. (1998). The role of nucleus accumbens dopamine in leverpressing and response allocation: Effects of 6-OHDA injected into core and dorsomedial shell. *Pharmacology, Biochemistry & Behavior*, **59**, 557-566.
- SPIVAK, K. J., & AMIT, Z. (1986). Effects of pimozide on appetitive behavior and locomotor activity: Dissimilarity of effects when compared to extinction. *Physiology & Behavior*, **36**, 457-463.
- STADDON, J. E. R. (1979). Operant behavior as adaptation to constraint. *Journal of Experimental Psychology: General*, **108**, 48-67.
- STADDON, J. E. R. (1983). *Adaptive behavior and learning*. Cambridge: Cambridge University Press.
- STADDON, J. E. R., & ETTINGER, R. H. (1989). *Learning: An introduction to the principles of adaptive behavior*. New York: Harcourt Brace Jovanovich.
- STEFURAK, T. L., & VAN DER KOOP, D. (1994). Tegmental pedunculo-pontine lesions in rats decrease saccharin's rewarding effects but not its memory-improving effects. *Behavioral Neuroscience*, **108**, 972-980.
- SZECHTMAN, H., TALANGBAYAN, H., GANARAN, G., DAI, H., & EILAM, D. (1994). Dynamics of behavioral sensitization induced by the dopamine agonist quinpirole and a proposed central energy control mechanism. *Psychopharmacology*, **115**, 95-104.
- THORNDIKE, E. L. (1911). *Animal intelligence*. New York: Macmillan.
- TIMBERLAKE, W. (1993). Behavior systems and reinforcement: An integrative approach. *Journal of the Experimental Analysis of Behavior*, **60**, 105-128.
- TIMBERLAKE, W., & ALLISON, J. (1974). Response deprivation: An empirical approach to instrumental performance. *Psychological Review*, **81**, 146-164.
- TOMBAUGH, T. N., ANISMAN, H., & TOMBAUGH, J. (1980). Extinction and dopamine receptor blockade after intermittent reinforcement training: Failure to observe functional equivalence. *Psychopharmacology*, **70**, 19-28.
- TOMBAUGH, T. N., SZOSTAK, C., & MILLS, P. (1983). Failure of pimozide to disrupt acquisition of light-dark and spatial discrimination problems. *Psychopharmacology*, **79**, 161-168.
- TOMBAUGH, T. N., SZOSTAK, C., VOORNEVELD, P., & TOMBAUGH, J. W. (1982). Failure to obtain functional equivalence between dopamine receptor blockade and extinction: Evidence supporting a sensory-motor conditioning hypothesis. *Pharmacology, Biochemistry & Behavior*, **16**, 67-72.
- WILLNER, P., CHAWALA, K., SAMPSON, D., SOPHOKLEOUS, S., & MUSCAT, R. (1988). Tests of functional equivalence between pimozide pretreatment, extinction and free feeding. *Psychopharmacology*, **95**, 423-426.
- WIRTSCHAFER, D., & ASIN, K. E. (1985). Haloperidol and nonreinforcement produce different patterns of response slowing in a food-reinforced runway task. *Pharmacology, Biochemistry & Behavior*, **22**, 661-663.
- WISE, R. A. (1982). Neuroleptics and operant behavior: The anhedonia hypothesis. *Behavioral & Brain Sciences*, **5**, 39-87.
- WISE, R. A. (1985). The anhedonia hypothesis: Mark III. *Behavioral & Brain Sciences*, **8**, 178-186.
- WISE, R. A., SPINDLER, J., DEWIT, H., & GERBER, G. J. (1978). Neuroleptic-induced anhedonia in rats: Pimozide blocks reward quality of food. *Science*, **201**, 262-264.

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