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Brain Research Reviews 28 (1998) 309–369

BRAIN RESEARCH REVIEWS

Full-length review

What is the role of dopamine in reward: hedonic impact, reward learning, or incentive salience?

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Accepted 23 June 1998

Abstract

What roles do mesolimbic and neostriatal dopamine systems play in reward? Do they mediate the *hedonic impact* of rewarding stimuli? Do they mediate hedonic *reward learning* and *associative prediction?* Our review of the literature, together with results of a new study of residual reward capacity after dopamine depletion, indicates the answer to both questions is 'no'. Rather, dopamine systems may mediate the *incentive salience* of rewards, modulating their motivational value in a manner *separable from hedonia and reward learning*. In a study of the consequences of dopamine loss, rats were depleted of dopamine in the nucleus accumbens and neostriatum by up to 99% using 6-hydroxydopamine. In a series of experiments, we applied the 'taste reactivity' measure of affective reactions (gapes, etc.) to assess the capacity of dopamine-depleted rats for: 1) normal affect (hedonic and aversive reactions), 2) modulation of hedonic affect by associative learning (taste aversion conditioning), and 3) hedonic enhancement of affect by non-dopaminergic pharmacological manipulation of palatability (benzodiazepine administration). We found normal hedonic reaction patterns to sucrose vs. quinine, normal learning of new hedonic stimulus values (a change in palatability based on predictive relations), and normal pharmacological hedonic enhancement of palatability. We discuss these results in the context of hypotheses and data concerning the role of dopamine in reward. We review neurochemical, electrophysiological, and other behavioral evidence. We conclude that dopamine systems are not needed either to mediate the hedonic pleasure of reinforcers or to mediate predictive associations involved in hedonic reward learning. We conclude instead that dopamine may be more important to *incentive salience attributions* to the neural representations of reward-related stimuli. Incentive salience, we suggest, is a distinct component of motivation and reward. In other words, dopamine systems are necessary for '*wanting' incentives*, but not for 'liking' them or for learning new 'likes' and 'dislikes'.

Keywords: Neostriatum; Nucleus accumbens; Substantia nigra; Tegmentum; Mesolimbic; Nigrostriatal; Mesotelencephalic mesostriatal; Dopamine; 6-hydroxydopamine; Lateral hypothalamus; Brain; Reinforcement; Motivation; Self-administration; Conditioning; Reward; Emotion; Palatability; Pleasure; Feeding; Food intake appetitive behavior; Consummatory behavior; Affect; Anhedonia; Hedonic; Diazepam; Conditioned taste aversion; Taste; Taste reactivity; Aphagia; Aversion; Appetite; Ingestion; Neurotransmitters; Substance-related disorders; Addiction

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0165-0173/98/$ - see front matter
PII: S0165-0173(98)00019-8

Appearances to the mind are of four kinds. Things either are what they appear to be; or they neither are, nor appear to be; or they are, and do not appear to be; or they are not, and yet appear to be. Rightly to aim in all these cases is the wise man's task.

Epictetus (60 A.D. Translation: Elizabeth Carter [142] — Thomas Higginson [143])

1. Introduction

Among the most thoroughly studied of all brain substrates for reward are dopamine projections from the substantia nigra and ventral tegmentum to forebrain structures such as the nucleus accumbens and neostriatum. It is generally recognized that mesolimbic and neostriatal dopamine projections are crucial to *sensorimotor* function, and so the sensorimotor consequences of dopamine manipulations complicate understanding the role of dopamine in reward [66,202,216,286,303,378,379,381,383,391,392, 456,487]. Nevertheless, many investigators have concluded that dopamine projections play a role in mediating the *reward* value of food, drink, sex, social reinforcers, drugs of abuse, and brain stimulation, above and beyond sensorimotor contributions [13,17,19,26,52,115,117,145,152,155, 158, 225, 254, 259, 266, 268, 310, 325,345,347,362,363,401, 423,429,505,513,518]. The focus of this paper is on the *nature* of the contribution of mesolimbic and mesostriatal dopamine systems to reward.

Reward is often conceptualized as if it were a single psychological process or a unitary feature of a reinforcing stimulus. It is sometimes identified with the pleasure or hedonic impact of a stimulus, and is viewed by some as necessarily subjective in nature. We will argue that reward is *not a unitary process*, but instead a constellation of multiple processes many of which can be separately identified in behavior, especially after the component processes are dissociated by brain manipulations. Nor is reward a necessarily subjective event. Evidence for the proposition that reward and motivational processes are not necessarily subjective has been presented and reviewed elsewhere [34,35,161,271,273,316,366] (for discussion see Berridge, in press [35]). Here we will be concerned solely with the separation of component processes of reward, and with the particular component mediated by dopamine-related brain systems.

2. Evidence for a role of dopamine in reward

Mesolimbic and neostriatal dopamine projections have been suggested to serve as a 'common neural currency' for rewards of most kinds sought by animals and humans [268,325,347,421,505]. Activation of dopamine systems, as quantified by electrophysiological, microdialysis, or voltammetric measures, is triggered in animals by encounters with food, sex, drugs of abuse, electrical stimulation at brain sites that support self-stimulation, and by secondary reinforcers for these incentives [5,52,159,233,259,260,263, 283,300,301,344–346,359,401,403–405,425,478]. In humans, presentation of rewards such as cocaine, drug-associated stimuli, and even a video game ('tank combat'), has similarly been reported in PET and fMRI imaging studies to modulate activity in dopamine target sites such as the nucleus accumbens, neostriatum, or prefrontal cortex [62,160,265,477].

Much of the causal evidence that dopamine systems mediate reward comes from studies of pharmacological blockade of dopamine receptors in animals. [2] Many studies show that dopamine antagonists reduce reward-directed instrumental and consummatory behavior in subtle but definite ways—ways that cannot be explained by sensorimotor impairments alone [7,50,145,146,182,234,236,325, 395,429,448,499,500,514,517,518]. Even more dramatic effects are produced by extensive dopamine depletion caused by intracranial application of dopamine-selective neurotoxins such as 6-hydroxydopamine (6-OHDA). After extensive destruction of ascending dopamine neurons, animals become oblivious to food and many other rewards. Rats typically are aphagic and adipsic after 6-OHDA lesions, and will starve to death unless nourished artificially, even though food may be readily available

[2] Regarding *subtypes* of dopamine receptors, a great deal of evidence has implicated the D1 family of dopamine receptor subtypes (containing D1 and D5 receptors) in food and drug reward [13,26,94,457,458,490]. Considerable evidence also suggests that the D2 family of dopamine receptors (containing D2, D3, and D4 receptor subtypes) plays a role in reward [13,83,88,415,429,457,458,490]. To the degree that individual receptor subtypes can be separately manipulated by selective drugs, D1, D2, D3, and D4 dopamine receptor subtypes have all been suggested to participate in at least some aspect of food, drug, or brain stimulation reward [13,27,77,185,228,312,457,458]. Indeed among the dopamine receptors subtypes so far known, it may be safe to say that no subtype has been conclusively ruled out as involved in reward. The proliferation of dopamine receptor subtypes greatly multiplies the complexity of identifying the role of dopamine systems in reward. If individual subtypes are considered separately, the question of 'does dopamine mediate hedonic pleasure', for example, is converted into at least five questions: ''does the D1 dopamine receptor subtype mediate hedonic pleasure?, does the D2…?'' and so on. Given that the specific roles of different dopamine receptor subtypes in reward are not yet clear [13,457,458], we decline to address the roles of subtypes here. Rather we will be concerned with mesostriatal dopamine projections in general, as dopamine is the endogenous ligand for all subtypes of dopamine receptors. Our approach is based on the logic that *if dopamine systems do not mediate the hedonic impact of reinforcers*, then it is unlikely that the *D3 or any other particular dopamine receptor subtype* will be found to do so. The question if answered negatively for dopamine in general, is answered for each dopamine receptor subtype in turn. Our aim is to identify the *particular reward functions* that are most likely mediated by mesolimbic and mesostriatal dopamine systems. Once that is done, future analyses may answer the important question of which receptor subtypes mediate particular functions. That lies beyond our present scope.

[287,394,407,451,471,531]. Such rats retain the motor capacity to walk, chew, swallow, perform other movements, and to generate many other movement components required for eating, at least under certain conditions, but fail to employ those movements to gain food even if it is available literally under their noses [32,45,111,352,353, 456].

2.1. Nature of dopamine's role in reward: hedonia, incentive salience or reward learning?

Although most investigators would agree that mesolimbic and mesostriatal dopamine systems are crucial to reward in some sense, they disagree about the exact nature of the psychological reward function mediated by dopamine. Perhaps the most influential interpretation has been the *anhedonia* hypothesis, developed by Wise et al. [174,175,499,500,514] to explain the effect of dopamine receptor blockade on behavior. The anhedonia hypothesis (or, regarding normal dopamine function, the *hedonia hypothesis* [181]) suggests that brain dopamine systems mediate the *pleasure* produced by food and other unconditioned incentives such as sex or drugs of abuse, and also the conditioned pleasure elicited by secondary reinforcers. After the administration of dopamine antagonists, according to the anhedonia hypothesis, ''all of life's pleasures—the pleasures of primary reinforcement and the pleasures of their associated stimuli—lose their ability to arouse the animal'' (Wise, p. 52) [499]. Wise himself has subsequently retracted the hypothesis that dopamine blockade reduces pleasure [504]. However, the anhedonia hypothesis has become so widely accepted that even contemporary media reports often refer to dopamine as the 'brain's pleasure neurotransmitter' [314,491].

The wide acceptance of the hedonia hypothesis has extended to neuroscience investigators as well as to the lay public. This is illustrated by repeated suggestions that suppression of dopaminergic neurotransmission mediates the *anhedonia* of drug withdrawal in addiction [107,268,284,373,477,480,491]. For example, Koob et al. [267,268] suggested that suppression of dopamine neurotransmission in withdrawal produces 'hedonic homeostatic dysregulation', and that addicts seek drugs that activate dopamine systems in order to re-establish 'hedonic homeostasis'. Changes in dopamine neurotransmission appear to move an individual up and down along a 'hedonic scale', according to a recent account by Koob and Le Moal (Fig. 4, p. 56 [268]), in a fashion that follows opponent-process rules [434,435]. Similarly, when Gardner (p. 69 [180]) asks the question ''What, then, is the actual role of the ascending DA reward-relevant neuron and the seemingly crucial DA synapse to which it feeds?'', he replies (while noting that hedonic encoding by dopamine systems is complex) that, ''Even after more than a decade and a half, no suggestion appears to have bettered Wise's hypothesis that ''the dopamine junctions represent a synaptic way station... (where) sensory inputs are translated into the hedonic messages we experience as pleasure, euphoria or 'yumminess''''' (quotation from Wise [497], p. 94). A recent commentary by Di Chiara and Tanda ''proposes as a biochemical test for anhedonia... the blunting of reactivity of DA neurotransmission in the NAc 'shell''' (p. 353) [119], going so far as to equate anhedonia with a reduction in measured dopamine. Many other investigators have suggested that dopamine specifically mediates the *reinforcing* properties of food, drugs, and other rewards, often using the term 'reinforcement' in a way difficult to distinguish conceptually from hedonic impact [17,148, 234,236,291,310,421,422,429]. [3]

There are, however, alternatives to the an-hedonia/hedonia hypothesis to explain the role of brain dopamine systems in reward. They sprang from the realization that dopamine function in reward often appears linked to *anticipatory*, *preparatory*, *appetitive*, or *approach phases* of motivated behavior (as opposed to the consummatory

[3] The term 'reinforcement' can be used in a purely behaviorist sense instead: to mean either *strengthening a stimulus–response habit* (Hull's sense of reinforcement [237,238] or to *increase the rate (probability) of response emission* (Skinner's sense of reinforcement [427,428]). Used in those ways, it is purely descriptive (describing an environment-behavior relation). It applies only to responses that have actually been reinforced, and is equivalent to the measured strength or rate of a behavioral response. White has suggested a distinction between 'reinforcement' (strengthening of stimulus–response tendencies, equivalent to the meaning of non-Skinnerian behaviorists [237,333,459]) and 'reward' (conferring ability to elicit approach, more similar to incentive motivation) [488]. However, these meanings are often combined, and the term 'reinforcement' is typically used by behavioral neuroscientists in ways that differ from the original behaviorist meaning of increased habit strength (quite reasonably, since the behaviorist meaning is inadequate to account for many effects [356,460,502]). For example, place preference measures are sometimes used to assess 'reinforcement' even when no response has been 'reinforced' (as when the animal is trained by putting it passively in the 'reinforced place'). Or, as another example, some have inferred a *decrease* in reinforcement from an *increase* in drug self-administration responses after neuroleptic treatment (e.g., [13,112,267]), a direct contradiction of the behaviorist definition that reinforcement is proportional to the change in response strength. Or, as a final example, 'reinforcement' has been used to refer to a *neural* event elicited by a food or drug *stimulus*, independent of whether any behavioral response is strengthened (e.g., [215,301,359]). Reinforcement always carries additional non-behaviorist connotations whenever it is used in these and many other ways to refer to a psychological or neural property other than response strength. When used in such ways, 'reinforcement' becomes at least implicitly a synonym for a hidden psychological process—typically equivalent to hedonic impact—and often is used as a way of invoking this psychological process without naming it and without giving any other clear definition of what is meant. As Kiyatkin (p. 582 [259]) puts it, ''Although it has not been clearly stated, implicit in much of the current literature is the hypothesis that phasic activation of VTA DA cells with subsequent increase in DA release, particularly in NAcc, is the principal neurochemical event associated with natural and drug reinforcement.'' Dopamine hypotheses of 'reinforcement' that are not restricted to behaviorist S–R habit strengthening will be treated here as implicit equivalents of the hedonia hypothesis (see Wise [502] for more discussion of meanings of 'reinforcement', and Berridge [35] for discussion of meanings of 'hedonic impact').

phase, when hedonic activation is maximal) [51,157,322, 325,378,381,400,401,405,508]. This has led to the proposal of alternative hypotheses regarding the psychological function mediated by mesolimbic dopamine systems in reward.

First, a number of behavioral neuroscientists have suggested that dopamine mediates some aspect of reward learning, or the capacity to predict rewarding events based upon associative correlations [3,4,23,24,89,116,117,304, 400,405,416,488].

Second, we have previously suggested that dopamine-related neural systems mediate a different psychological component of reward, the attribution of incentive salience to otherwise neutral events [34,44,45,347,366].

The incentive salience hypothesis in particular is built on earlier incentive theory formulations of motivation and of dopamine's role [52,157,322,460,508]. It goes further in that it suggests the process of reward can be dissociated into separate components of 'wanting' and 'liking', and that these two psychological processes are mediated by different neural systems. It suggests that dopamine mediates the 'wanting' but not the 'liking' component of rewards. [4] The two words combined in the phrase 'incentive salience' are jointly crucial to its meaning. Incentive salience has both perceptual and motivational features. According to our hypothesis, it transforms the brain's neural representations of conditioned stimuli, converting an event or stimulus from a neutral 'cold' representation (mere information) into an attractive and 'wanted' incentive that can 'grab attention'. But incentive salience is not merely perceptual salience. It is also motivational, and is an essential component of the larger process of reward. Its attribution transforms the neural representation of a stimulus into an object of attraction that animals will work to acquire. It can also make a rewarded response the thing rewarded. By the incentive salience hypothesis, dopamine-related neural systems that mediate 'wanting' interact with hedonic and associative learning components (but is separable from them) to produce the larger composite process of reward. Although incentive salience attribution ordinarily is coordinated by associative learning and hedonic activation, it can be triggered independently of them by some neural and pharmacological manipulations [44,366]. Further,—as will be shown here—incentive salience can be stripped away by other neural manipulations, which leave the hedonic and predictive learning components of reward able to occur normally, but by themselves, and unable to be translated into goal directed behavior.

In principle, 'liking' and 'wanting' are separate psychological components of reward, corresponding to the hedonic impact of a reward vs. its attributed incentive salience [34,366]. In practice, the two processes can be distinguished by comparing appropriate behavioral measures of reward. Traditional methods directly measure reward value by the degree to which the reward is 'wanted': *consumption tests, choice tests, place preference, instrumental performance*. Such behavioral measures require an animal to seek the reinforcer, and infer 'liking' only indirectly from 'wanting', on the assumption that something is 'wanted' if and only if it is 'liked'. By contrast, measures based on *affective reactions*, such as described originally by Darwin [109], provide a more direct measure of whether a stimulus is 'liked'. Affective reactions more specifically reflect the hedonic or aversive affect evoked by a stimulus [34,35,144,241,273] (for discussion of the use of affective reactions to study motivation in animals, see Berridge [35], Epstein [144], or LeDoux [273]). Affective reactions can be used to assess 'liking' for a stimulus independently of 'wanting' it—a fact that will be exploited and discussed below.

The purpose of this paper is to explicitly compare various formulations of hedonia, reward learning, and incentive salience hypotheses of dopamine function. We will present evidence from the literature, and new data, to indicate that dopamine systems contribute to reward by mediating incentive salience attributions to neural representations of stimuli associated with primary hedonic rewards. This evidence indicates that dopamine systems do not mediate the hedonic impact of a stimulus, nor are they necessary for learning new associative relationships involving hedonic stimuli.

2.1.1. Anticipatory dopamine activation: implications for the hedonia hypothesis

One source of data that has been taken as evidence against a hedonia interpretation comes from correlational studies of the *timing* of dopamine activation. Neurochemical studies using microdialysis or in vivo electrochemistry indicate that dopamine systems are often activated *before* animals actually receive a pleasurable incentive such as food or a drug. The hedonia hypothesis predicts dopamine systems to be *maximally* aroused during *maximal* pleasure, that is, during physical commerce with a hedonic reward. Although dopamine systems may indeed be activated during a palatable meal [225,289,290], they are often activated before the meal, *prior* to the taste of food, to the same or even to a greater extent than during food con-

[4] We will place 'liking' and 'wanting' in quotation marks because our use differs in an important way from the ordinary use of these words. By their ordinary meaning, these words typically refer to the subjective experience of conscious pleasure or conscious desire. However, evidence reviewed elsewhere indicates that the conscious experience of these and similar states is separable from the underlying core processes that normally constitute them: the core psychological processes can exist and control human and animal behavior even in the absence of the subjective states [35,273,366]. By 'liking', we refer to the underlying core process of hedonic evaluation that typically produces conscious pleasure, but that can occur without it. By 'wanting', we refer to the underlying core process that instigates goal-directed behavior, attraction to an incentive stimulus, and consumption of the goal object. For a recent review of evidence for 'unconscious core processes' of reward, see Berridge [35].

sumption. For example, Simansky et al. [425] found that hypothalamic DOPAC/dopamine ratios were increased by conditioned stimuli that ordinarily preceded a meal as much as by the meal itself. Blackburn et al. [52] showed that nucleus accumbens DOPAC/dopamine ratios were more highly elevated by *conditioned stimuli* for food presented alone, without food itself, than by the unexpected opportunity to eat. Using in vivo voltammetry, Phillips et al. found that, during the course of a meal, dopamine release was triggered *before* the meal by conditioned stimuli, and remained high until after the end of the meal [345–347]. Richardson and Gratton similarly reported that, as rats became experienced with the associative relationship between cues and food, dopamine release in the nucleus accumbens shifted forward in time from the presentation of food itself to presentation of conditioned stimuli that had been paired with food [359]. Using voltammetry, Kiyatkin and Gratton [260] found that a dopamine-related signal increased in *anticipation* of a food reward as trained rats performed a bar press response, and that increments in dopamine activity were time-locked to the goal-directed response in advance of food delivery.

Electrophysiological studies by Schultz and colleagues also have shown that dopamine neurons discharge in response to conditioned stimuli predictive of food rewards to a greater extent than when animals actually eat the food (i.e., before they presumably experience the pleasurable taste of food). In *inexperienced* monkeys mesolimbic and mesostriatal dopamine neurons discharged only when a palatable liquid was delivered to their mouth or when they were allowed to touch food with their hand [5,278,398,403]. But after a neutral conditioned stimulus (e.g., light) was repeatedly paired with food, dopamine neurons *stopped* responding to food itself and instead fired vigorously in response to the newly established *conditioned incentive* stimulus [5,278,398,403]. In direct contradiction of a 'hedonia prediction' the neurons often failed to discharge when an experienced animal actually obtained the sensory pleasure of food in the mouth [450]. Nor was dopaminergic discharge, according to the investigators, coupled to ''mnemonic or preparatory representational task components'' [277] (p. 337), to the execution of reaching movements to obtain and retrieve food, or to sensory properties of a light unrelated to food [5,278,398,401–404,450,467]. Similarly, Kosobud et al. [269] reported that in rats trained to bar press for sucrose, ventral tegmental area (VTA) unit activity increased *prior* to the presentation of sucrose. The discharge of VTA neurons was not correlated with the moment when sucrose actually was in the mouth, when presumably the animal would experience the greatest sensory pleasure produced by the taste of sucrose, but rather preceded it [269]. Based on findings such as those described above, Schultz (1992, p. 134) concluded ''that dopamine neurons respond specifically to salient stimuli that have alerting, arousing and attention-grabbing properties''.

A similar pattern of anticipatory dopamine activation has been reported for drug rewards such as cocaine and heroin [194,263]. The mere presentation of conditioned stimuli for cocaine or amphetamine may trigger dopamine activation [120,262]. In some cases, dopamine neurons may even be more active when an animal 'wants' a drug reward than when it receives and presumably 'likes' it. For example, Kiyatkin and Rebec (p. 2583 [261]) recorded the electrophysiological activity of presumed dopamine neurons in the VTA, and found that the neurons increased their discharge rate as a rat approached and began to press the lever that would earn heroin delivery, but then decreased their discharge rate once the heroin was on board. As those authors put it, their analysis ''revealed a frank neuronal activation that began and amplified during approximately the last 40 s before the lever-press at a time when searching behavior was most intense. After the lever-press, neuronal activity declined and this change (decline) became statistically significant at 36–38 s after the onset of drug injection at a time when the rat completely froze.''

2.1.2. Failures to find conditioned anticipatory dopamine activation

By contrast, several microdialysis studies have failed to find anticipatory dopamine activation, instead finding it only when the food or heroin reward was actually obtained [493,511]. For example, Wilson et al. reported that dopamine in dialysate increased during the act of eating, but not following mere placement in a location predictive of food [493]. [5] In that study, however, it is not clear whether the training procedure (10 exposures for 10 min) sufficed to give strong *incentive* properties to the conditioning location. Wise et al. found a good relationship between dopamine overflow in the nucleus accumbens and the timing of a bar press for heroin, but dopamine levels in dialysate typically declined slightly before each new bar press, and then rose again after the drug was delivered [510,511]. This contrasts with the voltammetric and electrophysiological studies discussed above [5,120, 194,260,262,263,269,278,345–347,359,398,403,425]. Furthermore, once the first heroin reinforcer was administered, dopamine levels were 2 to 8 times higher than baseline throughout the entire session. It is important to remember that in drug self-administration studies, after the first reinforcer is delivered, small bar press-related 'peaks' take place on a 'mountain range' of already-elevated dopamine overflow. Still, Hemby et al. [224] reported that dopamine overflow in the nucleus accumbens (the average height of the mountain range) was higher for rats that

[5] It is interesting that Wilson et al. [493] also found that prior food deprivation increased the dopamine overflow triggered by actual eating. Greater dopamine activation when hungry is consistent with both a hedonia and incentive salience view, since hunger increases both the hedonic palatability and the incentive value of food [33,70,71,73,212].

self-administered cocaine than for rats that passively received cocaine on a yoked schedule. It is difficult to choose among possible explanations for an enhancement of dopamine by response contingency, but the effect suggests that dopamine overflow is influenced by more than the pharmacological properties of cocaine itself. Finally, Bassareo and Di Chiara [14] found that a conditioned stimulus that predicted a palatable food elicited an anticipatory dopamine response in the prefrontal cortex but not in the nucleus accumbens.

These negative microdialysis results (also Wilson et al. [493]) are difficult to interpret. One major problem in making strong inferences from negative microdialysis results concerns the inherent insensitivity of the microdialysis method for detecting small transient events in vivo [279,342] (of the sort to be expected in response to a conditioned stimulus). Lu et al. [279] and Peters and Michael [342] have provided a powerful illustration of these limitations. Negative results must be considered, therefore, in light of the positive results from the voltammetric and electrophysiological studies reviewed above. It remains unclear what experimental factors determine a positive vs. negative outcome. In conclusion, although the literature remains a little mixed, there is ample evidence to support the contention that mesolimbic and mesostriatal dopamine systems often are activated in advance by conditioned stimuli for hedonic incentives.

2.1.3. Anticipatory dopamine activation: multiple interpretations

Anticipatory responses by dopamine neurons to conditioned incentive stimuli have provided the grounds for various 'reward learning' hypotheses of dopamine function. These anticipatory dopamine responses have often been interpreted to reflect a form of 'neural expectation', a prediction of subsequent reward value, a correlational error detector, a teaching signal, or similar component of an associative mechanism that is dedicated to learning about rewards [3,4,23,24,61,89,116,304,400,405,416,488]. However, anticipatory responses to salient stimuli that have alerting, arousing and attention-grabbing properties are equally compatible with the incentive salience hypothesis. If the conditioned stimulus itself is attractive to the animal, and serves as a conditioned reinforcer, then it has acquired incentive salience of its own. The difference between the two views is that a learning hypothesis posits that dopamine neurons mediate *associative learning* and expectations *based on previous experience* with a stimulus. It ascribes conditioned dopamine activity chiefly to the *predictive* value of the conditioned stimulus: what has been in the past is predicted for the future. The incentive salience hypothesis, by contrast, ascribes conditioned dopamine activity to its *incentive* value: whether it is 'wanted'. This difference will be elaborated below.

But even the hedonia hypothesis of dopamine function could be reconciled with anticipatory neural activity if one interpreted early neural activity to reflect *conditioned hedonic activation*. Conditioned stimuli that have been paired with hedonic stimuli can sometimes evoke a conditioned hedonic response on their own [42,49,63,113,377, 460,463,499,500]. Conditioned stimuli for pleasant tastes or unpleasant shocks, for example, do indeed evoke a variety of hedonic or fearful affective reactions [42, 113,273,358].

As mentioned above, however, it is difficult for the hedonia hypothesis to explain why a conditioned hedonic response should sometimes be of *greater magnitude* than the unconditioned hedonic response to food itself. It is also difficult for the hedonia hypothesis to explain why with training neurons should *stop responding to the unconditioned reward itself*, and respond only to a conditioned stimulus, as described by Schultz et al. [5,278,398,403,450]. However, it should be noted that some of these experiments involved overtraining of a rewarded response (10,000 to 30,000 trials). Extensive overtraining has been shown to detach motivational properties from conditioned responses, leaving the response relatively automatic and habitual in nature, devoid of hedonic/incentive features that characterized it earlier (see Dickinson [124,125]).

A further defense of the hedonia hypothesis could be mounted if the activation of dopamine neurons turns out to have *self-limiting* properties, which shut the neurons off after they have fired. There may be some grounds for this defense. Depolarization inactivation may inhibit dopamine neurons from subsequent activation under some circumstances [192,502]. For example, phasic bursts of firing may produce post-burst inhibition of dopamine neurons [192,193], and post-burst inhibition of subsequent neural firing is especially strong for dopamine neurons that project to the nucleus accumbens [84]. A 'burst pattern' of firing seems to be a strong feature of dopamine neurons [321]. The phenomenon of post-burst inhibition of dopamine neurons means that a robust response to a conditioned hedonic stimulus could conceivably inhibit the response to the unconditioned event that follows, at least under some conditions.

3. Brain manipulations of behavior for revealing dopamine's function in reward

The electrophysiological and neurochemical studies of dopamine activity discussed above do not allow us to conclusively exclude any hypothesis of dopamine function in reward. At best, these studies provide *correlational* evidence for a particular functional hypothesis, and at worst, the evidence is compatible with more than one hypothesis, perhaps with all. Thus, the results of electrophysiological and neurochemical studies so far do not by themselves justify rejection of the anhedonia hypothesis, or permit a choice between reward prediction and incentive salience alternatives.

A different approach to the question is to *manipulate neural systems* by drugs, electrical stimulation, or lesions, and to apply *behavioral measures* designed to choose among competing hypotheses. Of special interest to our discussion are behavioral measures of *affective reactions* designed specifically to detect the hedonic impact of a reinforcer. A behavioral measure that separates *hedonic impact* ('liking') from incentive value ('wanting') or reward prediction (expected reward) could potentially distinguish between the effects of dopamine manipulations on hedonia, incentive salience or reward learning.

3.1. Traditional measures of reward: instrumental behavior and choice ('wanting')

Traditional behavioral methods for measuring reward typically quantify preference (choice), consumption of a goal (intake), or instrumental behavior (bar press, runway, or approach). Whether an incentive stimulus is 'liked' is then *inferred* based on behavioral evidence that it is 'wanted' (i.e., whether an animal will choose it, consume it, or work to acquire it). The inference is grounded on the assumption that rewards are always 'wanted' to the same degree as they are 'liked'. With these traditional methods 'wanting' cannot be discriminated from 'liking', because both are viewed through the same lens (measured by the same dependent variable). Direct evidence that dopamine mediates 'wanting' specifically or 'liking' specifically would require that changes in reward '*liking*' be measured *separately* from reward '*wanting*'.

3.2. Measures of reward based on affective reactions ('liking')

An entirely different approach to studying brain mechanisms of reward (especially food reward) is to use a measure of hedonic impact such as behavioral affective reactions [35,144,273]. Unlike measures of instrumental behavior, affective expressions do not assess the 'wanting' for a reward in advance of obtaining it. Instead, as pointed out over a century ago by Darwin [109] and James [241], affective reactions typically reflect the *emotional impact* of a motivational event once the event is actually encountered. Regarding reward, emotional or hedonic impact corresponds more closely to 'liking' than to 'wanting'.

Most familiar to readers are human *affective facial expressions* as a measure of emotional impact. Affective facial expressions often reflect emotional states, but have the potential limitation (in socially competent individuals) of being feigned or suppressed in the service of social intentions [109,140,141,177]. The human ability to voluntarily control affective expressions to pleasant or unpleasant tastes and odors appears in childhood [184,436]. But newborn humans show distinct facial affective reactions to sweet or bitter tastes *even on the day of birth*, before they are subject to social control. Thus, in newborns, facial affective reactions are thought to reflect relatively directly the infant brain's hedonic or aversive evaluation of the taste [441,442,445]. Human infants, and both infant and adult apes and monkeys, show similar hedonic and aversive expressions to sweet and bitter, and the expressions become increasingly different in pattern from humans' as phylogenetic distance grows [443–445]. Related patterns of hedonic and aversive affective reactions are found even in rats: patterns of tongue protrusion by rats to sweet sucrose, and of gapes and headshakes to bitter quinine (described originally by Grill and Norgren [210]).

3.2.1. Taste reactivity patterns as a measure of 'liking'

The taste reactivity test is a method that can be used to assess the hedonic impact of tastes ('liking' or perceived palatability) by quantifying behavioral affective reaction patterns elicited by tastes [34,206,210]. Rats, which are generalized omnivores, prefer sweet foods and avoid bitter ones, as do many primates [377], and these preferences are reflected in their affective reactions to tastes. Some affective reactions of rats to food overlap with those of primates (including gapes to quinine and rhythmic tongue protrusions to sucrose [445]), whereas others are different [210,445]. The taste reactivity test measures the immediate 'liking' reaction of a rat to a taste reward after it is received, even if delivered by an intra-oral cannula. *(The rationale and evidence for this proposition are summarized in Addendum 1)*. Thus, with the taste reactivity test affective 'liking' evaluations of a taste can be quantified independently of whether a taste stimulus is 'wanted' (i.e., of whether an animal will work for it or choose it). Indeed, taste reactivity can be measured even in animals incapable of any instrumental action or voluntary eating [211].

There is now considerable evidence that measures of taste reactivity reflect core evaluations of a taste's hedonic and aversive impact [34,206]. That is, taste reactivity patterns are true affective expressions, connoting core processes of 'liking' and 'disliking' (see Addendum 1). Thus, the taste reactivity test provides a means to explore the neural substrates for hedonic 'liking', and can complement studies of human hedonic affect. Of course, data for human subjective reports are available for only a few selective manipulations, usually pharmacological (which will be discussed later). By comparison, an important strength of the taste reactivity technique is that it can be applied to many diverse brain systems using animal subjects. Hedonic and aversive reaction patterns have been used in neurobehavioral studies to identify brain substrates of food 'liking'.

- The opioid agonist, morphine, administered systemically, intraventricularly, or directly into the shell region of the nucleus accumbens enhances hedonic reactions to sweet and other tastes under conditions similar to those in which it elicits feeding [131,336,338]. Aversive reactions, by contrast, are not enhanced, but instead inhibited by morphine [86,131,332]. In other words, an accumbens opioid neural circuit is involved in hedonic activation or 'liking'.

This is consistent with suggestions that opioid systems mediate food palatability [87,98,186,226,227,276,481], a hypothesis that receives some support from human subjective rating studies [133,520].

• Benzodiazepines, such as diazepam, chlordiazepoxide, or midazolam, promote feeding in animals and humans [92,97,257,509]. This has been argued by Cooper et al. [92,93] to be driven by a drug-induced increase in the hedonic palatability of food. Taste reactivity studies confirm this hypothesis. When administered to rats systemically, into the cerebral ventricles, or directly to the hindbrain, benzodiazepines enhance hedonic reaction patterns just as morphine does [40,43,95,328,337,431,465]. Aversive reaction patterns are never enhanced by benzodiazepines. In other words, a brainstem benzodiazepine/GABA circuit contributes to hedonic taste processing [40].

• Conversely, blanket 'disliking' for food is produced by several forms of brain damage that result in aphagia. After electrolytic lesions of the lateral hypothalamus, circumscribed excitotoxic lesions of the ventral pallidum, or ablation of the ventral forebrain even sweet foods elicit aversive reactions, and hedonic reactions are suppressed or abolished [36,106,211,446,455]. These lesions overlap each other in their pattern of neuronal destruction, and have been suggested to involve the loss of a common 'liking' circuit in the ventral pallidum, resulting in disinhibition of aversion [34].

3.3. Dopamine manipulations dissociate 'wanting' vs. 'liking'

Manipulations of mesolimbic/neostriatal dopamine systems also potently modify the motivation to eat ('wanting' measured by voluntary intake, preference tests, or instrumental behavior for food). However, dopamine-related manipulations *fail to alter 'liking'* (measured by hedonic or aversive reaction patterns).

3.3.1. Pharmacological manipulations

Haloperidol, pimozide, and other dopamine receptor blockers decrease the incentive or reward value of food, as measured by intake, preference, or instrumental measures [429,499,500,514]. But dopamine antagonists do not shift the hedonic palatability of tastes toward aversion, as measured by taste reactivity [339,465]. [6] Conversely, dopamine agonists do not increase hedonic reactions to tastes [34,465], although they can alter their incentive value [150,151,424], and produce sensorimotor disruption of elicited reactions [326,379,382,386,391,392,452].

3.3.2. Electrical stimulation of the lateral hypothalamus

Electrical stimulation of the lateral hypothalamus (LH) can elicit robust eating and is typically rewarding in its own right [231,474]. LH stimulation involves many neural systems, but activation of ascending dopamine projections appears to be one crucial link in the chain of neural events important to feeding and reward [157,348,375,472,519]. A stimulation-induced increase in perceived palatability has been suggested as one way by which LH stimulation might increase feeding [232]. The hedonia hypothesis also predicts LH stimulation would increase food hedonics, if dopamine activation mediates the effect of stimulation. But Berridge and Valenstein found that electrical stimulation of the lateral hypothalamus *fails to enhance hedonic taste reactivity patterns* in rats even though they eat avidly when the stimulation is on [44]. If anything, electrical stimulation increases *aversive* reactions to palatable tastes. That is, LH electrical stimulation apparently elicits eating not because it makes food 'taste better', but despite making it 'taste worse' [44]. The feeding induced by LH stimulation is strikingly unlike that produced by opioids or benzodiazepines, and unlike natural hunger or specific appetites such as salt hunger. All of these other manipulations make the eaten food both 'liked' and 'wanted'—that is, they enhance both feeding and hedonic reaction patterns [38,40,73,131]. The paradoxical 'wanting' without 'liking' produced by LH stimulation can be explained by hypothesizing that the electrode activates dopamine substrates of incentive salience selectively, but bypasses hedonic neural systems of food reward [34,44] (see Fig. 6).

3.3.3. 6-Hydroxydopamine (6-OHDA) lesions

The massive destruction of ascending dopamine neurons with 6-OHDA causes profound aphagia [470,471]. But an earlier study by us of whether dopamine depletion diminishes the *hedonic impact* of foods found that intranigral 6-OHDA lesions, which produced both aphagia and adipsia, *failed to suppress hedonic reaction patterns or to increase aversive reaction patterns* [45]. Instead, hedonic and aversive taste reactivity patterns to sweet, sour or bitter tastes remained normal after 6-OHDA lesions. From those results, we concluded that the nigrostriatal dopamine pathway was not necessary for a normal hedonic response to food rewards, and that dopamine depletion did not induce anhedonia [45].

4. Effects of mesolimbic and neostriatal dopamine depletion on subcomponents of reward

This brings us to our current study, which was intended to deal with short-comings in our previous study, and to determine if any aspects of reward remain intact after the

[6] The conclusion that dopamine antagonists do not shift 'liking' was the focus of an earlier controversy, because several studies by Parker and colleagues had indicated that pimozide might gradually reduce hedonic 'liking' and increase aversive 'disliking' if the taste stimulus was sustained continuously for more than a few minutes [274,331]. However, crucial evidence for anhedonia has failed to replicate in a recent collaborative re-examination of those data by Peciña et al. (discussed below) [339]. It can be stated as a general conclusion, now shared among all laboratories that have studied the effect of neuroleptics on affective taste reactivity, that dopamine antagonists do not produce anhedonic palatability shifts in taste reactivity patterns.

brain is depleted of mesolimbic and mesostriatal dopamine. First, several objections can be raised to our earlier conclusion that dopamine loss fails to produce anhedonia.

· The average dopamine depletion in our earlier 6-OHDA study was only 85% [45]. Our animals were aphagic, but some have argued that dopamine depletion above 90% to 95% may be required in order for 6-OHDA lesions to produce their full behavioral impact [451,452].

· Dopamine concentrations in the nucleus accumbens were not measured in our earlier study [45]. Residual accumbens dopamine probably exceeded 15% because 6-OHDA lesions in the substantia nigra would have spared substantial projections from the ventral tegmentum to the nucleus accumbens. Therefore, the normal hedonic reactions could have been mediated by residual dopamine in the nucleus accumbens.

· Only *unconditioned* affective reactions to novel tastes were investigated in our earlier study [45]. This leaves open an alternative interpretation: namely, that dopamine depletion may have *decoupled control of taste reactivity patterns from forebrain control* rather than preserving normal hedonic evaluations (an alternative originally suggested to us by Jane Stewart) [449]. That interpretation hinges on the following logic. The evidence that taste reactivity patterns ordinarily reflect forebrain hedonic evaluations comes from demonstrations that associative experience alters affective taste reactivity patterns [30,42,63,209,330,530]. This effect is eliminated after decerebration or certain forebrain lesions [206,207,209,426]. The capacity of decerebration to block modulations of affective reactions indicates that the modulation normally reflects forebrain hierarchical control of brainstem circuitry [206]. The possibility arises, therefore, that 6-OHDA lesions might also eliminate the forebrain's capacity for *hierarchical control* of affective reactivity patterns based on forebrain hedonic evaluations, even though they spare unconditioned taste reactivity reflexes mediated by the brainstem. If the 'forebrain decoupling' hypothesis were true, then it would be possible for dopamine depletion to have rendered the forebrain anhedonic without any evidence appearing in behavioral taste reactivity patterns. It is possible to test this hypothesis. If it is true, then effects such as conditioned aversion shifts in taste reactivity patterns, induced by associative taste-LiCl pairing, would no longer be possible in animals that had extensive 6-OHDA lesions.

· Finally, no attempt has been made in previous taste reactivity studies to examine the *reward learning hypothesis* of dopamine function. There is evidence that dopamine systems are not needed for all types of associative learning [23]. However, dopamine might still be required to mediate *learning of reward associations*, which would be needed to give new hedonic reward properties to a stimulus, for example, as has been suggested by Di Chiara [116,117] and by Beninger and Miller [26]. Can hedonic reactions to a stimulus be transformed by new learning after dopamine depletion, based on conditioned relations that predict later consequences of that stimulus?

4.1. General experimental approach

The present experimental study was undertaken in order to deal with these issues. It aimed to test more adequately whether mesolimbic and neostriatal dopamine systems are needed for normal hedonic reactions to food reward, or for modulation of hedonic reward properties. In this study 6-OHDA lesions were placed in the lateral hypothalamus at a point where fibers from both the substantia nigra and the ventral tegmentum pass closely together. This produced, in some animals, a 98% to 99% depletion of dopamine in the nucleus accumbens and neostriatum (caudate/putamen).

In Experiment 1, we assessed unconditioned hedonic and aversive taste reactivity patterns to sucrose and quinine in aphagic rats that had extensive dopamine depletion.

In Experiment 2, we assessed the capacity of dopamine-depleted rats to *change the hedonic reward value* of a stimulus by *forebrain-mediated associative learning*, using a taste-aversion conditioning procedure. A novel preferred taste was associatively paired with systemic administration of LiCl. The affective reactions emitted by 6-OHDA rats were monitored to determine whether their reactions switched from hedonic patterns to aversive patterns as a consequence of associative learning.

In Experiment 3, we assessed the capacity of dopamine-depleted rats to show *enhancement of hedonic reactions* after administration of a benzodiazepine agonist, diazepam, that normally induces hyperphagia and that increases hedonic palatability.

In every experiment, the affective taste reactivity patterns of 6-OHDA rats were similar to those of control rats. The elimination of dopamine from the nucleus accumbens and neostriatum does not appear to produce anhedonia for food rewards, nor to block the pharmacological modulation of food 'liking', nor to block the learning or expression of new likes and dislikes.

5. Experiment 1: Unconditioned affective reactions to sucrose or quinine

5.1. Methods

5.1.1. Surgery

Thirty-eight female and male Sprague–Dawley rats (260–310 g at surgery) were housed individually in plastic tub cages with wood shaving bedding.

Rats were anesthetized with ketamine (87 mg/kg. i.p.) and Rompun (13 mg/kg, i.p.). Each was pretreated with atropine methyl nitrate (5 mg/kg, i.p.) to prevent respiratory distress, bicillin (30,000 units, i.m.) to prevent infec-

tion, and desipramine (15 mg/kg, i.p.) and pargyline (50 mg/kg) to protect norepinephrine terminals and maximize dopamine depletion. Thirty min after drug pretreatment, a midline incision was made, the dorsal skull was exposed, skull screws were placed, and bilateral holes were drilled for microinjections. The dura was opened, and a 30-gauge injection cannula was lowered to intercept ascending dopamine projections (AP = −4.0 mm from bregma; L = +1.8 mm from midline; V = −8.3 mm from skull surface). Twenty-eight rats received bilateral infusions of 8 μg of 6-hydroxydopamine HBr (6-OHDA) dissolved in 4 μl of vehicle (0.9% NaCl solution containing 0.1 mg/ml ascorbic acid). Ten control rats received microinjections of the vehicle solution alone. Infusions were delivered over an 8 min period using an infusion pump, and the injection cannula was left in place for 5 min after the infusion.

In the same surgery, bilateral chronic oral cannulae to permit taste reactivity testing were implanted. The PE-100 cannulae, heat flared at the oral end, entered the mouth lateral to the first maxillary molars, where they were anchored with a Teflon washer. Oral cannulae ascended lateral to the skull, beneath the zygomatic arch, and exited the head dorsally where they were attached to 19-gauge. steel tubing and anchored to the skull screws with dental acrylic cement.

5.1.2. Postsurgical maintenance and recovery

Rats that received lesions were artificially fed and watered by intragastric intubation as follows. On the day after surgery, each rat was intubated twice with 10 ml of water to prevent dehydration. Each day a palatable cereal mash (moistened Gerber's baby cereal) and fresh Purina rat chow pellets were provided on a free access basis. Food and water intake and body weight were monitored daily. Beginning on the second day after surgery, rats that lost weight were intubated with a liquid diet. For every 5 g body weight loss, the rat was intubated with 12 ml of a liquid diet (made of equal parts of sweetened condensed milk and water, with a multivitamin supplement added), up to a maximum of three intubations per day.

Rats were classified as *aphagic* on a given day if they ate neither cereal mash nor chow. Aphagic rats received all of their nourishment by intubation of liquid diet. If rats ate *any* cereal mash or chow pellets on a given day, they were classified as *not aphagic* and were excluded from the study. Rats that were aphagic for at least one week were used in this study, and *only data collected during their period of aphagia* were used for the analysis presented below. Non-aphagic rats were excluded because for this study it was of interest to determine if 'liking' remained only if 'wanting' was abolished.

Of the twenty-eight rats that received 6-OHDA lesions, two died during the 7-day recovery period before testing began. Four 6-OHDA rats began to eat cereal mash or chow during this time, and were dropped from the study. Twenty-two 6-OHDA rats remained aphagic on the 8th day after surgery, and proceeded to taste reactivity testing. Of these, 12 remained aphagic throughout the entire test series (17 days after surgery), and data are presented only for these long-term aphagic rats.

5.1.3. Behavioral taste reactivity testing

Behavioral testing began on the eighth day after surgery. A single taste reactivity trial was given each day, using one of three stimulus solutions: Sucrose (either 0.3 M or 1.0 M), or Quinine HCl (3×10^{-4} M). Each stimulus solution was administered three times, in counter-balanced order, over a period of nine days.

On each trial, a rat's oral cannula was connected to an infusion line (PE-50 tubing with a PE-10 nozzle). The rat was placed in a transparent test chamber and allowed to habituate for 5 min. A 1 ml volume of the stimulus solution was infused into the rat's mouth over a period of 1 min. A mirror positioned beneath the transparent floor of the chamber reflected the image of the rat's face and mouth into the close-up lens of a video camera. Videotaped records were saved for later slow-motion analysis of taste reactivity.

Taste reactivity components were scored in slow-motion, ranging from frame-by-frame to 1/10th actual speed [210]. Three classes of affective taste reactivity patterns were scored: hedonic, aversive, and neutral (for discussion of hedonic/aversive classification of taste reactivity patterns, see [34,40,206]. *Hedonic* reaction patterns were considered to be: lateral tongue protrusions, rhythmic tongue protrusions, and paw licks. *Aversive* reaction patterns were considered to be: gapes, chin rubs, face washing, forelimb flails, paw tread, and locomotion (see [210] for descriptions). Several reaction patterns are less reliable as indicators of an acceptability evaluation, and were classified here as *Neutral*: rhythmic mouth movements, passive drip of the solution, and sequential alternation between face washing and paw licks with less than 1 s transition (a sequential combination which is typical of self-grooming, and which when combined in sequential alternation is not associated with other hedonic or aversive reactions; for hedonic/neutral/aversive classification of taste reactivity patterns, see [40]). Each lateral tongue protrusion, gape, and chin rub were counted as individual events. Each *instance* of face washing, forelimb flailing, and locomotion (in which several rapid movements are typically chained in a brief bout) was counted as a separate event. Rhythmic midline tongue protrusions, which may be emitted in continuous bouts of several seconds, were counted in 2-s bins (one tongue protrusion or a continuous series of up to 2 s duration were counted as 1 bin; 3–4 continuous seconds of tongue protrusions were counted as 2 bins, etc.). Rhythmic mouth movements and paw licks, which often are emitted in even longer bouts, were counted similarly in 5-s bins. This scoring system helps equalize the contribution of different reaction types to the final hedonic or aversive scores, by preventing actions that

occur more frequently from dominating the affective category [39].

5.1.4. Neurochemistry

At the end of the experiments 7 control rats and 12 6-OHDA lesion rats that had remained aphagic for at least 2 weeks were killed humanely by instantaneous decapitation, and their brains were removed and placed in iced saline within 40 s of death. Each brain was cooled for 1 min, placed on a cutting block, and sliced [222]. The left and right neostriatum (caudate-putamen) and the left and right nucleus accumbens were extracted by micropunch. Each tissue core was weighed, and the left and right sides from each structure were placed together in separate tubes containing 400 ml $HClO_4$ (0.05 N), to which 250 ng dihydroxybenzylamine was added. The tissue was homogenized, and the suspension was centrifuged for 45 min ($5000 \times g$). The supernatant was filtered through 0.45-mm pore filters, and the samples were frozen at -20°C. Within two weeks, the samples were assayed by HPLC with electrochemical detection, using procedures similar to those described previously [368]. Dopamine concentrations in the neostriatum and nucleus accumbens were ascertained for each rat, and the *percentage of dopamine depletion* for each 6-OHDA brain was calculated based on the mean concentrations of dopamine in the neostriatum and the nucleus accumbens of control rats.

5.2. Results

5.2.1. Neurochemistry

The mean concentration of neostriatal dopamine in control rats was 10.36 ± 0.51 ng per mg wet tissue weight, and was 8.50 ± 0.31 ng/mg in the nucleus accumbens (Fig. 1). Rats that had received 6-OHDA lesions had reduced concentrations of dopamine: 1.09 ± 0.58 ng/mg in the neostriatum, and 2.19 ± 0.49 ng/mg in the nucleus accumbens. Overall, the group of 12 rats with 6-OHDA lesions had dopamine depletion of 90% in the neostriatum and 74% in the nucleus accumbens.

Many of the 6-OHDA lesion rats, however, had more severe dopamine depletion. Eight of the 12 were depleted of neostriatal dopamine by more than 98%. In this group of 8 rats, *neostriatal dopamine was depleted by 98.8 ± 0.5%, and nucleus accumbens dopamine was depleted by 85.0 ± 4.8%* (Fig. 1). A further subgroup of 3 rats from this group were depleted of dopamine by over 99% in *both* the neostriatum and the nucleus accumbens (*99.8 ± 0.1% in the neostriatum and 99.0 ± 0.2% in the nucleus accumbens;* Fig. 1).

Since the purpose of this study was to assess the consequences of the most severe dopamine depletion on affective reaction patterns, separate analyses were conducted for each group and subgroup in every experiment described below: a) aphagic 6-OHDA group as a whole

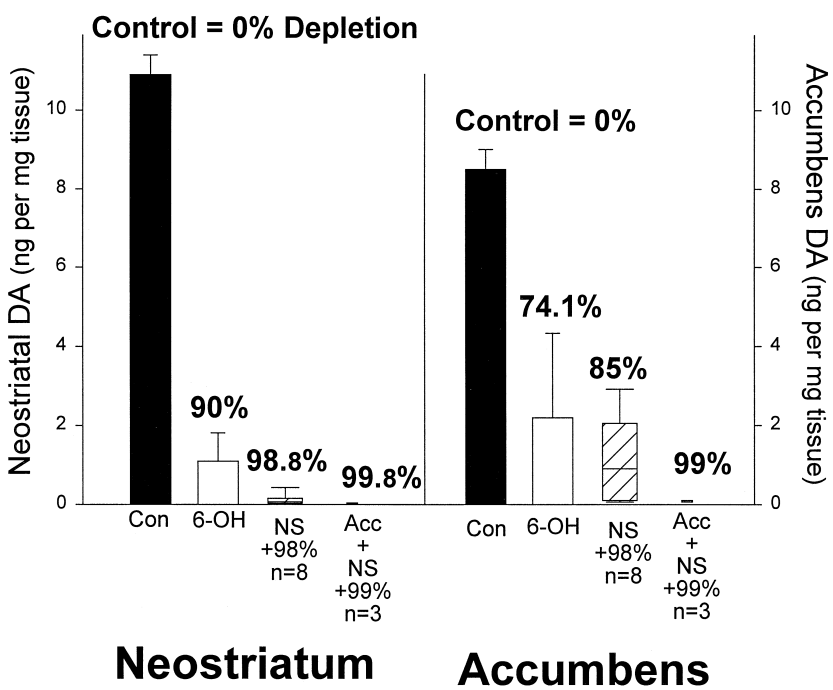


Fig. 1. Dopamine concentrations in the neostriatum and nucleus accumbens of control and 6-OHDA lesion groups. Absolute concentrations shown by bars and boxes (ng/mg tissue). Relative percent depletion of each group compared to controls is listed at top of each plot. Control and aphagic 6-OHDA groups are shown by filled and open bars (mean ± S.E.M.). The 6-OHDA subgroup with neostriatal depletion > 98% is depicted by hatched box plot (box = 25th to 75th percentile range, line shows median, error bar shows 90th percentile). The 6-OHDA subgroup with accumbens and neostriatal depletion > 99% had values too low to be graphed.

($n = 12$); b) confirmed *> 98% dopamine depletion in neostriatum* ($n = 8$); and c) confirmed *> 99% depletion in both neostriatum and accumbens* ($n = 3$).

5.2.2. Hedonic taste reactivity patterns to sucrose

Hedonic reactions. Sucrose elicited hedonic reaction patterns (rhythmic tongue protrusions, lateral tongue protrusions, paw licks) from both aphagic 6-OHDA rats and control rats; the groups did not differ in total number of hedonic reactions (Fig. 2; two-factor analysis of variance (lesion condition × sucrose concentration) $F(1,40) = 2.66$, n.s.). Concentrated 1.0 M solution elicited more hedonic reactions than did 0.3 M sucrose in both control and 6-OHDA lesion groups ($F(1,40) = 10.15$, $p < 0.01$; in this and subsequent analyses, interaction effects between lesion/control groups and other factors were never significant). In other words, aphagic 6-OHDA rats emitted the same number of hedonic reactions to sucrose as did controls, and they modulated their number of reactions appropriately to sucrose concentration.

The group of rats with > 98% neostriatal dopamine depletion ($n = 8$) similarly showed a concentration-dependent increase in hedonic reactions when compared with controls ($F(1,34) = 20.24$, $p < 0.001$). This group of severely depleted rats actually appeared to emit *more* hedonic reactions overall than did controls (mean ± S.E.M. = 5.9 + 0.9 for the neostriatum depletion > 98% group compared to 3.3 + 0.8 for the control group; $F(1,34) = 4.79$, $p < 0.05$; Fig. 2). The hedonic elevation disappeared for the subgroup of lesion rats with > 99% depletion from both accumbens and neostriatum ($n = 3$; Fig. 2). There were no significant interaction effects between dopamine group and stimulus concentration. Taken together, these data demonstrate that extensive dopamine depletion in the neostriatum and nucleus accumbens fails to impair the emission of hedonic reactions to sweet stimuli.

5.2.3. Taste reactivity component distribution

There were no differences between the control group and 6-OHDA lesion groups in the *distribution* of motor components *within* the hedonic category. For example, the groups did not differ in terms of the relative number of rhythmic tongue protrusions vs. of lateral tongue protrusions or other reactions elicited by sucrose (compared by the Mann–Whitney test). Nor did the groups differ in the *incidence* or proportion of rats that emitted each particular reaction (compared by the z test of proportion).

5.2.4. Few aversive reactions to sucrose

Sucrose elicited relatively few aversive reaction patterns from either group. The 0.3 M solution elicited slightly more aversive reactions than the concentrated 1.0 M solution ($F(1,40) = 6.12$, $p < 0.02$), but the aphagic 6-OHDA lesion rats did not differ from the control group, ($F(1,40) = 0.76$, n.s.), nor did the group of 6-OHDA rats with neostriatal depletion > 98% ($F(1,34) = 1.82$, n.s.). When the analysis was restricted to rats that were confirmed to have both accumbens and neostriatal dopamine depletion > 99%, 6-OHDA rats emitted slightly more aversive reactions to 0.3 M sucrose (3.0 + 0.5) than did control rats (1.4 + 0.3). However, neither group emitted any aversive reactions at all to more concentrated 1.0 M sucrose.

5.2.5. Aversive taste reactivity patterns to quinine

Quinine HCl elicited predominantly aversive reactions, and few hedonic reactions, from both 6-OHDA lesion rats and from control rats (Fig. 3). There was no difference between the aphagic 6-OHDA and control groups in the number of (few) hedonic reactions ($F(1,18) = 2.0$, n.s.) or aversive reactions ($F(1,18) = 0.01$, n.s.). Separate analyses restricted to the 6-OHDA 'neostriatal depletion > 98% group' or 'both accumbens and neostriatal depletion > 99% group' produced identical outcomes: in each case, 6-OHDA reactions to quinine were not different from control group reactions.

These data suggest that although some 6-OHDA rats may occasionally be more responsive than controls in both hedonic and aversive reaction patterns, dopamine depletion did not shift reactions consistently toward aversive patterns, nor did it shift reactions away from hedonic patterns. No consistent difference in hedonic/aversive reaction patterns to sucrose or quinine was produced by severe dopamine depletion.

5.3. Discussion of Experiment 1

The results of Experiment 1 confirm our earlier report that unconditioned affective reaction patterns elicited by sucrose and quinine solutions are essentially normal in rats after 6-OHDA lesions of the striatal/accumbens dopamine system [45]. They extend our earlier results to show that affective reaction patterns remain normal even after essentially complete depletion of dopamine from these structures, at levels exceeding 99% depletion from both nucleus accumbens and neostriatum.

The loss of dopamine from the neostriatum and accumbens does not appear to lead to anhedonia or a motor inability to emit affective reactions. Rats with nearly complete dopamine depletion showed no suppression of unconditioned hedonic reaction patterns to sucrose.

But the possibility remains that dopamine depletion might disrupt the expression in taste reactivity patterns of *learned hedonic shifts* induced by manipulations that depend on the forebrain. If that were true, it would raise the possibility that hedonic reaction patterns might no longer provide evidence of forebrain evaluation of hedonic events. After all, decerebration or other forebrain lesions that isolate the brainstem from forebrain control leave basic unconditioned taste reactivity motor patterns intact—but only as simpler reflexes, no longer modifiable by associative or neural manipulations that change forebrain affective

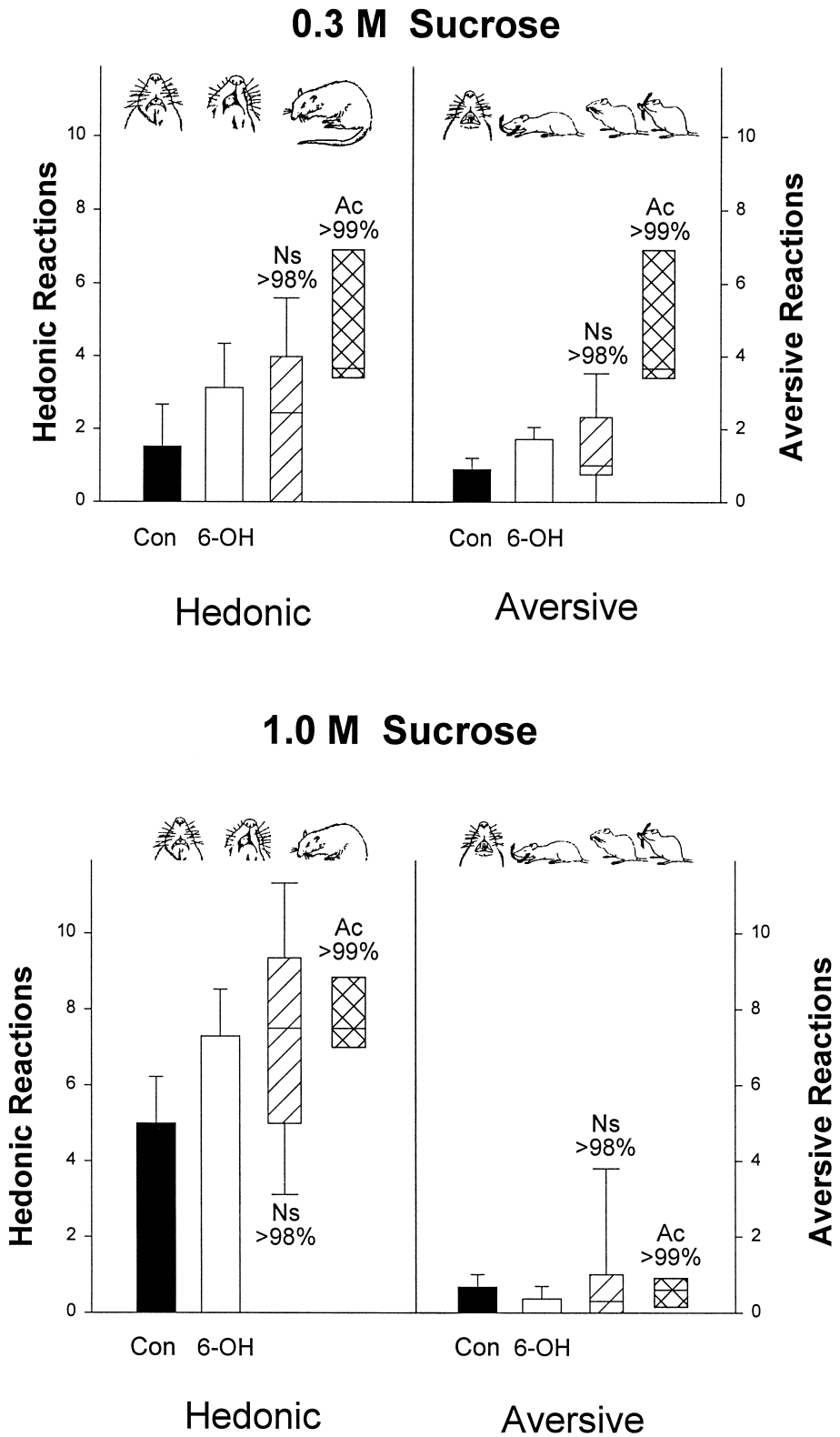


Fig. 2. Hedonic reaction patterns of control and 6-OHDA groups to oral infusions of 0.3 M (top) and 1.0 M (bottom) sucrose. Hedonic reactions are on the left half and aversive reactions on the right half of each graph. Each shows the reactions of the control group (solid bar), aphagic 6-OHDA group (open bar), 6-OHDA group with neostriatum depletion > 98% (hatched box), and 6-OHDA subgroup with accumbens + neostriatal depletion > 99% (double hatched box). Bars for control and aphagic 6-OHDA groups depict mean ± S.E.M. Hatched box plot shows affective reactions for neostriatum depletion > 98% group ($n = 8$; median shown by horizontal line, box ends show 25th to 75th percentile range, and error bars show 10th to 90th percentile range). Double hatched box plot shows entire range of affective reactions for accumbens/neostriatum depletion > 99% group ($n = 3$; horizontal line shows middle member; box end shows extreme members).

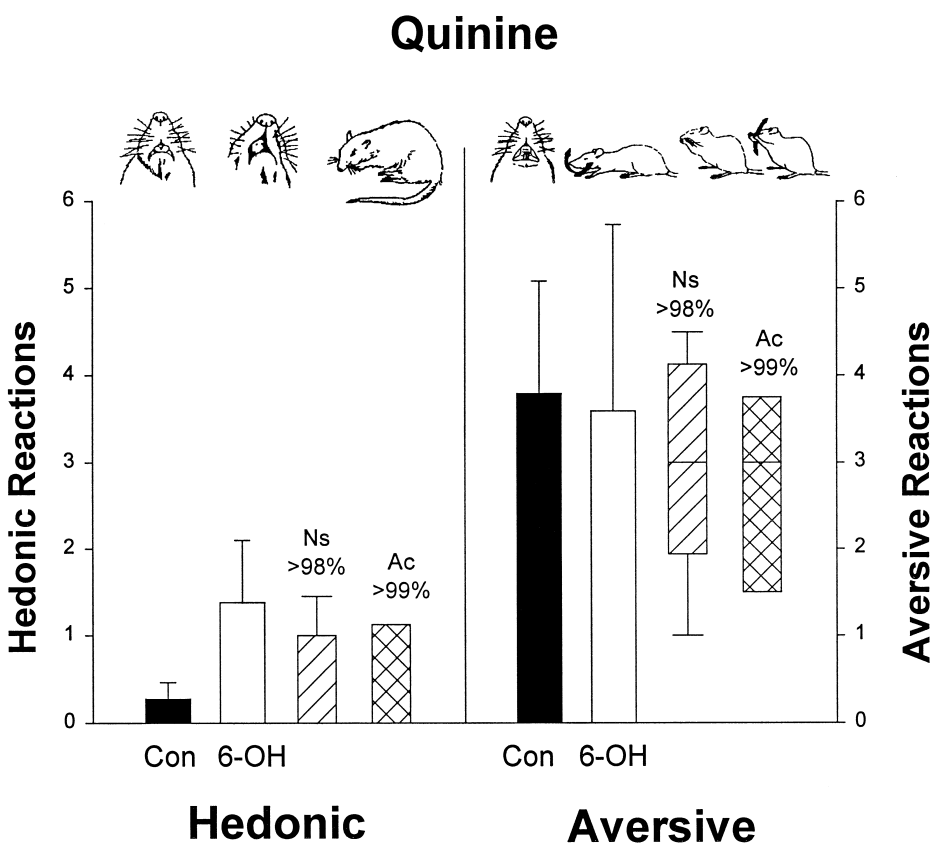


Fig. 3. Aversive taste reaction patterns of 6-OHDA and control groups to oral quinine infusion (3×10^{-5} M quinine HCl). Symbols as in Fig. 2.

evaluations [206–209,258]. On the other hand, if associative taste aversion learning still produced a normal shift from hedonic to aversive reaction patterns after dopamine depletion, it would imply that taste reactivity patterns still reflect palatability evaluations that require the forebrain.

The role of dopamine in *reward learning* is another issue that hinges importantly on whether associative conditioning can alter affective taste reactivity patterns after dopamine depletion. If 6-OHDA lesions disrupted the capacity of taste aversion conditioning to shift affective reactions, it would support the hypothesis that dopamine is especially important in order for a stimulus *to acquire new hedonic value via associative learning*, and that this is its major role in reward. But if severe dopamine depletion does not prevent the shift from hedonic to aversive reaction patterns after taste aversion learning, it indicates that dopamine is not needed to mediate associatively-acquired shifts in hedonic value.

6. Experiment 2: Modulation of affective reactions by taste aversion conditioning

6.1. Methods

6.1.1. Subjects

Eight 6-OHDA lesion rats that remained aphagic 20 days after surgery but were otherwise in good health, and 7 control rats, were used in this Experiment. The 6-OHDA group included 7 rats that had $> 98\%$ neostriatal dopamine depletion, and the 3 rats that had $> 99\%$ depletion in both nucleus accumbens and neostriatum.

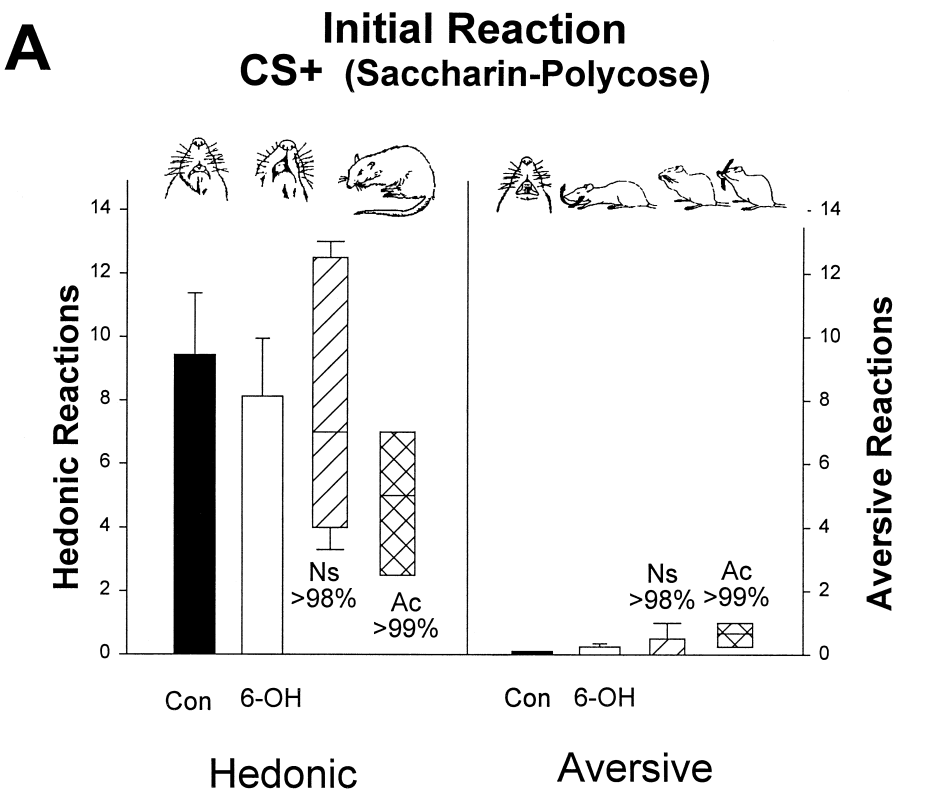
6.1.2. Taste CS +

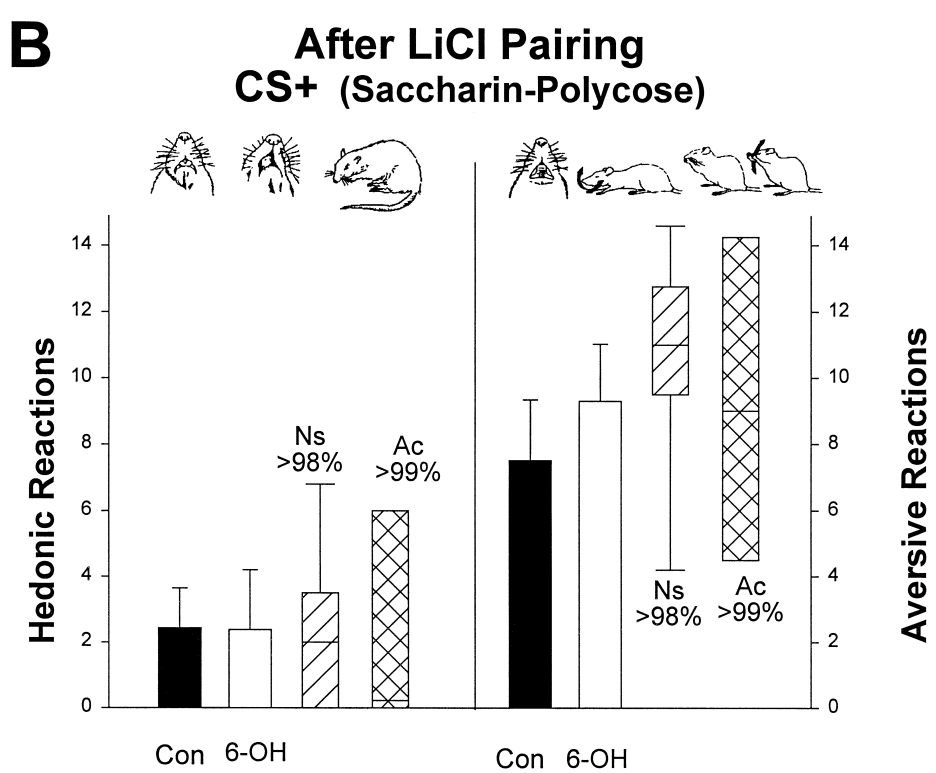
A palatable and novel saccharin/polycose solution (0.2% w/v sodium saccharin and 32% w/v polycose) was used as the conditioned stimulus [408]. Polycose by itself does not taste sweet to humans, but is a preferred solution for rats, and behavioral short term intake and electrophysiological studies indicate it to be recognized as a distinct taste by rats [156,187,313,409]. Adding saccharin to polycose increases its attractiveness to rats in preference tests [408]. Since our rats had never tasted either polycose or saccharin before, we expected this mixture to be palatable yet novel to them, suitable as a conditioned stimulus for aversion conditioning.

6.1.3. Associative conditioning and behavioral analysis

Three associative pairings were arranged of the CS + saccharin/polycose solution with a LiCl injection (unconditioned stimulus). On the first day, the oral cannula of a rat was connected to a stimulus delivery tube, and the rat was allowed to habituate in the taste reactivity test chamber for 5 min. Then a 1-ml volume of saccharin/polycose solution was infused into the rat's mouth via the cannula at a constant rate over 1 min. Taste reactivity was videotaped

during the infusion as in Experiment 1 for subsequent analysis. Immediately after the oral infusion, the rat was injected with 1.5 mEq/kg LiCl (1 ml per 100 g body weight of isotonic LiCl, i.p.), and returned to its home cage. This pairing was repeated two days later, and a third pairing was administered two days after that. A test infu-





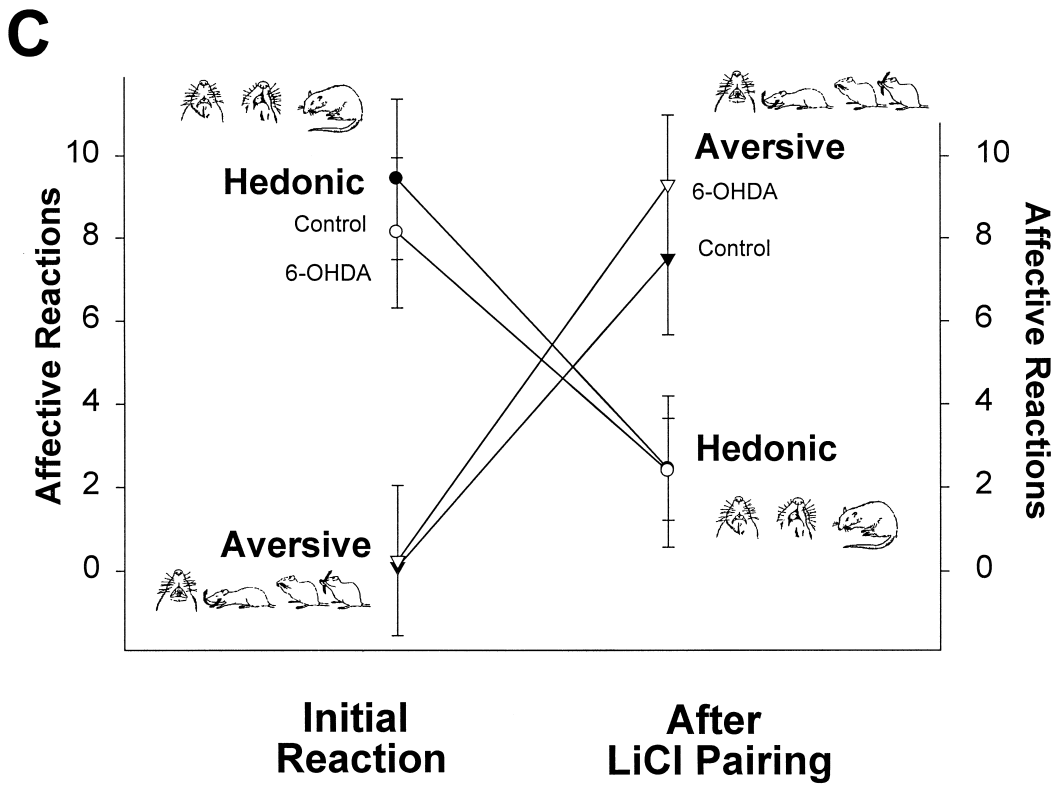


Fig. 4. Associative learning changes hedonic impact of gustatory reward. A. Initial hedonic and aversive taste reactivity patterns to saccharin/polycose solution by 6-OHDA and control groups. B. After associative pairings of saccharin/polycose taste (as CS+) with LiCl (as UCS). The relatively high hedonic reaction rate for the accumbens >99% depletion subgroup after aversion conditioning reflects the response of 1 rat (Bar shows entire range of subgroup). The other 2 rats in this subgroup had zero hedonic reactions after LiCl pairing. Symbols as for Fig. 2. C. Summary of 'before and after effects' of associative aversion learning on hedonic and aversive reactions produced by the entire 6-OHDA group and the control group. The change in hedonic impact of the CS+ taste is equivalent for the two groups.

sion of saccharin/polycose was administered a fourth time two days after the third pairing, and taste reactivity was recorded. A slow-motion videoanalysis of behavioral taste reactivity patterns was conducted as in Experiment 1.

6.2. Results

Strongly hedonic reaction patterns were emitted by both the aphagic 6-OHDA lesion and control groups to the saccharin/polycose infusion the first time it was delivered (Fig. 4). After 3 associative pairings, however, a marked shift in taste reactivity patterns toward aversion was seen for both groups (Fig. 4). A two-way ANOVA (associative conditioning × lesion group) showed that hedonic reactions were reduced for both groups by taste aversion conditioning ($F(1,29) = 13.8$, $p < 0.01$). 6-OHDA rats did not differ from control rats in hedonic reactions on either the first (naive) day or on the test day after conditioning ($F(1,29) = 0.1$, n.s).

Conversely, the number of total aversive reactions (gapes, headshakes, face washes, forelimb flails, chin rubs, paw treads) was dramatically increased for both aphagic 6-OHDA and control groups by associative pairing with LiCl ($F(1,29) = 28.6$, $p < 0.001$; Fig. 4). Again, there was no difference between aphagic 6-HDA rats and control rats in the number of aversive reactions ($F(1,29) = 1.4$, n.s.).

These results held true for both the group of 6-OHDA rats that had >98% depletion of neostriatal dopamine ($n = 7$), and for the subgroup that had >99% accumbens and neostriatal depletion ($n = 3$; Fig. 4). For the >98% neostriatal depletion group, hedonic reactions were reduced by associative conditioning ($F(1,27) = 11.2$, $p < 0.01$), whereas aversive reactions were increased ($F(1,27) = 23.9$, $p < 0.001$), and neither the hedonic nor aversive reactions of this group differed from the control group ($F(1,27) < 1.0$, n.s.). For the >99% accumbens and neostriatal subgroup, two of the three rats reduced their hedonic reactions to zero after aversion conditioning, but the third rat emitted as many hedonic reactions as it had before, so the hedonic reduction was only marginally significant ($F(1,19) = 4.3$, $p = 0.07$). However, even this subgroup showed a robust and unanimous increase in aversive reactions to saccharin/polycose after associative conditioning ($F(1,19) = 13.7$, $p < 0.01$), equivalent to that of control rats ($F(1,19) = 0.6$, n.s.; Fig. 4).

6.3. Discussion of Experiment 2

Severe dopamine depletion did not disrupt the acquisition or expression of an associative shift from hedonic reactions to aversion. This implies that *forebrain* neural

systems needed for the revaluation of rewarding stimuli remained functional. Associative taste aversions are mediated by distributed neural circuits that require the forebrain as well as the brainstem [258,318,390,426,438]. For example, Grill and Norgren [209] showed that taste-LiCl pairings fail to change behavioral taste reactivity patterns of mesencephalic decerebrate rats (which were transected above the superior colliculus). Our results indicate that forebrain evaluations of affective value still control affective taste reactivity patterns even after extensive 6-OHDA depletion of neostriatal and accumbens dopamine. Aversive reaction patterns to a LiCl-paired taste still reflect forebrain-based aversive evaluations. By implication, the normal hedonic reactions to novel polycose/saccharin prior to LiCl pairing (and to sucrose in Experiment 1) reflected a normal forebrain-based hedonic evaluation.

Our results also show that rats with extensive dopamine depletions are capable of changing their hedonic evaluation of a stimulus based on predictive relations with another event; that is, they are capable of reward learning. Associative decrements of old hedonic value and increments of new aversive value, at least, do not appear to require the integrity of ascending dopamine systems. Whether hedonic increments produced by associative pairing also persist after dopamine depletion remains an open question for the time being. But unless decreases in hedonic value are mediated by a neural system separate from that which mediates increases, it seems likely that learned hedonic increments might also be possible for these rats. And although some evidence has implicated a differential role for dopamine systems in pleasant vs. unpleasant events [301] (but see [380] and discussion below regarding dopamine mediation of aversive motivation), reward learning models have posited dopamine systems to play a similar role in learned increments and learned decrements in prediction of hedonic rewards [304,405]. Whatever role dopamine systems may play in learning about rewards, our results suggest they are not required to shift the hedonic or aversive value of rewards as a function of prior experience.

7. Experiment 3: enhancement of hedonic reaction patterns by diazepam

Experiment 2 demonstrated that dopamine depletion does not disrupt the capacity of learned negative associations to make tastes more aversive. But do 6-OHDA lesions eliminate the capacity to modulate palatability in the positive hedonic direction? Could *hedonic* reaction patterns still be enhanced? The conclusion that basic hedonic impact remains normal after dopamine depletion would be strengthened if that were true.

For normal rats hedonic reactions to taste are heightened by prior administration of benzodiazepine agonists such as diazepam, chlordiazepoxide, or midazolam [40, 43,95,97,199,328,431,465,466]. Benzodiazepine agonists also elicit feeding in normal rats [69,92,97,509]. Aphagic 6-OHDA rats would not be expected to show drug-elicited feeding. But if their deficit is primarily one of 'wanting' food rather than 'liking' food, and if their ability to modulate hedonic processes remains normal, then they ought to show enhanced hedonic reactions to a taste delivered to the mouth after treatment with a benzodiazepine agonist. Conversely, if dopamine depletion induces anhedonia, then hedonic enhancement ought to be impaired.

7.1. Methods

Seven 6-OHDA rats that had remained aphagic for 28 days after surgery, and 5 control rats, were used in this experiment. The 6-OHDA rats included the group of 6 rats that were later confirmed to have $>98\%$ neostriatal dopamine depletion, and the subgroup of 3 rats that had $>99\%$ depletion of both accumbens and neostriatal dopamine.

In order to minimize the sedative effects of diazepam on the day of testing, each rat received four daily pre-exposures to the drug (5 mg/kg, i.p.) prior to the day of behavioral testing. Taste reactivity tests were conducted on the fifth and sixth days.

On each test day, rats were injected with either diazepam (5 mg/kg, i.p.) or with sterile saline (0.5 ml, i.p.) in counterbalanced order across days. Oral cannulae were connected to delivery tubes, and the rats were placed in the test chamber and allowed to habituate for 10 min. An infusion of 0.3 M sucrose (1 ml) was delivered over a 1 min period, beginning 15 min after the drug injection, and taste reactivity was videorecorded for subsequent analysis, as in earlier experiments.

7.2. Results

Diazepam enhanced the hedonic reaction patterns of both control rats and aphagic 6-OHDA rats ($F(1,23) = 5.38$, $p < 0.05$; Fig. 5), and there was no difference between the two groups in hedonic enhancement ($F(1,23) = 0.5$, n.s.). Diazepam similarly enhanced hedonic reactions for the 6-OHDA group that had 98% neostriatal depletion ($F(1,21) = 6.01$; $p < 0.05$), which also did not differ from the control group ($F(1,21) = 1.13$, n.s). Even the subgroup that had 99% depletion of accumbens and neostriatal dopamine nearly tripled the number of hedonic reactions emitted to sucrose after diazepam (saline $= 4.65 + 3.2$, diazepam $= 14.3 + 2.9$; Fig. 5), although the change was not statistically significant due to the small size of the group ($F(1,5) = 6.32$, $p < 0.12$). Still, an inspection of Fig. 5 will show the reader that rats belonging to the 99% subgroup responded to the drug similarly to all other groups.

Aversive reactions were rarely emitted to sucrose even after saline, and were never altered by diazepam administration ($F(1,23) = 1.10$, n.s.).

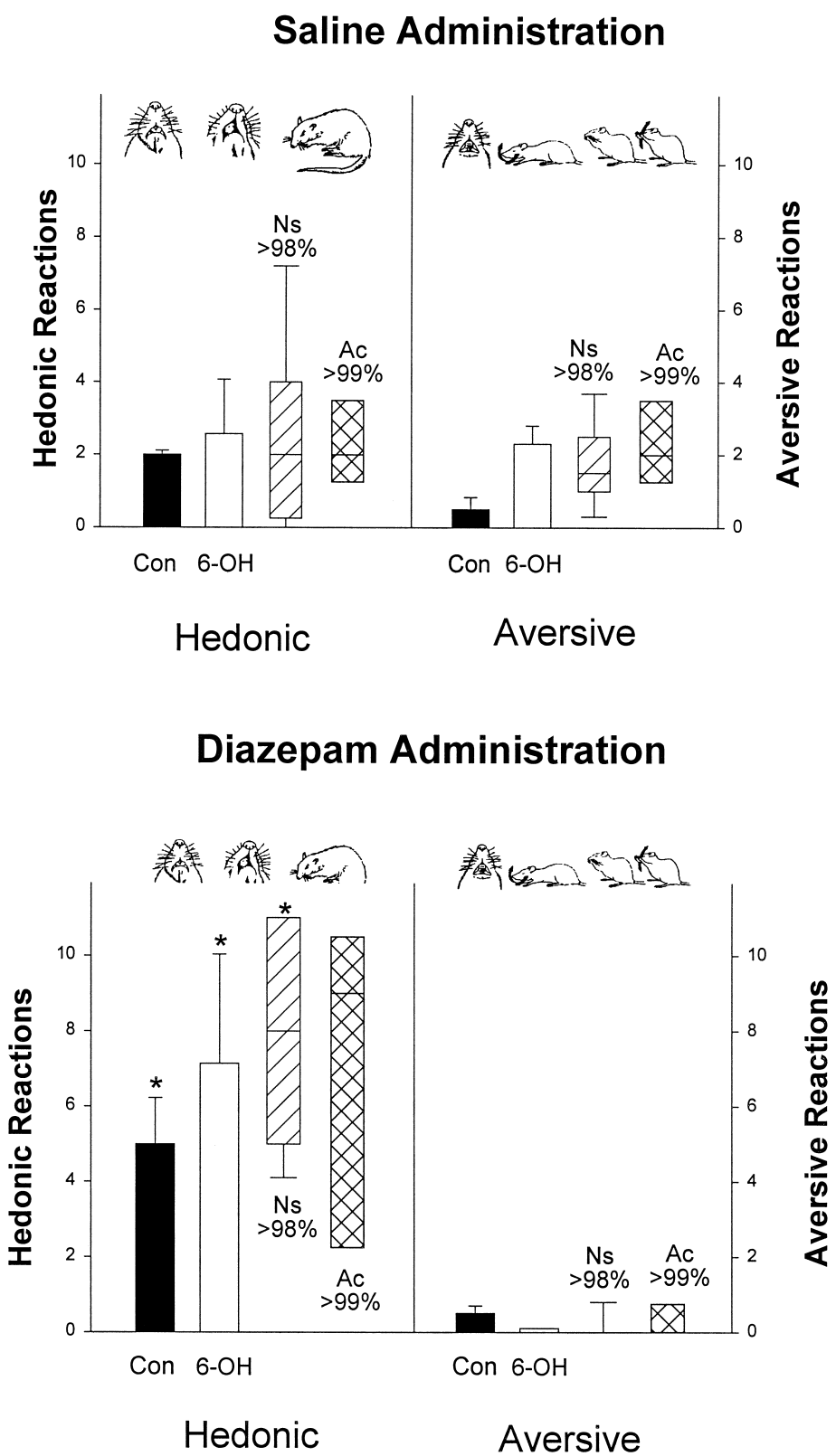


Fig. 5. Taste reactivity patterns to sucrose of 6-OHDA and control groups after diazepam (bottom) or saline (top) administration. Symbols as for Fig. 2.

7.3. Discussion of Experiment 3

The benzodiazepine agonist, diazepam, enhanced hedonic taste reactivity patterns to sucrose even in rats that had 98% to 99% depletion of dopamine. These results suggest that mesolimbic and neostriatal dopamine systems are not needed for the pharmacological enhancement of hedonic reactions. An anhedonic brain—one that was biased to-

ward negative evaluations—might not be capable of pharmacological palatability enhancement. However, a dopamine-depleted brain still is.

8. General discussion

Are dopamine projections to the nucleus accumbens or neostriatum needed for normal hedonic evaluations, for hedonic modulation, or for learned adjustments in hedonic value? Our results indicate the answer to all three questions is 'no'.

8.1. Unconditioned hedonic reactivity.

Unconditioned affective reaction patterns to sweet and bitter tastes remained normal after 6-OHDA lesions. Dopamine depletion failed to reduce hedonic reactions to a sweet taste or to increase aversive reactions to a bitter taste. Dopamine-depleted rats remained capable of discriminating appropriately between sucrose vs. quinine, and between weak and strong concentrations of sucrose (0.3 vs. 1.0 M). These results replicate our earlier report that unconditioned affective reactions to tastes remain essentially normal after 6-OHDA lesions [45]. They extend those findings by showing that this is true even for rats that have up to 99% depletion of mesolimbic and neostriatal dopamine. This far exceeds the 85% neostriatal depletion obtained in our earlier study, and also rules out the possibility that spared dopamine in the nucleus accumbens is needed to mediate normal unconditioned hedonic/aversive reactions.

8.2. Palatability modulation.

The present results also show that dopamine projections to the neostriatum and nucleus accumbens are not necessary for the normal *modulation* of either hedonic or aversive palatability. Enhancement of *hedonic* reaction patterns to sucrose was induced pharmacologically in dopamine-depleted rats by administration of the benzodiazepine agonist, diazepam. Enhancement of *aversive* reaction patterns to an originally palatable sweet taste, and suppression of hedonic reactions, was induced in dopamine-depleted rats by associative taste aversion learning. In both cases, the magnitude of the shift in affective reaction patterns induced by these manipulations was comparable in control and dopamine-depleted rats

9. Dopamine and reward: choosing among competing explanations

Why do individuals fail to eat or drink voluntarily or show goal-directed behavior toward incentive stimuli after dopamine depletion? Competing hypotheses provide several different explanations. First, *motor deficits* produced by nigrostriatal impairment might render the animals incapable of the movements needed to eat or drink. Second, *anhedonia* caused by dopamine depletion might eliminate the hedonic impact of all food or drink reinforcers. Third, disruption of *reward learning* might make it impossible for the individual to perceive the associative relationship between food-related stimuli in the environment and the hedonic consequences of ingesting food. Fourth, disruption of *incentive salience* might abolish the incentive properties of the sight or smell of food, leaving it unattractive and incapable of eliciting approach, even if those other functions remained intact. Which of these explanations, if any, provide a plausible account of the effects of dopamine depletion on behavior directed towards food and other rewards?

9.1. Not motor deficits

The failure to eat is not likely to be explained entirely by motor deficits induced by the lesions. Although the importance of sensorimotor impairment after dopamine depletion cannot be disregarded, and needs to be better understood [216,383], it is clear that rats can still make many forelimb and mouth movements after extensive 6-OHDA lesions. For example, in the present study the action patterns elicited by tastes appeared motorically normal. Dopamine-depleted rats made normal rhythmic mouth movements, rhythmic and lateral tongue protrusions, forelimb facial strokes, etc. Forepaw and licking movements similar to those needed to eat are also preserved and sometimes even enhanced in other situations. For example, when grooming, rats with extensive 6-OHDA lesions have been found to emit the same number as, or more, forelimb-stroke and body-lick movements than control rats [32,483] (and to further increase their emission of grooming and locomotion movements in response to a variety of drug treatments [135,288]). It is not so much that rats cannot generate the movements required for eating after 6-OHDA lesions, as that they *do not* do so.

There is no doubt that dopamine depletion impairs sensorimotor responsiveness in rats as well as in humans [46,285,287,340,379,384,386,391,392,451,485,515]. The critical question, however, is whether sensorimotor deficits alone explain the deficits in motivated behavior. Many behavioral neuroscientists have concluded that sensorimotor deficits by themselves do not suffice to explain the changes in reward effectiveness produced by dopamine manipulations [17,52,152,158,225,254,266,310,345, 347,362,401,429,505,513,518]. Thus, above and beyond sensorimotor deficits induced by dopamine depletion, the nature of the deficit in rewarded behavior needs explanation.

9.2. Not anhedonia

According to the anhedonia hypothesis dopamine depletion should reduce hedonic reactions to sucrose and/or increase aversive reaction patterns to quinine. That did not

happen. Affective reaction patterns remained normal. Normal affective reaction patterns can be explained by the anhedonia hypothesis only if it is assumed that after dopamine depletion taste reactivity no longer reflects normal hedonic or aversive evaluations. In other words, the anhedonia hypothesis would be compatible with these data only if one posits that brainstem circuits were disconnected from an anhedonic forebrain by the lesion, leaving the brainstem to produce normal reflexes in the absence of affective processing by the forebrain. Do rats have an 'anhedonic-but-disconnected' forebrain after 6-OHDA lesions?

Not hedonic disconnection of the forebrain. Our observation that 6-OHDA rats retain the capacity to shift from hedonic to aversive reactions based on aversion conditioning provides strong evidence against the 'anhedonic forebrain' hypothesis. The logic of our assertion derives from the descending hierarchical control known to be exerted by forebrain neural systems over taste reactivity patterns, and the role of hierarchical control in aversion conditioning [206,207,209,211].

Studies have shown that forebrain manipulations alter the responses of neurons in the brainstem parabrachial nucleus and solitary nucleus [121,122,308,317,390], and that affective taste reactivity patterns are modulated directly by lesions and drug microinjections localized in the forebrain [106,211,335,336]. They indicate taste processing to be modulated by descending hierarchical control. This idea is supported by anatomical evidence for descending pathways from gustatory cortex and other forebrain sites to gustatory processing sites of the brainstem. Most relevant to the present study, shifts in taste reactivity patterns produced by taste aversion learning require an intact forebrain [206,209,258,426]. For example, Grill and Norgren found that decerebrate rats were not capable of changing taste reactivity patterns, even after repeated taste-LiCl pairings [206,209]. Lesions of the basolateral amygdala or gustatory cortex have also been reported to impair conditioned shifts from hedonic to aversive behavioral reactions induced by LiCl pairing [258,426]. In a vivid neuroanatomical demonstration of hierarchical control of aversion learning, Schafe et al. [390] found that the induction of c-Fos immunostaining within the nucleus of the solitary tract, a neural marker of taste aversion learning after taste-LiCl pairing, was prevented ipsilaterally by a hemitransection of connections from the forebrain. In sum, as noted by a recent review of taste aversion learning by Norgren and Grigson [318], evidence points to ''the extensive projections of the PBN (parabrachial nucleus) *to the ventral forebrain* as the best candidate'' for neural mediation of aversion conditioning (italics added). Associative shifts from hedonic to aversive behavioral reactions cannot be carried out by the brainstem without guidance from descending forebrain projections.

Our finding that dopamine-depleted rats switch appropriately from hedonic to aversive patterns after aversion learning rules out the possibility that the 6-OHDA lesions produce an 'anhedonic forebrain' that is somehow prevented from modulating unconditioned reactions to tastes. If the forebrain were functionally disconnected, a rat would be unable to shift its affective reaction pattern after taste-LiCl pairing. The dopamine-depleted rat is not rendered functionally decerebrate by its 6-OHDA lesion. Hierarchical controls over palatability remain intact. We conclude that the hedonic evaluation of tastes by the forebrain is not impaired by mesolimbic and neostriatal dopamine depletion.

9.2.1. Further evidence against anhedonia

9.2.1.1. Hedonic enhancement of palatability by diazepam after 6-OHDA lesions. Benzodiazepine agonists enhance palatability and induce feeding by an appetite-related process that appears to be separate from their anxiolytic and sedative effects [92,93,96,97,509] and the hypothesis of benzodiazepine hedonic enhancement has been confirmed by many taste reactivity studies [43,199,328,337,466]. Our present results indicate that the ability of diazepam to enhance taste palatability does not require accumbens or neostriatal dopamine. In one sense, this may not be surprising, because benzodiazepines seem to enhance hedonic taste palatability via actions within the brainstem [31,97,337]. On the other hand, if dopamine depletion had rendered the forebrain anhedonic, that might be expected to impair hedonic enhancement and bias affective responses toward aversion, as a variety of other forebrain lesions do [106,211,393]. But it did not.

9.2.1.2. Comparison to lesions that produce real anhedonia. The preservation of normal hedonic and aversive reaction patterns and normal palatability modulation after 6-OHDA lesions stands in stark contrast to other aphagia-producing brain lesions. Indeed, lesions that disrupt feeding typically reduce hedonic reaction patterns or enhance aversive ones. For example, hedonic reaction patterns are replaced by aversive ones after either telencephalic ablation (removal of structures rostral to thalamus), or large electrolytic lesions of the lateral hypothalamic area [164,211,306,393,446,455]). Aphagia accompanied by anhedonia (plus aversive enhancement) is also seen after excitotoxin lesions of the basal forebrain [106,138,484] that damage a small site within the ventral pallidum [34,106]. Lateral hypothalamic lesions that fail to damage the crucial ventral pallidal site produce only aphagia, and do not increase aversion or reduce hedonic reaction patterns [34,106,393,496]. Aphagia [240,529] with anhedonia can also be produced by deafferentation of the bilateral mandibular and maxillary trigeminal nerve, although the affective taste reactivity shift is more specific to hedonic affect [37]. Trigeminal deafferentation suppresses hedonic reaction patterns to sucrose and other tastes, but does not alter aversive reactions [37]. Deafferentation results in a

selective anhedonia, which nonetheless *shifts* the balance between hedonic palatability and aversion, leaving foods relatively 'unliked'.

In short, most brain lesions that produce aphagia have been found to cause anhedonia, as assessed by affective taste reactivity patterns, and many aphagia-producing lesions also cause active aversion to food. Compared to other neural manipulations that produce aphagia, dopamine depletion is unusual in that it fails to alter either hedonic or aversive reactions to food. We conclude, therefore, the reason dopamine-depleted rats fail to eat is *not* because they are anhedonic.

9.3. Not reward learning?

In a prominent model of reward learning, Montague et al. (p. 1944, [304]) have argued that dopamine neurons deliver ''information about prediction errors between the expected amount of reward and the actual reward''. Their computational model is based on data collected primarily by Schultz and colleagues in an important series of electrophysiological studies on the relationship between the discharge rate of presumed dopamine neurons and the presentation of food rewards, and conditioned stimuli predictive of food rewards [5,277,278,300,301,371,398,399,401–403]. Accordingly, Schultz himself concurs that dopamine neurons ''signal deviations from the prediction of future appetitive events'' (p. 191, [400]). In a collaborative review, Schultz, Dayan, and Montague [405] concluded that ''dopamine activity encodes expectations about external stimuli or reward'' (p. 1594, [405]), and can signal both ''changes and errors in the predictions of future salient and rewarding events'' (p. 1593, [405]). Appetitive rewarding events, for Schultz, are things that ''elicit approach reactions..., serve as positive reinforcers..., serve as goals of voluntary behavior...'', and ''have an emotional function by inducing subjective feelings of pleasure and hedonia'' (p. 191, Schultz [400]), a view that seems to join both incentive 'wanting' and hedonic 'liking'. In these accounts, the activity of dopamine neurons seems to reflect reward learning in two ways. First, neuronal activation to a conditioned stimulus phasically registers an increment in the momentary strength of a prediction regarding an impending 'wanted' and 'liked' event. Second, dopamine neuronal activation to an unconditioned hedonic reward, such as the actual taste of food, encodes discrepancies between the prediction strength and the actual magnitude of 'liking' produced by the event itself [400].

Graybiel et al. have suggested a similar account for tonically active neurons (TANs) in the monkey striatum that respond to conditioned stimuli for reward [3,4,201,203]. TANs fire at 2 to 10 cycles per second, but phasically pause firing in response to certain events. For example, audible clicks or flashing lights that have been paired with a fruit juice reward gradually become able to produce phasic pauses in TAN activity on their own [3,4,201,203]. ''The cells modulate their spike activity in relation to stimuli that are predictive of reward'' (p. 1830, [201]). After dopamine depletion, TANs no longer modulate their firing in response to conditioned stimuli for reward [3]. Graybiel et al. conclude that TAN conditioned responses are ''compatible with a 'teaching' role for reward-related nigrostriatal dopaminergic input'' (p. 1830, [201]). Graybiel interprets these data, together with those of Schultz et al., to ''suggest a model in which dopaminergic nigral neurons are recruited by novel rewarding stimuli, and long-term procedural memories are built up...'' (p. 734, [200]). Thus, according to this account too, dopamine neurons help to entrain a type of learned *expectation* of an event that is both 'wanted' and 'liked'.

Others have similarly argued that dopamine mediates various types of reward-related *associations* between conditioned stimuli and hedonic stimuli [23,24,26,61,116,488]. For example, White (p. 181, [488]) proposed that ''dopamine release in the striatal matrix acts to promote the consolidation of sensori-motor associations'' whereas dopamine release in the striatal patches and nucleus accumbens primarily mediates other aspects of reward, such as 'the property to elicit approach' (p. 181, [488]) and 'responding to conditioned rewards' (p. 184, [488]). Beninger and Miller (p. 335, [26]) suggest that dopamine systems, especially D1 dopamine receptors, mediate incentive learning, ''defined as the acquisition by previously neutral stimuli of the ability to elicit approach and other responses and occurs in association with the presentation of rewarding stimuli''. In a related hypothesis, Di Chiara (p. 103, [116]) posited that dopamine release in accumbens and ventral striatum is crucial for ''enabling the acquisition of incentive properties by stimuli (incentive learning)'', specifically because of ''*facilitation by dopamine of learning of the association* between the stimulus and the reinforcers'' (p. 102, [116] italics added). In a more recent formulation, reminiscent of White's, Di Chiara emphasizes his belief that dopamine systems are required for the reward *association* itself: ''We hypothesize that DA release in the NAc in response to a novel or relatively novel primary stimulus facilitates the association between affective and discriminative properties of stimuli'' (p. 61, [117]). This 'reward association' hypothesis holds that mesolimbic dopamine is causally necessary for the formation of reward associations, and that dopamine neurotransmission is ordinarily a sufficient cause to form such associations. Di Chiara writes: ''In our hypothesis, DA is not only necessary for stimulus reward and stimulus response associations (motivational learning) but phasic activation of its transmission can actually facilitate these processes'' (p. 63, [117]). Thus, many authors, drawing on different lines of evidence, have emphasized that ascending dopamine systems are critical for *learning* about rewards.

9.3.1. Multiple types of reward learning?

In evaluating reward learning models of dopamine function, a question that must first be addressed is whether

there is only one type of reward learning or whether there are instead multiple subtypes. If there is only one type, and if dopamine plays a critical role, then dopamine manipulations should have a very general effect on learning about rewards in many different situations. Explicit cognitive expectation (as a declarative representation), instrumental approach, conditioned hedonic reactions, and other anticipatory behavioral or physiological responses to a conditioned stimulus for reward, which are based on expectations or procedural memories: all would reflect the same learning process, and all should be influenced together by manipulations of dopamine systems.

But our results (and others [16,127,128,218,341,439]) show that reward learning cannot be a single process, and that dopamine is not necessary for all reward learning, if it is necessary for any. In our study dopamine-depleted rats learned a new Pavlovian association between a taste and its affective consequences, and used this association to transform their subsequent hedonic reaction to that taste. If reward learning takes *multiple* forms, then dopamine projections might mediate some but not others. In that case, it will be crucial for reward learning hypotheses of dopamine function to specify precisely *which* forms or aspects of reward learning depend on dopamine systems and which do not.

Which aspect of reward learning is most likely to depend on dopamine systems? Contemporary 'reward learning' models of dopamine function often emphasize the role of dopamine neurons in 'prediction of future appetitive events' and 'expectations about rewards' [400,405]. But understanding the role of dopamine systems depends on exactly what is meant by the terms 'prediction' or 'expectation'. It may be useful to distinguish between four possibilities.

First, prediction or expectation could refer to the simplest procedure that instantiates classical conditioning: a neural algorithm that underlies the formation of basic Pavlovian associations (classically-conditioned procedural memories), and generates conditioned responses based on past correlations among stimuli. However, our results suggest that dopamine projections are not needed for forming such associations or generating new responses based on newly acquired associations. [7]

Second, 'expectation of reward' might mean a process separate from associative learning, but one that is closely controlled by it as a response. For example, Pavlovian associations are translated into hedonic responses, triggering pleasant or unpleasant *affect* as a conditioned emotional response [53,358,527], including gustatory affect [42,63,113]. The ability of a conditioned stimulus to elicit *conditioned affect* is an important feature of incentive motivation theories such as those of Bindra [47–49] or Toates [460–462], and of neurobiological theories of emotion such as those of LeDoux [273] or Panksepp [322,325,347]. But again, in the present study dopamine-depleted rats were able to translate a Pavlovian association between the taste of saccharin–polycose and LiCl-induced illness into an aversive shift in the palatability of that taste. That rules out the possibility that dopamine is necessary for transformations of affect based on Pavlovian associations.

Third, 'expectation of reward' might mean activation of a psychological system that is related to hedonic impact but not identical to it. Pavlovian associations alter the *incentive motivation* properties, as well as the hedonic properties, of conditioned stimuli (see Toates [460,463], Bindra [49]). Incentive property here means the ability of the stimulus to attract approach, to elicit behavior such as feeding, to be sought after, and to elicit and maintain instrumental behavior (all of which we suggest reflects 'wanting', and hold to be separable from hedonic 'liking'). It is possible that dopamine systems play a special role in the learning of incentive properties, and in the subsequent attribution of incentive properties to conditioned stimuli ('wanting'), even if they do not contribute to learning about hedonic properties ('liking'). This possibility will be explored further below under 'Comparison of reward learning and incentive salience hypotheses'.

Fourth, 'expectation about reward' might mean exactly what it says, in the strongest sense of 'expectation'. That is, an *explicit cognitive expectation* of a specific reward. This psychological process is of course more complex than simple associative learning, and involves additional neural mechanisms [16,20,85,439]. A declarative cognitive expectation must code a future event in terms of an explicit representation of its sensory and rewarding features, and be able to draw upon that information to guide current action [123]. It is not merely a procedure for generating an anticipatory response. In humans, for example, declarative forms of expectation include imagery and symbolic or semantic representations, which can be used to make new inferences about an event that has not yet occurred.

Identifying declarative cognitive representations in animals is generally recognized to be a formidable task. But in a fascinating series of experiments, Dickinson and colleagues such as Bernard Balleine have developed methods for detecting cognitive expectations that even rats have about rewards, and separating them from simpler Pavlovian-guided processes. Although explicit cognitive representations might be expected to be more important in *primates*, the learning tasks used in most primate studies of

[7] Admittedly, our experiment induced conditioned *aversion* and a hedonic *decrement* rather than a conditioned hedonic increment. It would be of interest to obtain conditioned 'liking' in dopamine depleted rats, and some readers might suspect that associative hedonic increments would not be possible. But that is a thin reed on which to hang a hedonic learning hypothesis. Most of the reward learning hypotheses reviewed above implicate dopamine systems in hedonic decrements as well as increments. A hedonic decrement was apparent in the 6-OHDA rats' loss of hedonic reactions to saccharin–polycose. We predict that associative hedonic increments are possible too, a prediction that future experiments conceivably could test.

mesolimbic activation and reward generally have not been designed to separate associative from cognitive aspects. By contrast, Dickinson and Balleine and their colleagues have used rats as subjects in their studies of incentive learning. Yet they successfully demonstrate in these animals the existence of cognitive 'act–outcome' expectations of incentives, and show that such expectations can be experimentally teased apart from simpler Pavlovian-based aspects of reward learning [8,9,11,12,123,126–128]. Their studies indicate that animals too can form cognitive expectations of rewards, at least in certain situations (See Addendum 2 for explanation of Dickinson et al.'s analyses, and of how they dissociate 'act–outcome expectation' of reward from simpler types of reward learning).

The multiplex nature of 'reward learning' illustrated by Dickinson and Balleine and colleagues (see Addendum 2) shows that there are many different ways in which dopamine systems could contribute. Depending on which type of reward learning is meant, 'expected reward value' could have different meanings at the same time and for the same reward. The results presented here indicate that dopamine systems are not needed either for learning simple predictive associations among events that arise from their correlation, or for hedonic transformations in reward value based on those associations. But dopamine systems could conceivably be involved in the translation of hedonic value into an associatively-guided attribution of incentive salience to a conditioned stimulus, or alternatively into a cognitive representation of act–outcome value. *A critical evaluation will require 'reward learning' hypotheses of dopamine function be specific concerning the form of 'reward learning' they seek to explain* (see below for further discussion of this point).

9.4. Loss of incentive salience?

In our original report that aphagic 6-OHDA rats have normal hedonic reactions to tastes we suggested that dopamine depletion disrupts the capacity to *attribute incentive salience to neural representations* of rewards, without disrupting either their hedonic impact or their ability to enter into new associative relationships. Incentive salience, we proposed, under normal conditions must be attributed to stimuli to transform a perceived and 'liked' stimulus into one that is also 'wanted' and able to elicit voluntary action [34,45,366]. The aphagia of dopamine-depleted rats, and their lack of other motivated behavior, is compatible with this hypothesis. Even if rats still 'like' food, and retain the capacity to learn hedonic associations about it, and to make the movements needed to eat, they do not 'want' food and so do not eat it.

The incentive salience hypothesis is an extension of earlier models of incentive motivation proposed by Bolles [53] and by Bindra [48,49], and developed by Toates [460,463]. Neurobiologically, it is an extension of earlier formulations of the role of dopamine in reward by Phillips et al. [51,157,345], Wise and Bozarth [499–501,508], and by Panksepp [322–324] among others. The incentive salience hypothesis is different from previous models in that it specifies that encounters with new incentives and rewards normally activate three distinct psychological processes mediated by dissociable neural substrates [34,44,45,366]. The 3 psychological processes that compose incentive motivation and reward are posited to be: *hedonic activation* by the unconditioned stimulus, *associative learning* of the correlation between the conditioned stimulus and the unconditioned stimulus, and *attribution of incentive salience* to the conditioned stimulus or its representation on subsequent encounters (Fig. 6). Finally, the incentive salience hypothesis proposes that dopamine systems are necessary just for the third process—attribution of incentive salience.

Regarding the role of conditioned stimuli in reward, one can imagine learning about a new incentive in this way. An individual's initial contact with a hedonic reward may occur incidentally, triggering 'liking' as the individual explores its world, sampling food, etc. Such natural rewards have hedonic value presumably because of their survival value in evolutionary history [72,315]. 'Liking' or hedonic pleasure is ordinarily a necessary component of reward, leading to the acquisition of new incentives. [8] Indeed, to many, 'liking' is synonymous with reward, and the term reward is often used as a surrogate for pleasure. This is consistent with the dictionary definition of reward as 'a pleasant stimulus' (p. 2584, Shorter Oxford Dictionary) [65]. We think, however, that neural and psychological reality are more complex than the dictionary would suggest. We argue that 'liking' by itself is not true reward any more than is 'wanting' by itself: nothing need be rewarded by hedonic activation alone. Pleasure is not itself goal-directed or necessarily associated with objects or events. Pleasure by itself is simply a *triggered affective state*—there is no object of desire. It is the process of incentive salience attribution that makes a specific associated stimulus or action the *object* of desire.

[8] 'Liking' may be bypassed in reward only by special stimuli, such as electrical brain stimulation or some drug rewards, events that directly activate the neural substrate of 'wanting' or incentive salience attribution [44,366]. Such cases will look like normal reward or motivation to an external observer, who watches instrumental or goal-directed behavior, but would in a sense be mere 'sham reward', composed only of 'wanting' without 'liking'. For example, stimulation of the lateral hypothalamus makes rats 'want' food (in the sense of eliciting eating) without making them 'like' it (in the sense of enhancing hedonic reactions) [44]. Whether real reward ('wanting' plus 'liking') or sham reward (mere 'wanting' without 'liking') is evoked by an event, incentive salience will be attributed specifically to conditioned stimuli that have been associated in the past with the unconditioned activation of its neural substrate. 'Wanting' is focused on a particular target by associative learning, making it the specific object of goal-directed behavior: the object of desire.

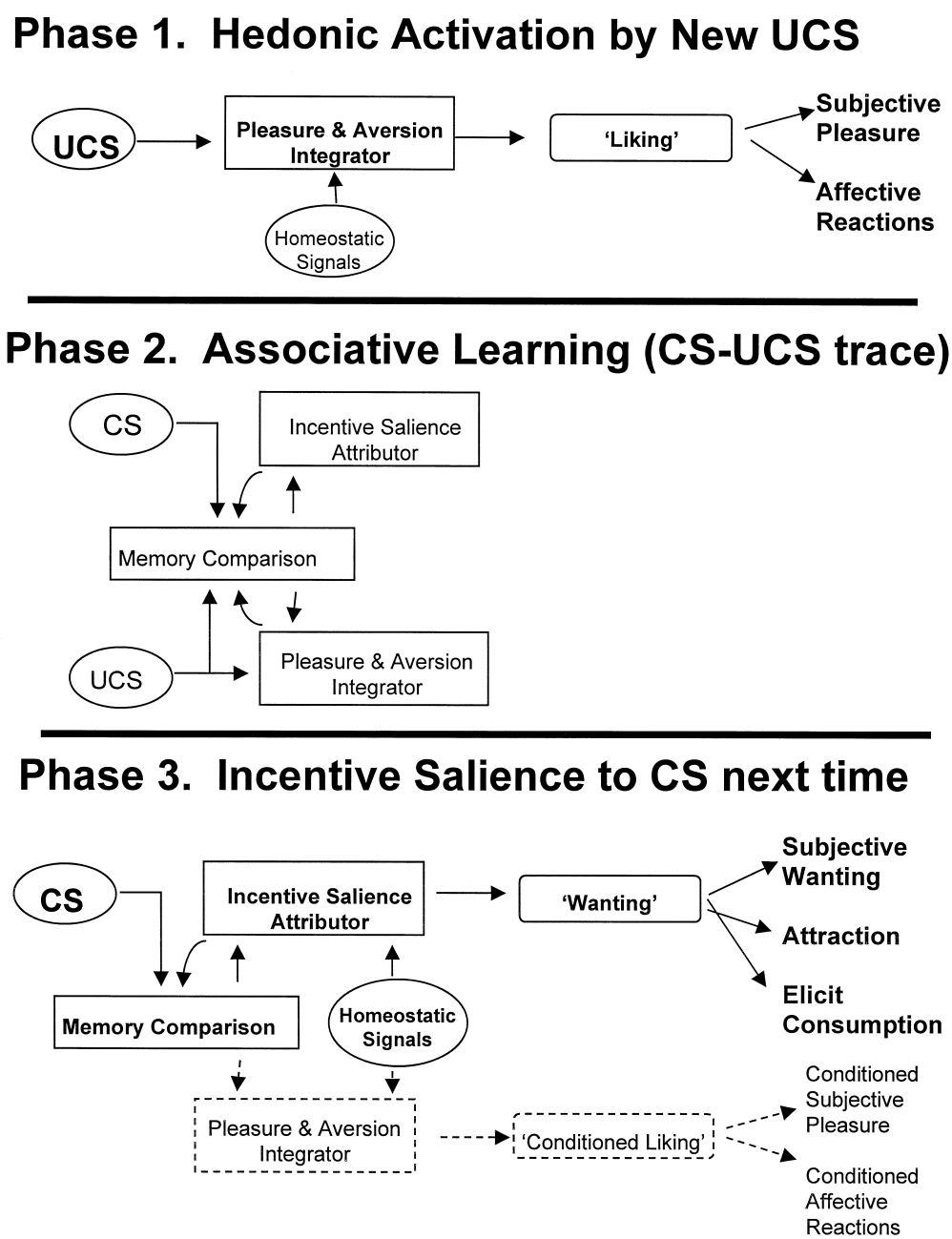


Fig. 6. Three processes in the acquisition of a new reward according to the incentive salience model. (1) The first time the unconditioned hedonic pleasure ('liking') is encountered, it acts as the normal trigger for the reward-building process, and activates the associative and incentive salience steps. But 'liking' by itself is not sufficient to motivate or direct instrumental behavior directed toward external stimuli (as the predicament of 6-OHDA rats illustrates) (2) Associative learning systems correlate the memory trace of predictive neutral events (conditioned stimuli) associated with the hedonic event. Originally the conditioned stimuli have little power to activate either 'liking' or 'wanting' systems, but associative learning links them to both. A similar process occurs during the 'reboosting' of familiar reward stimuli (3) When these conditioned stimuli are encountered on subsequent occasions, incentive salience is attributed to them by activation of dopamine-related systems, guided by associative learning. Attribution of incentive salience makes a conditioned stimulus itself the target of 'wanting', and able to act as a Bindra/Toates incentive to direct motivated behavior [49,460,463]. Separately, conditioned stimuli may also activate conditioned 'liking' (for example, as a taste paired with LiCl activates conditioned aversion). However, the burden of guiding goal-directed behavior toward Pavlovian reward stimuli falls on the incentive salience process of 'wanting'.

Associative learning, specifically Pavlovian or classical conditioning, is the second process required for a new incentive to become a 'real reward'. Associative learning identifies the correlation between hedonic activation and the predictive external event or conditioned stimulus that preceded it [355,356]. Together associative learning and hedonic/aversive activation are sufficient for the transformation of associative information into affect (i.e., a hedo-

nic or aversive response to a conditioned stimulus), such as the conditioned taste aversion seen in dopamine-depleted rats in the present study. Without the third process of incentive salience attribution, however, associative learning and hedonic activation do not suffice for goal directed behavior, nor to make a conditioned stimulus an *attractive* event. They simply make it possible for a conditioned stimulus to activate an affective state. They cannot by themselves elicit approach, or any other instrumental action, even so simple a one as reaching out with tongue or forelimb to a goal object that is literally in front of one's face.

Incentive salience attribution is the third component of reward according to this hypothesis. It corresponds roughly to 'decision utility', as that term is used in discussions of choice theory by, for example, Kahneman et al. [243,245] and Shizgal and Conover [90,422,423]. Decision utility refers to the degree to which a goal is chosen or sought. Incentive salience is needed to transform the 'neutral' perception of a conditioned stimulus or a goal object at a distance into an attractive incentive capable of eliciting appetitive or instrumental behavior towards it. Only if this last stage of incentive salience is added does the stimulus or event become a full reward, becoming 'wanted' as well as 'liked'. Further, on each subsequent encounter with the now 'wanted' and 'liked' stimulus, its capacity to support 'wanting' is maintained or strengthened by associative reboosting of the incentive salience assigned to its representation [44,366]. Reboosting happens when a 'wanted' incentive is followed again by activation of hedonic 'liking'. If *reboosting* occurs, the reward remains 'wanted' on later occasions. In the absence of reboosting of incentive

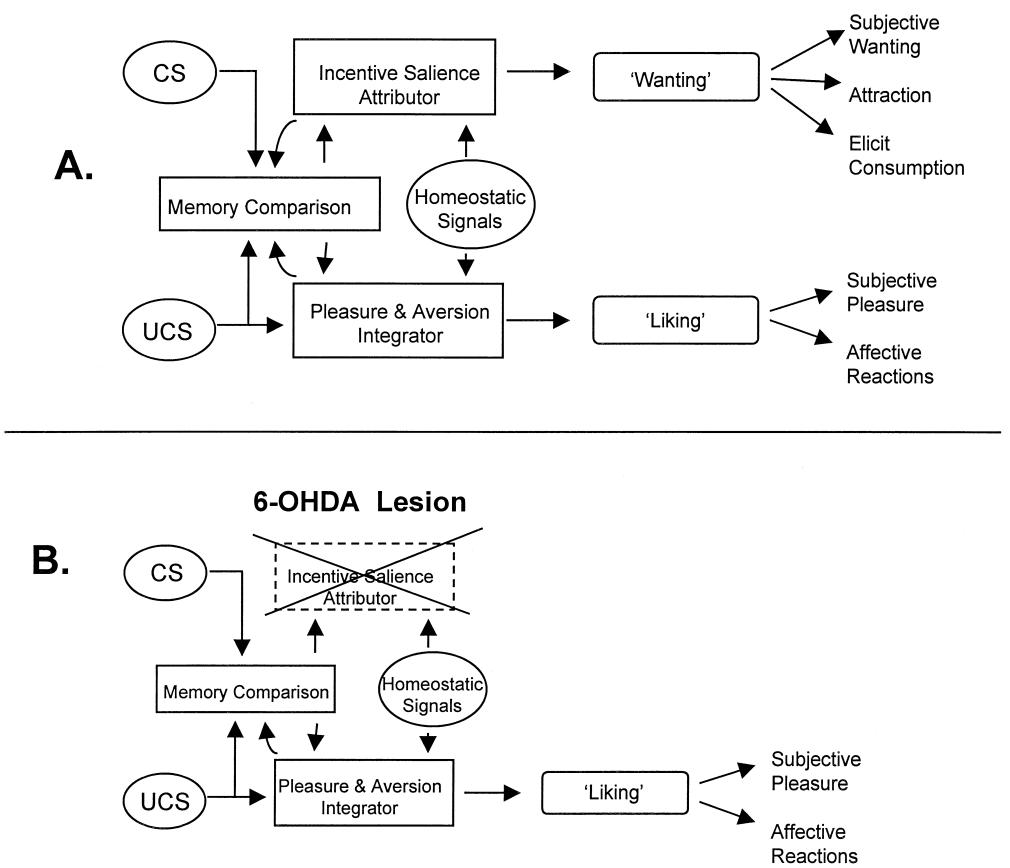


Fig. 7. Incentive salience model of incentive motivation (A; derived from Toates [460], based in part on Bindra, [49]), and of the effects of dopamine depletion on motivation and reward (B). A. 'Liking' and 'wanting' correspond to separate psychological and neural systems. Dopamine projections to the nucleus accumbens and neostriatum are needed to generate 'wanting' or incentive salience aspects of motivation, but not for hedonic 'liking' or for associative learning about rewards. Subjective pleasure and subjective wanting require further cognitive elaboration in order to produce conscious emotion from underlying 'liking' and 'wanting', but that is not depicted here. See Robinson and Berridge [366] and Berridge [34] for more discussion. B. Only incentive salience processes ('wanting') are mediated by dopamine neural systems. After 6-OHDA lesions that disrupt dopamine systems, the attribution of incentive salience is selectively abolished. Behavioral outputs of 'wanting' (appetitive, goal-directed, or instrumental action) are eliminated. Behavioral outputs of hedonic/aversive 'liking' (e.g., affective taste reactivity patterns), however, remain unimpaired. Even associative learning, which ordinarily interacts with both processes, is free to guide hedonic/aversive 'liking' after dopamine depletion (expressed in taste aversion learning in Experiment 2). But no incentive is 'wanted'. Part A modified from [366], Part B modified from [34].

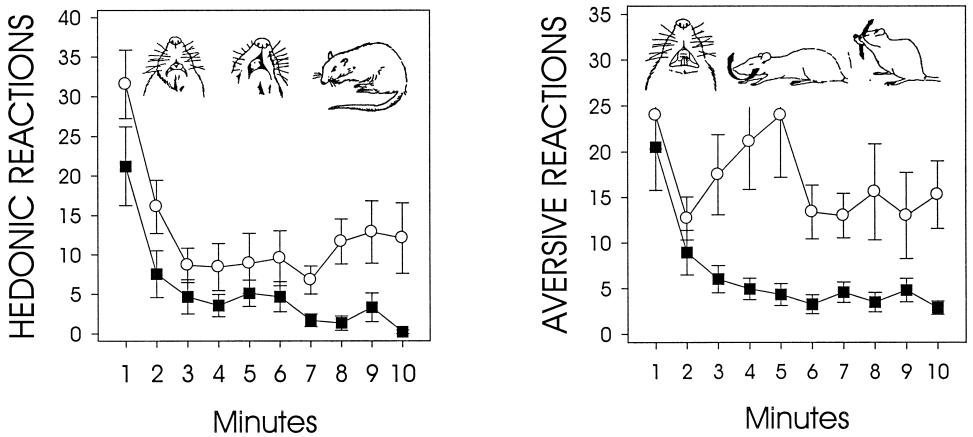


Fig. 8. Gradual sensorimotor suppression of taste reactivity by pimozide (0.5 mg/kg). Initial hedonic reactions to sucrose (left) and aversive reactions to quinine (right) are normal (pimozide = filled squares, vehicle = open circles). When the infusion continues for several minutes, a general suppression ensues for both hedonic and aversive reactions (and for other nonaffective movement patterns not shown). The suppression is equivalent regardless of hedonic/aversive or other category, and therefore does not appear to reflect a shift in palatability toward anhedonia or aversion. Modified from Peciña et al.[338].

salience, reward extinction ensues. Incentive salience is the only component of reward that we think depends upon mesolimbic and neostriatal dopamine systems.

The distinctive features of our model are that 'liking' and 'wanting' are separable psychological processes, although they typically occur together. Most important, they have separate neural substrates (Fig. 7; Fig. 8). Dopamine manipulations can directly alter 'wanting', whereas 'liking' is influenced by manipulations of other neural systems (such as GABA/benzodiazepine systems in the brainstem, ventral pallidal systems where lesions produce aversion, or opioid systems in the nucleus accumbens shell [34,40,106,337,338]). In the context of the present study incentive salience attribution is the only component of reward we posit dopamine depleted rats to lack (Fig. 7, and Berridge [34]).

10. Conditioned dopamine activity: re-examination of implications for incentive salience and reward learning hypotheses

Our hypothesis predicts that neurons which mediate incentive salience will respond to sensory stimuli that trigger 'wanting' regardless of whether they generate 'liking'. As reviewed above, both dopamine neurons themselves and their neuronal targets in the striatum respond to incentive stimuli related to food or other rewards [3–5,301,305,370,403,492]. Although anticipatory neural responses in advance of a hedonic reward are usually discussed with a *reward learning* hypothesis in mind, they are equally consistent with the *incentive salience* hypothesis. If dopamine activation is taken to reflect the attribution of incentive salience at a particular moment, then the hypothesis predicts that conditioned stimuli for hedonic events should become able to elicit activation, and that the activation will be directed by associative learning. [9]

10.1. Predictions of 'reward learning' vs. 'incentive salience' hypotheses of dopamine function

Although neuronal responses to a conditioned stimulus for a hedonic food reward are consistent with both a learning 'expectation of reward' hypothesis and the incentive salience hypothesis, the two are not identical. They may make different predictions, although the exact predictions depend, of course, on what is meant by 'reward learning'.

If a 'Bindra/Toates incentive' type of reward learning is meant, then the two hypotheses are not mutually exclusive. In this case dopamine activation could mediate specifically learning about the *incentive properties* of a classically-conditioned stimulus, as described in traditional incentive motivation theories developed by Bindra [49], Bolles [53], and Toates [460,463]. Of course, we would

[9] However, it must be granted that 'wanting' or incentive salience attribution is probably not isomorphic with the occurrence of action potentials in reward-related dopamine neurons. The firing patterns of dopamine neurons are very brief [278,301,401,405], whereas 'wanting' as a psychological process should be sustained as the goal is approached. It is plausible that the psychological process of incentive salience attribution outlasts dopamine neuronal activity in many situations. If so, the full psychological process of 'wanting' may require events later in the chain of neural causation. Dopamine neurons may well still serve to *trigger* the neuronal chain of events that instantiate incentive salience attribution. Neurons in the ventral striatum and nucleus accumbens, and their efferent targets, may mediate later events in the chain. This speculation is supported by reports that reward-related neuronal activity in the ventral striatum is more sustained than in dopamine neurons themselves, and that dopamine release in the nucleus accumbens also lasts longer [4,5,263,277,347,403,417].

argue that this does not include either acquisition of the association between the discriminative sensory properties of a stimulus and its hedonic reward properties, or the generation of a conditioned hedonic reaction when the discriminative stimulus is presented later (since we've shown these can occur without dopamine). Those would have to be mediated by non-dopaminergic systems.

The notion that there could be separate 'learning systems' for the acquisition of incentive value vs. hedonic value is not part of the original Bindra/Toates models of incentive motivation (although see Toates [463] for a formulation that incorporates the distinction). But 'liking' and 'wanting' must be separated in order to make a reward learning hypothesis of dopamine function compatible with the incentive salience model. The compatibility of specific reward learning models hinges on precisely what Montague, Schultz, Graybiel, White, Beninger, Di Chiara, et al., and other authors of reward learning hypotheses for dopamine function [3,23,26,116,117,200,304,400,401, 405,488,489] mean by 'expectation of reward'. If these reward learning hypotheses posit that dopamine mediates Pavlovian learning about *incentive value alone* (not stimulus-reward association per se, not hedonic value, not cognitive expectation of outcome), and that anticipatory neuronal responses to conditioned stimuli occur because those stimuli carry *incentive motivational* qualities, such as incentive salience, separately from mere association or from hedonic qualities, then those reward learning hypotheses are compatible with our incentive salience hypothesis. That is, predictive stimuli for reward could have associative, cognitive, hedonic, *and* incentive motivational properties, and the activation of mesolimbic dopamine systems may specifically reflect their *incentive* properties, separable from the other properties.

If, however, dopamine neurons are posited to mediate any other sense of 'expectation of reward' (see above), then either the reward learning hypothesis or the incentive salience hypothesis must be wrong. If dopamine systems mediated learning either a *conditioned hedonic response*, such as anticipatory activation of hedonic/aversive affect elicited by a conditioned stimulus, or a *cognitive expectation* of reward value in Dickinson's and Balleine's sense of instrumental incentive learning [125,128,129], then reward learning and incentive salience hypotheses would make different predictions, in at least some situations.

For instance, compare *cognitive expectancy* and *incentive salience* hypotheses. If the incentive value of a stimulus were changed *in the absence of an opportunity to learn its new reward value* (as in the experiments of Dickinson and Balleine; see Addendum 2), then an incentive salience hypothesis would expect dopamine systems to change. Without an explicit opportunity to learn the new reward value, a *cognitive expectancy* hypothesis based on Dickinson's and Balleine's concept of incentive learning would instead expect dopamine systems to follow the same expectancy value reflected in the animal's instrumental behavior. Dickinson and Balleine show that, when guided by act–outcome expectancies, the animal often behaves as if the reward will have the same value it had when it was encountered before—even under conditions when the reward won't [123,127,128]. Thus, dopamine neuron activation should remain constant under those conditions in which instrumental behavior remains constant. [10]

In contrast, the incentive salience hypothesis generally expects dopamine activation by all potent incentives. It does not matter whether the eliciting event is a conditioned stimulus that predicts a subsequent hedonic stimulus, or an unpredicted unconditioned stimulus, or the initiation of an action that is rewarding in itself (i.e., some species-specific activities [188,472]), or even perhaps merely an internal neuronal representation of the rewarding stimulus or action. And it does not matter whether a change in incentive salience has been triggered by prior associative experience or directly by a shift in physiological state (since they interact multiplicatively to control incentive value, in the Bindra/Toates sense of that term) [127,460]). This differential prediction potentially allows experimental discrimination of the incentive salience hypothesis from some forms of reward learning hypotheses of dopamine function.

Incentive reboosting and neural responses to unconditioned stimuli. The incentive salience hypothesis posits that incentive salience must be reboosted on every re-encounter with the 'wanted' stimulus and its 'liked' consequences. If this does not occur, subsequent attribution of incentive salience to the stimulus will decrease, leading to extinction of incentive value [34,45,366]. Is there direct evidence for reboosting or deboosting? Some may be

[10] A study by Balleine and Killcross [10] of instrumental performance after nucleus accumbens lesions suggests that the accumbens does *not* mediate the *cognitive representation* of act–outcome relations. They found that accumbens lesions did not impair a rat's ability to adjust its level of instrumental response based on a change in reinforcer value. They concluded that accumbens lesions ''do not influence sensitivity to the instrumental contingency'' (p. 191) and that the role of the accumbens is ''dissociated from the control of performance mediated by the act–outcome relation'' (p. 181) [10]. The lesions did impair overall rates of instrumental performance and also impaired classically-conditioned approach responses directed toward the food cup. Balleine and Killcross [10] interpreted the lesion deficit as reduced ''conditioned affective arousal produced by classical conditioning'' (p. 191), which seems to be more directly related to incentive salience attributions than to cognitive expectations of an outcome. Indeed, it is completely compatible with the incentive salience hypothesis, which would only assert that the 'arousal' hypothesized by Balleine and Killcross is not simply *affective* (hedonic) in nature, but reflects activation of incentive salience. It should be noted, however, that excitotoxin lesions rather than dopamine depletion were used by Balleine and Killcross, and that the test procedure was different from the extinction procedure used in the other experiments by Dickinson and Balleine described above [126–130]. Therefore a strong conclusion about dopamine's role cannot be made. Nevertheless, this study provides some evidence against the hypothesis that dopamine/accumbens systems mediate instrumental learning in the Dickinsonian sense of cognitive expectancy based on cause–outcome relations. Instead, it supports an incentive salience interpretation of accumbens function.

found in the electrophysiological studies by Schultz and colleagues.

Schultz et al. [300,405] have shown that dopamine neurons not only respond to a conditioned stimulus that predicts a hedonic reward, but *fail to respond to the unconditioned hedonic stimulus* if it has already been predicted. Dopamine neurons respond to food in the mouth if it is unexpected, but do not respond to food in the mouth that has been signaled by a predictive conditioned stimulus. At first glance, the failure to respond to a predicted event seems inconsistent with the assertion that dopamine neurons reboost incentive value on every trial. After all, the absence of neural activity seems to rule out the reboosting activity we expect.

However, the failure of dopamine neurons to fire robustly to a predicted hedonic stimulus may not reflect the complete *absence* of a response, but rather the presence of *two opposing* neuronal responses that cancel each other out [401]. This is suggested by the report by Schultz et al. that a conditioned stimulus that *fails* to be followed by the expected hedonic stimulus will elicit a decrease in firing of dopamine neurons *at the moment the hedonic stimulus usually would have been delivered* [401]. Similar firing decrements have been seen when a monkey encounters an inedible object instead of an expected food reward [371]. The demonstration of neuronal inhibition at the time an absent hedonic stimulus *should occur*, raises the possibility that such an opposing neuronal process might be generated even on trials in which the hedonic food *does occur*. In other words, on rewarded trials, excitation and inhibition might both occur and nearly cancel each other out. Consistent with this interpretation, Schultz et al. wrote, ''The visual inspection of rasters and histograms (for trials on which the expected hedonic food was delivered) revealed that *depressions occurred in many neurons even in the presence of reward responses*... such that the *activating response was added on top of the depressed activity*'' (p. 911, italics added [401]). In other words, the apparent lack of neuronal response to an expected hedonic event actually comprises two responses: an inhibition that corresponds to anticipation of the hedonic event, and an excitatory activation similar to that seen in naive animals.

These phenomena may provide a neuronal basis for both the 'deboosting' (i.e., extinction) of 'wanting' on nonrewarded trials (neural inhibition), and for the reboosting of incentive salience that maintains it at a constant level on trials in which the expected hedonic reward is received (neural excitation balanced together with neural inhibition). For reward extinction and deboosting, the following scenario could occur. Upon presentation of an established conditioned stimulus for reward that fails to be followed by hedonic activation, the conditioned stimulus elicits neuronal activation and is 'wanted' itself, but triggers neuronal inhibition moments later when the 'liked' hedonic unconditioned stimulus fails to materialize. If the inhibitory process is unopposed, it causes a reduction in subsequent attribution of incentive salience to the conditioned stimulus. The incentive becomes less 'wanted'.

On ordinary rewarded trials, hedonic activation does follow the conditioned stimulus. In these cases, the excitatory process *reboosts* or maintains subsequent incentive salience attributions. If the excitatory and inhibitory processes are in balance, no change occurs in the existing level of incentive salience subsequently attributed to the conditioned stimulus. 'Wanting' and instrumental performance are maintained at a constant level as long as neuronal excitation and inhibition are in balance. When the two processes are unequal, subsequent attributions of incentive salience are altered in the direction of the difference. Furthermore, not only should an *unexpected* hedonic event still activate dopamine neurons [300,301,401], but so should a *better-than-expected* hedonic reward even if *some* reward is anticipated. This would correspond to a 'positive contrast' or 'Crespi effect', in which animals over-respond to a better-than-expected reward [103,162]. Conversely, if the magnitude of the hedonic event were *less-than-expected* by the monkey an overall decrement of neuronal firing would be predicted, corresponding to a negative contrast effect [162]. Such a result would be compatible with both incentive salience and reward learning hypotheses (also see [341]).

On the other hand, the incentive salience hypothesis suggests that the balance between excitatory and inhibitory components could be altered even by manipulations that do not disturb the predictive relation between two stimuli, as long as they change their incentive value. For example, following a shift *in physiological* state a different prediction is made uniquely by the incentive salience hypothesis —and not by the 'explicit expectation of outcome' reward learning hypothesis (reward learning in Dickinson and Balleine's sense [12,127,128]). Certain physiological manipulations might shift incentive value and dopamine neuronal activity without altering either the magnitude of an unconditioned rewarding stimulus or its predictive relationship with a conditioned stimulus. This could provide a strong separation of the two hypotheses. For example, changing the physiological state of the animal to induce hunger, satiety, sodium appetite, etc., could conceivably alter the response of dopamine or striatal neurons to a conditioned stimulus for a hedonic food or salt reward, even if the stimuli themselves and their predictive relations were not changed from the animal's experience with them prior to the physiological shift.

As reviewed by Toates [460,463], the incentive value of Pavlovian conditioned stimuli (and of their hedonic unconditioned stimuli) are modulated directly by physiological states relevant to appetite, such as caloric hunger, satiety, or sodium deprivation (note: this is 'incentive value' in the Bindra/Toates and incentive salience sense of Pavlovian-acquired motivational features—not 'incentive value' in the more cognitive Dickinsonian sense [127,128] [see Addendum 2]). Such immediate shifts in the incentive value

of classically-conditioned stimuli contrasts with the lack of a shift in instrumental cognitive expectancies, as reviewed by Dickinson and Balleine [127]. Thus, the incentive salience hypothesis predicts that a shift in dopamine activity should occur directly under such conditions. By contrast, a cognitive expectancy of reward hypothesis (at least, as based on the Dickinsonian concept of reward expectancy [125,127,128]) predicts that the animal would need to experience the altered hedonic value of the reward while in the altered physiological state before its instrumental behavior (and dopamine activity) would be changed. [11]

There is as yet little experimental evidence to test between incentive salience vs. reward learning predictions of dopamine function. However, in the few instances where the models diverge there is at least some suggestive evidence to support an incentive salience interpretation. For example, in a microdialysis study Fiorino, Coury, and Phillips report that an unconditional increase in the value of a sexual incentive enhanced dopamine overflow in the nucleus accumbens, even though the change in incentive value did not arise from learning, and occurred on the first experience with the new incentive [159]. Their study focused on the 'Coolidge effect' (the name based on an apocryphal remark of the late U.S. President Calvin Coolidge regarding the ability of a chicken farmer's rooster to fertilize many hens). In that phenomenon, male sexual motivation is aroused again after satiety by the presentation of a *new* female. Fiorino et al. [159] found that dopamine overflow was elicited initially by the mere presentation of a female beyond reach behind a screen, and dopamine peaked during subsequent copulation, after the screen was removed. Dopamine levels then declined over the course of successive copulation bouts with the first female, eventually returning to baseline after copulations ceased. Presentation of a second novel female behind a screen elicited a slight increase in dopamine overflow, which rose significantly during a second series of copulations (but never to the same level as with the first female) before falling again.

This pattern of results is consistent with the notion that dopamine activity reflects shifts in incentive value, even those that come about independent of learning. The second female was by definition novel, as she had never been encountered before. Therefore, her heightened motivational value, and the heightened dopamine activity she elicited, were unlikely to arise from learning (the males had not apparently ever before experienced successive copulations with multiple females in a single day, so the enhancement could not have arisen by generalization from learning). This seems to be an example, therefore, of a case where changes in dopamine activity do not reflect *predicted* reward value based on learning, but instead reflect an *unconditional modulation of incentive value*, based on a change in the unconditioned stimulus; i.e., a change in incentive salience. [12]

11. Effects of dopamine antagonists: a re-examination of anhedonia, incentive salience or anergia explanations

11.1. Comparing dopamine antagonist effects on hedonic activation

A primary conclusion of our review is that mesolimbic and neostriatal dopamine systems are not necessary for normal hedonic processes. It is reasonable to ask then, whether our conclusion can be reconciled with the wealth of evidence for *anhedonia* obtained over several decades.

[11] In order to test in practice whether dopamine firing patterns follow cognitive expectation (Dickinson's experience-dependent revaluation) vs. incentive salience predictions (Bindra/Toates direct motivational shifts) it will be important to induce *strong motivational appetites* (e.g., strong sodium depletion) when comparing predictions made by the two models. Weak physiological shifts might not be sufficient to alter neuronal response. The issue has arisen before concerning whether motivational shifts change the electrophysiological coding of gustatory reward signals in primates as in rodents, since electrophysiological studies in primate have tended to use weaker motivational shifts, for ethical and practical reasons, than comparable experiments using rodents [410,411] (for discussion see Ref. [34]). An adequate electrophysiological test would either need to induce strong motivational shifts in primates or else would have to be done using rodents as subjects and motivational procedures similar to those of Dickinson and Balleine. There is at least suggestive evidence from rodent studies to support our prediction that dopamine activation may be potentiated directly by physiological or pharmacological enhancement of incentives. Mesolimbic dopamine overflow elicited by food in rats has been suggested to be higher the hungrier they are [290,482]. The incentive salience hypothesis predicts such effects even if the experience is novel to the animal (since Pavlovian incentive value is directly enhanced by hunger state [460,463]), in contrast to predictions based on the 'cognitive expectation of incentive value' (since the expectation is based on past experience, and the work of Dickinson and Balleine [12,127,128] shows that for accurate cognitive expectation, the animal must previously experience the value of the food while hungry). Given the paucity of evidence available, the question remains open as to whether dopamine neurons will most often follow the reward learning hypothesis or the incentive salience hypothesis when their predictions diverge. But Pennartz (p. 235 [341]) draws the tentative conclusion, that ''Altogether, these observations on SNpc DA neurons indicate functions in attention, orientation and the formation of behavioural responses to significant and salient stimuli, but not in reinforcement signalling per se.''

[12] Furthermore, when introduced, the second female had greater incentive value than the 'spent' first female, as assessed by behavior (the male renewed copulation), but less incentive value than the first female had initially (reflected by much less vigorous copulation with the second female). This behavioral incentive value was correlated with dopamine overflow: the increase in dopamine was much less during copulation with the second female than with the first. A 'hedonic' interpretation of dopamine function is also compatible with the Coolidge effect reported by Fiorino et al. [159], since the highest dopamine levels occurred during copulation. But Fiorino et al. note that the male rats actually spent much of the 'consummatory phase' in intense appetitive pursuit of the female between intromissions, so the enhanced dopamine overflow even surrounding copulation could still reflect peak activation of a 'wanting' process during that phase [159].

Nearly all the evidence for anhedonia came, as we pointed out above, from animal studies that involved either a measure of an instrumental behavior required to obtain a reward (bar pressing, running in a runway, etc.) or a measure of choice (such as place preference or food consumption). All such studies more directly measure 'wanting' (the willingness to work for or seek an incentive) than 'liking' (the hedonic consequences of reward consumption). In all such studies the effect of any experimental manipulation (e.g., dopamine antagonist treatment) on hedonics is only *inferred* (not directly measured) by changes in 'wanting'. No such study provides, therefore, evidence of a specific role for dopamine in hedonic processes. They can be discounted because they cannot discern between a change in both 'liking' and 'wanting' vs. a change in incentive salience alone.

But two types of studies with dopamine antagonists do not fit into that category, and cannot be so easily dismissed. They are (1) animal studies of the effects of dopamine antagonists on the same affective reactions to taste studied here after 6-OHDA lesions, and (2) self-report studies in humans of the effects of dopamine antagonists on the hedonic impact of stimuli such as drugs of abuse. Are the results of such studies compatible with our conclusion?

11.2. Affective taste reactivity and dopamine antagonists: sensorimotor anergia but not anhedonia

In an early study of a dopamine antagonist's effect on hedonic and aversive reactions to taste, Treit and Berridge [465] found that haloperidol (0.5 mg/kg or 1.0 mg/kg) failed to suppress hedonic reactions of rats to a 1 min infusion of sucrose infusion, and also failed to enhance aversive reactions to quinine. Failure of a dopamine antagonist to alter affective reactions patterns is in accord with our conclusion that dopamine does not mediate hedonia. However, two taste reactivity studies conducted by Parker et al. [274,331] at about the same time suggested that a different dopamine antagonist, pimozide, did shift palatability. Leeb et al. [274] reported that pimozide suppressed hedonic reactions to sucrose if the sucrose infusion was infused over 10 min, especially in the later minutes, and especially if the trials were repeated on successive days. Conversely, Parker and Lopez [331] reported that pimozide *enhanced aversive reactions* to quinine in a similar test. The authors of those studies interpreted their results as evidence for the anhedonia hypothesis.

In order to settle the controversy, a more recent collaborative study was undertaken by Peciña et al. [339]. They concluded that both 'anhedonia' and 'increased aversion' after pimozide were illusory artifacts [339].

- First, the initial hedonic or aversive responses were generally not altered by pimozide (0.5 mg/kg) during the first minute of a sucrose or quinine infusion, supporting the conclusion that initial hedonic impact remained normal [339]. Only later responses, emitted in subsequent minutes or trials, were diminished, and that appeared to reflect a progressive sensorimotor deficit and not a shift in palatability.
- Second, a reanalysis of the data of Parker and Lopez [331] by Peciña et al. [339] showed that the apparent enhancement of aversive reactions to quinine was an artifact of the motor suppressant effects of pimozide. Pimozide reduced locomotion, and therefore, pimozide-treated rats spent more time in view of the camera, giving rise to inflated aversion scores. When the sampling error was corrected, it eliminated the enhancement of aversive reactivity originally reported by Parker and Lopez [331].
- Third, Peciña et al. [339] found that when the duration of sucrose infusions and quinine infusions were equated pimozide actually suppressed aversive reactions (rather than enhancing them) in exactly the same gradual way as it suppressed hedonic reactions. This gradual and equivalent pattern of behavioral reduction, regardless of affective category, was the principal reason for concluding that the suppression was sensorimotor in nature (similar to Salamone et al.'s concept of 'anergia' [382,383]). The sensorimotor suppression appeared only during the later minutes of a continuous oral infusion, which elicited a prolonged and vigorous response, and grew as a stimulus was repeated or sustained over several minutes or trials.

Peciña et al. [339] concluded that a progressive general sensorimotor suppression was sufficient to account for all the effects of pimozide on taste reactivity patterns. There was no reason to conclude that pimozide additionally altered hedonic or aversive palatability. In short, *pimozide does not produce anhedonic shifts in palatability*, as assessed by taste reactivity [339].

In the present study using dopamine-depleted rats we found no evidence for sensorimotor suppression. However, a 1-min infusion was used and that duration may not encroach into the temporal zone of delayed sensorimotor suppression [339]. Perhaps if a longer sustained stimulus had been used sensorimotor deficits would have been detected. Alternatively, sensorimotor suppression of taste reactivity might be more pronounced after *acute* receptor blockade than after *chronic* dopamine depletion. Whatever the case, the results of 6-OHDA lesions and dopamine antagonists are now both consistent with the conclusion that dopamine is not crucial to hedonic impact as measured by affective taste reactivity patterns.

11.3. Subjective hedonic ratings by humans and dopamine antagonists: conscious pleasure persists

What about the effects of dopamine antagonists on self-reports of subjective wanting and liking in humans? In two recent studies Brauer and de Wit report that in humans the *euphorigenic* effects of amphetamine (10 or 20 mg; euphoria assessed by subjective hedonic ratings) are not altered by co-treatment with pimozide (1, 2 or 8 mg) [58,59]. That is, pimozide did not influence subjective ratings of '*like drug*' [59]. Similarly, Ohuoha et al. [320]

reported that the ability of cocaine to produce subjective euphoria was not diminished by prior administration of either haloperidol or fluphenazine.

By contrast with unchanged ratings of 'like drug', Brauer and de Wit [59] reported that subjective ratings of '*want drug*' elicited by amphetamine were significantly suppressed by the highest dose of pimozide used. In related studies, subjective *craving* elicited by a drug or conditioned stimulus has similarly been found to be suppressed by dopamine antagonists. Modell et al. [302] primed craving in alcoholics by giving them a small drink of alcohol, and found that the elicited craving (and actual consumption) was suppressed by prior administration of haloperidol. In a study of conditioned craving, Berger et al. [28] showed videotapes of crack cocaine preparation to addicts, and found that haloperidol significantly reduced their elicited ratings of subjective craving. In the Berger et al. study, it can be noted that haloperidol also reduced ratings of the 'conditioned high' elicited by watching the video, which is inconsistent with our notion that dopamine antagonists reduce 'wanting' but not 'liking'. However, the magnitude of change in the 'high' rating was less than the effect on subjective craving. In a review of the literature on dopamine drugs and subjective *hedonic* ratings, Brauer et al. [60] note that dopamine antagonists diminished the subjective euphoric effects of amphetamine in only 2 of 10 studies they surveyed (typically at antagonist doses that were sufficiently high to produce aversive symptoms by themselves), and that dopamine antagonists were even less effective in reducing cocaine-induced euphoria. Thus, dopamine antagonists may alter human subjective ratings of wanting more reliably than they alter ratings of liking. Chronic suppression of dopamine neurotransmission, such as occurs in Parkinson's disease, may be no more effective than neuroleptic drugs in suppressing the hedonic impact of rewarding stimuli. For example, Travers et al. [464] found that Parkinson's patients rated the perceived pleasantness of sweet and salty tastes no lower than normal subjects did (and in fact gave *higher* hedonic ratings than normal to the most intense sweet solutions).

Augmentation of dopamine function may lead to converse results and to a similar conclusion regarding the role of dopamine in subjective experience. Haney et al. [219] gave pergolide (a D1/D2 dopamine receptor *agonist*) or a placebo to human addicts, and then let them perform an operant task to earn cocaine as a reward. Pre-treatment with the dopamine agonist failed to increase the addicts' subjective liking for cocaine, when rated several minutes after taking the cocaine. On the contrary, their subjective ratings of 'I like dose' or feeling 'high' or 'stimulated' were actually suppressed by pergolide [219]. By contrast, pergolide did significantly increase subjective ratings of 'I want cocaine' measured at the same time—and simultaneously increased subjective craving for other drugs too (increased ratings of 'I want alcohol' and 'I want nicotine') [219]. Heightened dopamine neurotransmission thus appears to enhance subjective wanting, but not subjective liking, for drugs such as cocaine.

Admittedly, the effects of psychoactive drugs on subjective ratings by human subjects must be interpreted cautiously. Subjective reports by humans may sometimes diverge from underlying core processes of emotion and motivation [34,41,273,307,316,494]. Subjective ratings are cognitive interpretations of the subject's own feelings, and are influenced by many cognitive factors, rather than being direct readouts of underlying 'wanting' and 'liking' processes [273,307,316,494]. Even reports that dopamine antagonists decrease subjective craving may not be able to be taken at face value, and suppression of subjective hedonic ratings also sometimes occurs. The process of incentive salience attribution is held by us to be not directly accessible to conscious introspection [34,35,41,366]. Blurring of the distinction between 'wanting' and 'liking' core processes is therefore sometimes to be expected in conscious experience and subjective reports. To conclude, more study clearly is needed, but the available evidence from studies of human subjective reports are consistent with our hypothesis that dopamine has more to do with 'wanting' rewards than with 'liking' them.

12. Phenomena that don't fit: problems for the incentive salience model?

12.1. Euphorigenic dopaminergic drugs

Probably the most convincing original evidence for the hedonia hypothesis, aside from animal studies of reward suppression by neuroleptic drugs, were demonstrations that most drugs of abuse promote activation of mesolimbic dopamine systems [266,268,505–507]. Dopamine neurotransmission is generally enhanced by rewarding drugs, and many (though not all) addictive drugs of abuse produce subjective euphoria in humans. How can it be that so many drugs that enhance dopamine neurotransmission are euphorigenic if dopamine systems do not mediate hedonia?

There are several possible answers to this question. First, all euphorigenic drugs of abuse influence multiple neurotransmitter systems, not just dopamine systems. Indeed, for many, their primary action is not on dopamine. Opiates provide an obvious example, as they produce their actions via opioid receptors, mostly located on non-dopaminergic neurons. Furthermore, unlike dopaminergic agents, opioids do alter 'liking' for food rewards, as measured by hedonic taste reactivity patterns [34,131,332, 336,338,360]. Thus, some classes of drugs may produce 'liking' (hedonia) via their direct or indirect actions on endogenous opioid or other neurotransmitter systems that mediate hedonic impact.

Even psychostimulants, such as amphetamine and cocaine, have many actions in addition to their actions on

dopamine neurotransmission. For example, both drugs bind to norepinephrine and serotonin transporters, and increase the concentrations of these transmitters in dialysate, and via their actions on monoamines can influence many other transmitter systems. Serotonin systems in particular have been implicated in cocaine self-administration. For example, knockout mice lacking serotonin 1B receptors work more avidly for cocaine than wild-type controls, as indicated by higher 'breakpoints' on a progressive ratio schedule (and they also appear to be hypersensitive to the psychomotor stimulant effects of cocaine) [369,486]. Although this does not imply that serotonin, any more than dopamine, mediates the hedonic impact of cocaine, it does highlight the multiplicity of neurotransmitter systems that contribute to the rewarding effects of even psychomotor stimulant drugs. It is reasonable to hypothesize, therefore, that euphorigenic drugs produce their hedonic effects via their actions on neurotransmitter systems other than dopamine, even if their incentive properties are mediated by dopamine systems.

Furthermore, the neural circuits responsible for 'liking' and 'wanting' may be closely intertwined in the brain (albeit not identical). For example, microinjections of opioid agonists into the shell region of the nucleus accumbens enhances taste hedonics [334,338]. Thus, in the same accumbens region where dopamine plays a critical role in mediating reward 'wanting', opioid receptors have been implicated in 'liking', and there are probably direct synaptic connections between the two systems [223,246,253, 255,281,350]. Neural circuits involved in 'wanting' and 'liking' may also be found together in the ventral pallidum. The ventral pallidum receives a dopamine input from the ventral tegmental area [189,190,264], and lesions of the ventral pallidum, which produce aphagia (elimination of food 'wanting'), abolish hedonic reactions to food (elimination of 'liking'), and cause rats to respond aversively even to normally palatable food [34,106,393]. How 'wanting' and 'liking' are integrated neurobiologically remains an important challenge for future research, but some drugs that promote dopamine neurotransmission may activate both systems.

In support of our contention that dopamine is not hedonia, it is important to note that many drugs that increase dopamine neurotransmission are not euphorigenic. Rothman and Glowa [374] review evidence of multiple dissociations between the ability of drugs to enhance dopamine neurotransmission and their ability to produce euphoria. For example, there are a number of dopamine uptake blockers that are used clinically, some of which are more potent than cocaine at inhibiting [^{3}H]dopamine uptake, but many do not produce cocaine-like euphoria. One of them, mazindol, is reported to be *dysphoric* in humans. Direct dopamine receptor agonists provide another interesting example that can dissociate 'wanting' and 'liking'. Many of these agents support self-administration in animals, but the available evidence indicates people do not find them to be euphorigenic [374]. Similarly, monoamine oxidase inhibitors and L-Dopa increase extracellular dopamine but are not euphorigenic. In conclusion, the evidence reviewed by Rothman and Glowa [374] indicates that increasing dopamine neurotransmission is not a sufficient condition for producing euphoria.

Finally, in relating the effects of drugs on 'wanting' vs. 'liking' in humans it is important to keep in mind the potential for cognitive confusion regarding subjective effects. Although unlikely to explain reports of an 'orgasmic rush', a person who took a drug that made the world seem a more attractive and rewarding place, by selectively enhancing incentive salience, might find it difficult to describe those effects without invoking hedonic concepts. Also, addicts who 'want' drugs might sometimes mistakenly infer they necessarily 'like' them in order to explain to themselves their own addiction [366]. Although it may seem nonintuitive to claim that addicts could be wrong about their own feelings, there is ample evidence that people sometimes are wrong about and sometimes unaware of their own underlying emotional 'core processes' [35,141,243,244,316,494,495,528]. For a more complete discussion of addiction and drugs of abuse see Robinson and Berridge [366,367]. For discussion of how 'liking' and 'wanting' core processes contrast to subjective experience, see Berridge [35].

12.2. Paradoxical effects of dopamine antagonists

What about 'problem' phenomena from animal experiments that contradict our predictions? There are several effects of dopamine antagonists that appear to pose difficulty for an incentive salience hypothesis. First, the ability of dopamine antagonists to suppress motivated behavior is sometimes delayed. Second, under some conditions dopamine antagonists actually appear to *increase* the preference or consumption of rewards. These phenomena present a paradox in that dopamine receptor blockade, which ought to reduce incentive motivation, either apparently fails to do so or appears to do the opposite. In this section, we show how paradoxical effects can be understood in light of the incentive salience hypothesis.

12.2.1. Reinforcement extinction without motivational suppression?

Ettenberg and colleagues [82,145,148,234,235,291,292] have shown in several studies that moderate doses of pimozide, haloperidol or other dopamine antagonists can block the ability of a reward to strengthen or reinstate *future* instrumental behavior for that reward, without reducing reward-directed behavior on the trial the neuroleptic is given. This effect is similar to 'extinction mimicry', in which neuroleptics produce gradual declines in instrumental performance without altering the initial level of response when the drug is first given [175,176,179,479].

When given particular doses of pimozide or haloperidol, for example, rats may still run as fast in a runway for the reward they have received earlier as they would without neuroleptic, and a conditioned stimulus for reward still prompts locomotion [235,291]. However, subsequent running on a later drug-free day is suppressed for the reward that had been experienced earlier under the neuroleptic [291]. McFarland et al. [291] interpret the delayed effect to mean that dopamine antagonists have no effect upon the rat's motivation to run when it first receives the drug, but that neuroleptics do prevent the ability of the reward to serve as a *reinforcer*, here meaning to sustain or strengthen subsequent running. Ettenberg et al. [82,148,234,292] have also demonstrated that neuroleptics block a related reinforcement effect, namely, *reinstatement*. In reinstatement, animals are first trained on a rewarded task, and then are extinguished by the withholding of reward. They are then given a single rewarded trial—which typically reinstates future instrumental performance. Reinstatement is blocked if rats are given a neuroleptic immediately prior to the rewarded trial.

The ability of dopamine antagonists to block reinforcement and reinstatement of a subsequent response is consistent with an *anhedonia* interpretation of dopamine function [499,500,503,514]. Preventing the reward's hedonic impact should prevent reestablishment of behavior motivated to regain it, but need not impair motivation before the diminished pleasure has been experienced. Reinforcement and reinstatement suppression is also consistent with a '*reward learning*' interpretation of dopamine function [3,304,400,405]. Preventing the growth of an association between a reward and a particular stimulus or response should attenuate subsequent behavior that is guided by the association, but not necessarily other aspects of behavior. Blocking of reinforcement and reinstatement is also consistent with the *incentive salience* hypothesis if the neuroleptic prevented 'reboosting' of incentive salience (see above) [34,44,45,366]. But these results also present some unique problems for the incentive salience hypothesis. The problem for the incentive salience hypothesis is that it also predicts that *'wanting' for incentive stimuli should be impaired on the day of neuroleptic administration*, as well as on subsequent days. How can an incentive salience hypothesis reconcile the failure to observe a performance impairment on the day of neuroleptic administration with suppressed performance for the reward on a subsequent undrugged trial?

The answer may hinge in part upon the dose of neuroleptic used and in part on the conditions of testing. We posited several years ago that neuroleptics differentially impair incentive salience attributions under different conditions [34,44,366]. Neuroleptics most readily disrupt the *acquisition* of new incentive salience by conditioned stimuli and the *re-boosting* of incentive salience, both of which occur once a hedonic reward is obtained. These disruptions, we suggested, occur at *lower doses* of neuroleptic than are needed to disrupt the attribution of incentive salience to a familiar, and already 'wanted', conditioned stimulus [34,44,366]. This means that after low to moderate doses of dopamine antagonists, pre-established incentive salience may still be attributed to conditioned stimuli, but the drug may block the reboosting of incentive salience to those conditioned stimuli and the acquisition of incentive salience by new conditioned stimuli [34,44,366].

Acquisition requires an actual *increment* in incentive salience attribution. Even re-boosting that maintains the incentive value of a conditioned stimulus when hedonic reward is obtained may require an incremental process, as described earlier, to oppose the automatic de-boosting that would otherwise occur. In both acquisition and re-boosting, the occurrence of the hedonic event triggers a process that increments the incentive salience assigned to conditioned stimuli. These incremental processes may be blocked relatively easily by dopamine antagonists. By contrast, the pre-established incentive salience of a familiar 'wanted' reward is based on earlier experiences with it that occurred in the absence of a dopamine antagonist. Such pre-established attributions of incentive salience are posited by our hypothesis to be less vulnerable to neuroleptic blockade. Pre-established attributions may initially persist even if increments and re-boosting are disrupted [44,45].

If acquisition and re-boosting are preferentially blocked, then an animal may be unable to acquire a new incentive under neuroleptic blockade, but may still respond to an 'old' one. Therefore, the blocking of re-boosting for the familiar incentive may prevent reinstatement and produce 'extinction mimicry': a gradual decline in responding during or across sessions [175,176,479]. According to our hypothesis, this works as follows. First, the perception or representation of the familiar conditioned stimulus for reward triggers attribution of incentive salience based upon past associative experience with the reward and hedonic activation. The familiar conditioned stimulus is still 'wanted' since 'wanting' attributed on the basis of pre-established associations is relatively resistant to neuroleptic administration. If the individual responds and acquires the full unconditioned reward, hedonic 'liking' systems are activated just as they would be in the absence of neuroleptic. But the triggering of incentive salience systems by hedonic 'liking' is no longer sufficient to generate the re-boosting of incentive salience that would be needed to *maintain* the ability of a conditioned stimulus to elicit 'wanting' each time it is encountered [44,45]. The brain expects a 'wanted' conditioned stimulus to be followed by hedonic 'liking', just as in the past, and in a sense poses on each trial a question that has one of two answers. Does the 'wanted' reward still carry its old hedonic impact ('liking')? If hedonic activation occurs, the answer is 'yes': it triggers dopamine-related systems to reboost the incentive salience attributed to the stimulus, and the stimulus remains 'wanted' in the future. If hedonic activation fails to trigger incentive salience systems, however, the

answer is 'no': then reboosting fails to occur, and 'wanting' for the conditioned stimulus is automatically devalued. [13]

Prevention of incentive salience reboosting means that the stimulus will be less 'wanted' the *next* time it is encountered: blocking reinstatement and producing 'extinction mimicry'. As Berridge and Valenstein (p. 11, [44]) put it, ''reboosting appears to be especially vulnerable to neuroleptics and may be suppressed by doses that do not prevent the attribution of preestablished incentive salience''. Higher doses of neuroleptics, or behavioral test procedures that more sensitively reveal modulation in appetitive motivation, would reveal motivational or 'wanting' suppression even on the day of the drug. Many studies have indeed reported an immediate motivational suppression by the dopamine antagonist drug, reducing the likelihood and strength of instrumental responding or of approach to the incentive target [17,28,50,51,157,310,382, 383,429]. Extensive dopamine depletion by 6-OHDA, as in the present study, even more effectively eliminates all aspects of incentive salience attribution, leaving the individual oblivious to all incentives and rewards [287,451, 452,471,531].

12.2.2. Paradoxical 'motivation increase' after dopamine antagonists?

Worse than preservation of motivation after neuroleptics, from the point of view of the incentive salience hypothesis, are *increases* in incentive motivation. In some situations, administration of a dopamine antagonist causes an animal to *increase* its self-administration of a drug or, less commonly, a food incentive.

A paradoxical enhancement of *food* intake after dopamine blockade has been reported by Salamone et al. The situation must be arranged quite carefully to achieve the effect, which actually involves a redirection of consumption from one food, which is normally preferred, toward another food, which is less preferred but more easily obtained. Rats normally ignore the nonpreferred-but-free food and work to obtain the preferred-but-hard-to-get one. After mild dopamine impairment, however, they switch to the less preferred food—and *actually increase consumption of that food relative to their normal intake of it*. For example, in a Skinner box hungry rats may choose between bar pressing to gain a preferred sweetened pellet or to eat ordinary chow that is freely available in the box. After administration of haloperidol, SCH 23990, flupenthixol, or sulpiride rats not only stop bar pressing for the preferred sweetened food, but they also *increase* their consumption of the free chow [101,382,385]. The tasty but expensive food reward loses out to bland but cheap. Similar effects are seen after localized 6-OHDA lesions of the nucleus accumbens, especially of the accumbens core [100,382,432].

Although an increase in consumption of a food, any food, might appear to be a paradoxical increase in the motivation to eat, and difficult for the incentive salience hypothesis to interpret, an increase in motivation after dopamine disruption is probably not the right explanation. Further insight into the nature of the effect is provided by additional experiments by Salamone et al. [99,382]. In these experiments rats were given a choice between two arms in a T-maze. One arm contained several food pellets, but to get to them the rats had to climb over a formidable barrier (44 cm high). The other arm contained only half the number of pellets as the first arm, but had no barrier and so was easy to reach. Normally, rats preferred to climb for the larger reward. After haloperidol or partial depletion of accumbens dopamine, however, rats switched their preference to the smaller-but-easier reward [99,382]. The failure to persist in the demanding task was not due to absolute incapacity: that was demonstrated by giving a group of rats a slightly different choice between an obstructed arm that contained the large food reward and an unobstructed arm that was *empty*. Faced with that choice, the rats continued to struggle over the obstacle to gain the food even after dopamine impairment [99,382]. The typical switch by the other groups to the less preferred reward—and their concomitant increase in consumption of the normally unchosen food—was clearly a default consequence of abandoning the difficult task in favor of any acceptable alternative. The dopamine impairment was not sufficient to eliminate all appetitive behavior and consumption. The animals were still disposed to eat some food, and the food most readily available was therefore consumed. Salamone et al. [380–383] contrast this impairment to anhedonia, and describe it instead as a form of 'anergia': a complex sensorimotor deficit manifest in motor slowing, reduced reaction to certain stimuli, and a biased response selection away from vigorous instrumental behavior toward easier alternatives (possibly related to the sensorimotor suppression of taste reactivity by neuroleptic administration described earlier [339]). Salamone et al. conclude that this impairment alters

[13] Even on the day of neuroleptic treatment, prevention of incentive salience reboosting and consequent devaluation of 'wanting' can lead to discernable consequences. Rats are reported to disengage from the food or other incentive object earlier after neuroleptic administration than they otherwise would, or similarly fail to maintain pursuit or contact as the trial goes on [175,429,430,499,512]. A possible neurological correlate consistent with this interpretation has been reported by Chang et al. [81] in an electrophysiological study of rats that bar pressed to receive cocaine infusions. Nearly 20% of neurons they recorded in the nucleus accumbens showed anticipatory responding before the cocaine was administered as the rat oriented toward the lever or began to press. Some of these neurons also responded to the cocaine itself. Pre-administration of a dopamine antagonist did not block the anticipatory neural activity correlated with incentive salience or 'wanting' triggered as the rat oriented, and the rats still pressed at the beginning of the session. The dopamine antagonist did, however, block the post-cocaine neuronal response of the same neurons [81]. That could be viewed as blocking the normal reboosting of incentive salience consequent to hedonic activation, which could cause behavioral bar pressing to extinguish.

many aspects of behavior, and that it may not be possible to parse among motivational and sensorimotor effects.

These important studies by Salamone et al. illustrate the subtle diversity of function mediated by dopamine systems. They also provide an instance in which consumption of a particular food (the normally less preferred one) is increased by a dopamine antagonist, which normally decreases food consumption. In this case the paradox of increased consumption seems easily resolved: the antagonist does not actually increase motivation to eat, it merely preserves a degree of incentive motivation (not necessarily the original level) while biasing choice away from the difficult task, probably due in part to sensorimotor effects of the drug.

Paradoxical increases in drug self-administration (e.g., cocaine or amphetamine) have also been reported to follow neuroleptic administration [112,149,267,268,522,523]. Unlike a shift in food choice, the paradoxical increase in the rate of cocaine or amphetamine self-administration reported following a dopamine antagonist cannot be explained simply by reallocation of the remaining response. In the case of drug self-administration, the *sole response* is potentiated by the dopamine antagonist. In early studies, Yokel and Wise [522,523] showed that low doses of pimozide could increase the self-administration of amphetamine by rats (followed by extinction in the case of higher doses). De Wit and Wise [112] found a similar effect of pimozide on cocaine self-administration. Increased self-administration of cocaine can be induced by low-doses of other neuroleptics such as alpha-flupenthixol too (though again, higher doses have the opposite effect of suppressing self-administration) [149]. These effects were interpreted within the anhedonia framework: reduced hedonic pleasure could prompt an individual to strive for more of the 'watered down' reward [514].[14] The 'hedonic homeostasis' framework of Koob et al. provides essentially the same explanation as that of de Wit and Wise [112], in that it posits dopamine neurotransmission to be tied to hedonic activation [267,268]. Koob et al. (p. 514, [267]) argue that suppression of dopamine-related reward systems must blunt ''in the case of cocaine,... the acute hedonic response'', and that individuals must therefore work to obtain more cocaine in order to maintain their desired level of hedonic activation (i.e., hedonic homeostasis) [267,268].

This effect certainly has the appearance of an increase in incentive motivation. How can an increased rate of self-administration after treatment with a dopamine antagonist be explained by the incentive salience hypothesis, which must posit that incentive motivation, if changed at all, should be decreased by a dopamine antagonist?

First, it can safely be said that the *incentive motivation ('wanting')* to take drugs is probably never increased by neuroleptic administration. There are several reasons to believe that dopamine antagonists *reduce* the incentive value of cocaine and other drugs, even if the rate of bar pressing increases. And there are alternative explanations for the increase in response rate.

Limitations of response rate as a measure of motivation. It has been clear for nearly 4 decades that under some conditions absolute rate of response is a misleading measure of reward and motivation [473]. For example, Hodos and Valenstein [230,473] showed in 1962 that, given a choice between two levels of rewarding brain stimulation, rats typically preferred the higher intensity, even though they pressed at a faster rate for the lower intensity. Some limitations of absolute response rate as a measure of incentive value may also apply to drug reward. In a review of the usefulness of response rate measures in drug self-administration experiments, Arnold and Roberts (p. 441, [6]) concluded that ''the rate of drug intake cannot directly address the issue of increased or decreased reinforcer efficacy''. They note that dopamine impairments sometimes increase the rate of self-administration and sometimes reduce it, and that both effects are often taken as evidence for reduced reinforcement (i.e., reduced reward or hedonic impact): ''how can both an increase and a decrease in rate of drug intake be used to draw the same conclusion? The dilemma is unmistakable: rate is an ambiguous measure of reinforcing efficacy'' (p. 442, [6]).

Progressive ratio 'breakpoint designs', in which the response requirement is progressively elevated throughout a session, have been argued to provide a better measure of incentive value [6,229]. In such experiments, the first reward requires only 1 or 2 bar presses, the second reward requires more responses, the third more still, and so on. The question is, how far will an animal escalate its response to gain the reward? The results of such experiments typically indicate that motivation is *decreased*, not increased, by dopamine antagonists. For example, Depoortere et al. trained rats to bar press for cocaine on a progressive ratio schedule, and found that the D1 antagonist SCH 23390 lowered the breakpoint, so the rats quit pressing sooner [114]. This was not due to a motor deficit, Depoortere et al. [114] concluded, because rats pressed at a comparable rate under the neuroleptic as they did without it. If anything, there was a slight tendency to press more rapidly after the antagonist, again underscoring the ambiguity of absolute response rate. Similarly, Roberts et al. [364] found that preadministration of haloperidol significantly *increased* the absolute rate of cocaine self-administration, but simultaneously *lowered* the highest response ratio achieved (breakpoint). Equivalent dissociations have been reported by McGregor et al. [293,294] after microinjections of dopamine antagonists into the accumbens, and

[14] Interestingly, *decreases* in reward consumption after neuroleptics have been interpreted identically in the anhedonia framework, as reflecting reduced pleasure, on the grounds that consumption should be proportional to the hedonic intensity of the reward. For examples, see [182,429,498,499,514,517]. The contradiction points to the need for an explicit and consistent theoretical framework in which to relate behavioral changes to psychological processes.

after central 6-OHDA lesions. In all these studies there is dissociation between response rate (which typically goes up after central dopamine suppression) and breakpoint (which typically goes down). If breakpoint is a better measure of motivation than the absolute rate of self-administration, as has been suggested [6], then dopamine antagonists usually reduce the motivation for a drug reward—as the incentive salience hypothesis would suggest.

Finally, prior *sensitization* of dopamine systems has been reported by Mendrek et al. [297] to produce the *opposite* effect on progressive ratio tests, *increasing* the breakpoint for amphetamine (an effect that has been replicated by Vezina [476]). Thus, as assessed by progressive ratio schedules, manipulations that increase dopamine neurotransmission (e.g., sensitization) increase motivation for drugs, and manipulations that decrease dopamine activity (e.g., neuroleptics) decrease motivation for drugs. This is consistent with the incentive salience hypothesis that dopamine systems mediate 'wanting'. It also supports our related proposal regarding addiction, presented elsewhere, that sensitization of dopamine systems may increase 'wanting' for drugs, and produce compulsive seeking and taking of drugs (for discussion of the Incentive–Sensitization theory of addiction see Robinson and Berridge [366,367]).

12.2.3. Resolutions for the rate paradox

Still, it is important to understand why the absolute response rate of drug self-administration might increase under the influence of a neuroleptic. There are several factors that may help illuminate this phenomenon.

- First, it should be noted that neuroleptics increase response rates for cocaine or amphetamine only over a limited range of neuroleptic doses. High doses of dopamine antagonists suppress even the absolute rate of responding below baseline [149,267], which could be due to motivational deficits as well as motor deficits.
- Second, neuroleptics may diminish some of the *aversive* properties [183] (e.g., paranoia, cardiovascular responses, etc.) of cocaine or similar drugs, as well as their rewarding effects. A decrease in the aversive effects could lead an animal to increase the highest cocaine dose that it tolerates, so that it takes higher doses than normal. A rat that was still motivated at all to self-administer cocaine after a low dose of a neuroleptic might take more cocaine because its aversive impact, not its hedonic impact, was reduced.
- Third, neuroleptics themselves may sometimes have aversive effects. Dopamine antagonists, for example, can sometimes establish a conditioned place avoidance when paired associatively with a new location [78,310,361] (though not all studies find this). Dopamine antagonists by themselves also induce unpleasant symptoms in humans, manifest in subjective reports of confusion and impaired psychomotor performance [60]. To the extent that a neuroleptic has any aversive properties, cocaine and similar drugs could be an effective antidote. Animals might increase their self-administration of a drug like cocaine in part to combat the aversive effects of the neuroleptic.
- Finally, interactions among self-administered dopamine indirect agonists and low doses of neuroleptics are especially difficult to interpret. If the neuroleptic dose were low enough, the animal might soon administer sufficient indirect agonist to effectively replace any motivational impairment with dopaminergic stimulation. In that case, its neural and motivational condition early in the session (suppression of dopamine neurotransmission) would be qualitatively different from later in the same session (activation of dopamine neurotransmission). It is not clear which drug should be expected to win when the neuroleptic dose is low.

In short, increases in the rate of drug self-administration after neuroleptics are subject to a host of interpretive complications. Reward or motivation cannot be simply inferred from absolute response rate.

12.3. The 'Two Motivational Systems' hypothesis (Bechara et al.)

A different type of potential problem for the incentive salience view is posed by a novel proposal developed by Bechara et al. [17,19,310], which they call the '2 systems' hypothesis. The '2-systems' hypothesis does not propose a specific *alternative* to incentive salience ('wanting'), hedonia ('liking'), or reward learning for the *specific reward function* mediated by dopamine. Instead, it proposes a major constraint on when dopamine can mediate reward. They suggest that dopamine systems mediate reward, but only under certain conditions: *only when individuals are in a state of physiological deprivation* (e.g., caloric hunger or drug withdrawal). They suggest that an entirely separate neural system mediates the incentive value of rewards when animals are in a nondeprived state. This latter system is hypothesized to depend especially on the tegmental pedunculopontine nucleus (TPP).

Thus, Bechara et al. [22,310] suggest that there are two separate systems of reward in the brain—a dopamine-related system that is operative in the deprived state and a TPP system that is operative in the non-deprived state. The 'two systems' are held to be mutually exclusive: they contribute similarly to behavior, but at different times. At any moment only one of these neural reward systems should be active, according to their model. Activation of the dopamine reward system (deprived state) itself inhibits the TPP system (nondeprived state), they argue, and the dopamine system is activated by conditions of deprivation (for reviews, see Nader and van der Kooy, 1997 [22] and Nader et al., 1998 [310]). If the '2 systems' hypothesis of Nader et al. is true, it means that dopamine can mediate incentive salience (or hedonia or reward learning) only when individuals are in some form of a deprivation state.

Their novel suggestion is based on a series of conditioned place-preference experiments, which showed that alpha-flupentixol, a dopamine receptor antagonist, diminishes the reward value of food when rats are hungry, but not when they are sated [17,310]. Similarly, flupentixol diminishes the reward value of morphine when rats are in withdrawal, but not when they are drug-naïve [17,18,311]. By contrast, lesions of the TPP disrupt the reward value of both food and morphine only if rats are tested while sated or while drug-naïve, respectively, but not if they are hungry or in drug withdrawal [21,22].

Nader et al. make a cogent case that motivational systems are influenced by physiological depletion states and certainly show that depletion states influence the ability of neuroleptic drugs to disrupt reward. Yet there are several reasons why one might hesitate to adopt their hypothesis that reward is mediated by dopamine systems if-and-only-if an individual is in a state of physiological deprivation.

One reason is that dopamine antagonists such as pimozide, haloperidol, raclopride or SCH-23390 have been reported in many studies to suppress the reward value of food and other incentives *even in the absence of physiological depletion* [56,420,429]. Nader et al. [309,310] have attributed such apparent reward suppression during nondeprived states to the *aversive* effects of neuroleptics, rather than to putative reward-blocking effects. They argue that in tests for reward suppression it is critical that the dopamine antagonist be given only *under conditions in which it has no aversive properties* (measured by whether it supports conditioned place aversion training by itself). They suggest that in those studies where dopamine antagonists were found to suppress reward in nondeprived animals this effect was due to either the aversive consequences of antagonist treatment, or motor incapacity [22,309,310].

It must be recognized, however, that the literature on reward suppression by dopamine antagonists contains an enormous variety of test procedures, many of which contained measures intended to separate reward and motor effects. Also, many different dopamine antagonists, of various degrees of specificity for dopamine receptor subtypes, have been used to suppress reward. One might expect at least some of these drugs or test procedures to escape the confound of aversion. For example, the atypical neuroleptic drug, olanzapine, has been reported to suppress cocaine reward and food reward even at doses too low to produce a conditioned place aversion [295]. Further, it has been suggested by Shippenberg et al. [419,420] that typically only D1 receptor antagonists induce place aversions, whereas selective D2 antagonists do not. Yet D2 receptors have often been implicated in blockade of reward [13,83,88,415,429,457,458,490]. Under some conditions, even dopamine D1 antagonists may fail to produce place aversions, and may instead *inhibit* them: Acquas et al. [1] reported that, rather than produce a conditioned place aversion itself, SCH 23390 actually *blocked* the conditioned place aversion normally produced by administration of naloxone or other drugs. It seems possible, therefore, that at least *some* 'reward suppression' studies of diverse dopamine antagonists, conducted in nondeprived animals, may actually reflect the reward suppression their authors claim to have found.

Whether that is true or not, there is an additional problem for the '2 motivational systems' hypothesis. Even flupentixol, the antagonist of choice for Bechara et al., has been reported to suppress reward in the absence of a deprivation state. Van der Kooy reported, in a study with Mackey [280], that flupenthixol blocked an amphetamine conditioned place preference in naive rats. [15] There are other similar examples of reward suppression by flupenthixol in non-deprived animals. For example, Agmo et al. [2] found that flupentixol blocked the formation of a conditioned place preference normally produced in nondeprived rats by the opportunity to drink sucrose. Further, Duvauchelle et al. [139] reported that micro-injections of flupenthixol into the nucleus accumbens prevented place-preferences produced by electrical stimulation of the ventral tegmental area. It is unclear whether it is even possible for there to be a 'deprivation state' for brain stimulation reward. Yet Ettenberg et al. [147] also found that bar pressing for brain stimulation was suppressed by intra-accumbens flupenthixol and Stellar and Corbett [447] reported similar results for lateral hypothalamic stimulation after microinjection of flupenthixol into the medial fore-

[15] It should be noted that van der Kooy et al. [475] regard the amphetamine-induced place preference in nondeprived rats, or electrical brain stimulation reward, to be anomalies due to the ability of these treatments to directly activate dopamine neurotransmission, and so to bypass controls regulating physiological depletion states (personal communication). They suggest that these rewards may always be dopamine dependent because they directly activate dopamine systems. Thus, it appears that the critical variable may be not so much 'physiological deprivation state', but the ability of different rewards to directly engage dopamine-relevant motivational systems. Recent results by Laviolette and van der Kooy further suggest that it may depend even on the *direction* in which dopamine activity is directly changed: they show that reward is produced by VTA microinjections of either a GABA-A agonist (likely to inhibit dopamine neurons) or an antagonist (likely to disinhibit), but that flupentixol blocked only the agonist reward effect, and not the antagonist reward effect [272]. It is difficult to know whether the directional dependence on dopamine of VTA GABA-mediated reward reflects a 'switch' between two separate motivational systems, as its authors suggest, or is instead further evidence that no clear boundary separates the putative dopamine-dependant reward system from the dopamine-independent one. At best, the gating effect of deprivation on whether flupenthixol will block reward seems to hold for some rewards (food and opiates; GABA agonist in VTA) but not others (amphetamine, lateral hypothalamic electrical stimulation, accumbens neuropeptide Y, GABA antagonist in VTA etc.). Further, as noted above, flupentixol may block nondeprived reward value even for stimuli that do not act directly on brain dopamine systems, such as the taste of food [2]. It becomes difficult to predict, therefore, when the '2 systems' dopamine-dependence rule will apply and when it won't.

brain bundle. Related logic applies to the demonstration by Josselyn and Beninger [242] that intra-accumbens flupenthixol blocked conditioned place preferences normally produced by intra-accumbens injection of neuropeptide Y. Once again it seems difficult to posit that a deprivation state is responsible for that reward phenomenon. Finally, in non-deprived rats the intra-raphe administration of 8-OH-DPAT enhances feeding and that effect is blocked by flupenthixol [163]. The ability of flupenthixol to block the incentive motivational effects of food, drugs and electrical brain stimulation, in the absence of any physiological deprivation state, poses a serious problem for the '2 motivational systems' hypothesis. It begins to dissolve the boundary between the two motivational systems, which were posited by the hypothesis to be mutually exclusive, by showing that the dopamine system may actually mediate reward in both deprived and nondeprived states. [16]

Finally, if dopamine systems mediate reward only in deprivation states, as the '2 systems' hypothesis posits, then they *should not be activated by reward in nondeprived states*—but they apparently can be. Food rewards (the taste of saccharin or of a palatable chocolate drink, sucrose pellet, or butter cookie) can elicit dopamine overflow in the accumbens even in nondeprived rats [282,290,345,347]. Drug rewards (morphine, ethanol, nicotine, amphetamine, cocaine; given systemically or centrally) elicit dopamine overflow in accumbens the *first time they are given* [105,118,275,354,516] (when the animals are drug-naïve, and so, by definition, not in a withdrawal or deprivation state), and despite their diverse cellular mechanisms of action (only amphetamine and cocaine act directly on dopamine neurons; opiates, nicotine, ethanol must activate dopamine neurons *indirectly*). Sex elicits mesolimbic dopamine overflow in nondeprived males: a male rat who has copulated on recent days or even several times during the past hour (hardly a deprivation, no matter how 'deprived' one regards the ordinary male state), still shows elevated dopamine overflow when allowed to copulate again [159]. Sexually-receptive female rats and hamsters similarly activate mesolimbic dopamine systems when allowed to copulate under the conditions they prefer [296,299]. Maternal reward (reunion with her pups) elicits mesolimbic dopamine overflow in a mother rat after just one night away from them [220]. The list of rewards that trigger dopamine activation in 'nondeprived' rats is likely to grow. An ever growing set of deprivation states must be posited by the '2-systems' hypothesis to account for these effects (some of which appear to triggered after only hours or minutes of 'deprivation'). Otherwise it must be granted that dopamine systems are involved in many rewards (including natural rewards whose access to dopamine neurons is indirect) even in nondeprived conditions.

Our own results do not directly address this hypothesis because our 6-OHDA rats were intubated daily with food and water in order to avoid debilitation. Thus, our rats were generally not in a seriously depleted state. Nader et al. might predict that dopamine-depleted rats would show deficits only when tested in a food deprived state. However, a recent study by Qian et al. [353] examined this issue indirectly. They compared the passive consumption of an orally-infused sweet solution by aphagic 6-OHDA rats in two conditions: on a day when the rats had been artificially fed vs. after a 16-h period of caloric deprivation. There was, however, no effect of caloric deprivation on the response to food [353].

Even if dopamine mediates reward in nondeprived states, contrary to the original '2 systems' hypothesis [17,19, 310,311], there are still several ways in which deprivation states might influence the neural mediation of motivation and reward. For example, to the degree that deprivation states are unpleasant, individuals might be motivated to reduce the aversive drive-like properties of deprivation, even if incentive or hedonic reward effects of food or drugs were missing. That might be why TPP lesions do not suppress morphine's rewarding effects if animals are in withdrawal. The withdrawal state may involve different neural systems than those implicated in reward [57], and therefore, it may be possible to relieve withdrawal and thus motivate behavior after TPP lesions that impair reward systems.

It is less clear why neuroleptic suppression of dopamine systems should disrupt reward to a greater extent during deprivation states than during nondeprived states [22,310]. But one possibility is that deprivation states might activate neural systems involved in incentive motivation, including dopamine systems, to a high degree (as the value of relevant incentives increases). That might allow the impact of neuroleptics to become more visible in behavior. When the initial motivation is high, scaling effects could multiply the absolute magnitude of a neuroleptic-induced deficit, compared to when the initial state is low. A different possibility is that deprivation states might alter dopamine systems in biochemical ways that increase their vulnerability to neuroleptic blockade. For example, food restriction and weight loss have been reported to reduce levels of extracellular dopamine in the nucleus accumbens, and increase the tissue concentrations of dopamine [351]. The implication of these effects of physiological depletion for dopamine receptor blockade and reward is unclear. However, it seems safe to say that any interaction between

[16] The boundary between 'dopamine-dependent' and 'dopamine-independent' systems may be further weakened by Stefurak and van der Kooy's report that TPP lesions block the reward value of saccharin even when rats are in a deprived state [440]. The 2 systems hypothesis posits that the dopamine system *suppresses* the TPP system, and that deprivation activates the dopamine system [22,310,475]. But it appears that the TPP system may participate in reward regardless of deprivation state, just as dopamine systems do. The systems may not be mutually exclusive after all.

dopamine systems and physiological deprivation states is likely to be complex, and will not easily be reduced to a single hypothesis.

When the effect of deprivation states on dopamine systems is better understood, it may turn out that the observations that prompted the '2-systems' hypothesis will be compatible with the incentive salience distinction between 'liking' and 'wanting'. The incentive salience model and the '2 systems' model have several features in common. Both posit multiple neural systems of reward, both posit that the neural systems have functions that can be separated in behavior via experiments that manipulate dopamine systems, and both posit a modulating role for physiological deprivation states. Despite their differences regarding reward mechanisms during ordinary nondeprived states, it may yet be possible to reconcile the incentive salience hypothesis with the otherwise elegant and extraordinary hypothesis of Bechara, Nader, and van der Kooy.

13. Caveats to the 'Incentive Salience' hypothesis

13.1. Beyond reward to aversion

We would be remiss to end a discussion of the role of dopamine in reward without mention of its role in *aversive* motivational states such as fear or pain. There can be no doubt that behavior needed to actively *avoid an unpleasant outcome* is impaired as strongly by dopamine suppression as behavior directed toward a positive reward (for review, see Salamone [380]). The question is how involvement in aversive motivation bears on the role of dopamine in reward. For some investigators the involvement of dopamine in aversive motivational states raises serious doubts about whether dopamine neurons contribute to reward at all. As Gray et al. [198] put it, for example, ''the most important evidence against this hypothesis (that accumbens dopamine mediates positive reinforcement or pleasure)... is that unpleasant events such as footshock increase extracellular levels of dopamine'' (p. 1148, [198]).

Dopamine contributes to aversive motivational states. A variety of additional evidence supports the notion that aversive events activate dopamine systems (see below for example).

- Not only footshock but also other types of unconditioned stressors (e.g., enforced immobilization) increase dopamine overflow in accumbens and other forebrain structures [110,134,136,247,252,354,365,526]. Craig Berridge et al. [29] report neuroanatomical evidence that stress modulates dopamine neurotransmission in the caudal portion of the shell of the nucleus accumbens, via local intermingling between dopamine terminals and the norepinephrine projections from locus coeruleus that are activated in stress.
- Fear-eliciting *conditioned* stimuli, which are themselves innocuous but which have been paired with shock, also increase dopamine overflow [110,197,372,524–526]. Similarly, dopamine may be even higher during instrumental escape responding than when the unconditioned aversive stimulus is presented alone, again implicating a special involvement in aversive learning of some sort [354].
- Administration of dopamine receptor antagonist drugs suppresses behavioral performance on active avoidance learning tasks in a variety of situations [25,54,380,383].

It is possible, however, for a neural system to participate in more than one behavioral function. That dopamine systems are activated by fear-evoking stimuli, and are important for avoidance learning, says little by itself about whether they also mediate a specific aspect of reward.

In fact it is possible that dopamine systems are involved in both reward and aversively motivated behavior, and it is even possible that dopamine systems play a similar role in each. We have suggested before that a process related to incentive salience attribution might also be involved in aversively motivated behavior [35,366]. How could a positive process such as 'wanting' be involved also in aversive situations? There are several ways.

One possibility is that aversive tasks, such as active avoidance, may have a hidden appetitive component (see Gray [195]). Individuals in a fearful situation may 'want' to escape to a safe place or to perform another response that gains safety [195]. The safe place or the avoidance response may take on positive incentive properties, because they achieve a relatively positive outcome. To the degree that behavior is motivated by a desire for the more positive outcome, incentive salience, or 'wanting' for safety, could work in precisely the same way it does for conventional rewards.

'Motivational salience': Potential link between incentive and aversive states? But even in a situation in which the motivation was *entirely aversive*, a process related to incentive salience might still be at work. If so, it would no longer be appropriate to call the process *incentive* salience, but it might still be appropriate to call it *motivational* salience—with many of the same perceptual, attention-grabbing, and response-instigating properties of incentive salience. The same dopamine-based motivational salience process might be interpreted by the brain as positive incentive salience in some situations, causing events to be 'wanted', but to be perceived as *frighteningly* salient under other conditions, imbuing the attributed stimuli with a menacing motivational/perceptual tone.

What could determine whether motivational salience creates a positive incentive or an aversive fear? One way this might be achieved would be for each type of salience to be mediated by different dopamine neurons. In other words, dopaminergic labeled lines for positive vs. negative motivational salience. Separate dopamine/accumbens/amygdala subsystems could conceivably mediate 'wanting' and 'fear' as distinct processes: 'incentive salience'

vs. 'aversive salience'. Consistent with the idea that dopamine systems might be segregated by motivational valence is the report by Mirenowicz and Schultz [301] that ascending dopamine neurons which are activated by a conditioned stimulus for food reward, may *not* be activated by a conditioned stimulus for an aversive air puff. Thus, dopamine neurons may be segregated by motivational valence.

An alternative possibility is that positive and negative psychological functions might be combined together into a single 'generic' motivational salience, mediated by the same dopamine neurons. In that case, the positive 'wanting' vs. negative 'frightening' valence caused by their activation would need to be gated by other mechanisms. One option is that the direction of valence could arise from the *pattern or intensity* of activation *within* the dopamine system itself. For example, low to moderate levels of activation might cause attraction, but very high levels might become frightening (as in the phenomenon of amphetamine-induced psychosis, in which the reward aspects of the drug are replaced by paranoia or frightening hallucination). A different option would be for the co-activation of non-dopaminergic neural systems to determine whether a positive valence or a negative valence would be imparted to the motivational salience of the stimulus.

The notion that dopamine systems might mediate a shared 'motivational salience' process in fear and in incentive motivation implies that dopamine activation correlates with the 'motivational attention-grabbing' properties of a particular stimulus, combining motivational and perceptual features [34,196,198,366]. That is consistent with a study on conditioned fear and latent inhibition by Young et al. [526]. Latent inhibition refers to the diminished capacity of a conditioned stimulus that is already familiar to support new learning. It is induced by presenting the conditioned stimulus (without the affective unconditioned stimulus) on occasions prior to the conditioning trial. In a microdialysis study Young, Joseph, and Gray found that following establishment of latent inhibition in a fear conditioning paradigm there was a reduction in dopamine overflow in the nucleus accumbens in response to the conditioned stimulus. This makes sense if dopamine release mediates motivational salience—in this case, a frightening motivational salience—and if the motivational salience of the conditioned stimulus was reduced by latent inhibition. That interpretation is bolstered by reports that amphetamine administration at training disrupts latent inhibition [104,197,433], an effect that appears to involve the nucleus accumbens [196]. Amphetamine, in other words, effectively re-instates the ability of the conditioned stimulus to be attributed with fearful motivational salience despite its familiarity.

For positive incentive motivation, amphetamine delivered directly into the nucleus accumbens produces comparable effects, even though the affective valence is opposite: enhancement of the ability of a conditioned stimulus to support motivated behavior. For example, Everitt and Robbins, et al. have shown in several elegant experiments that amphetamine microinjections into the accumbens potentiate the ability of a conditioned reinforcer to support incentive-oriented behavior [67,68,75,76,152–155,349,362,363]. Amphetamine microinjections increase bar pressing for conditioned reinforcers, which have previously been paired with sucrose (for hungry rats) [68,154,349], or with water (for thirsty rats) [75,76], or with a sexually-receptive female (for sexually-experienced male rats) [152,153]. Robbins and Everitt et al. offer compelling demonstrations that amphetamine microinjections even reverse, at least partly, the deficits in conditioned reinforcement that are produced by basolateral amygdala lesions [152–155,362, 363]. Kelley and Delfs further showed that microinjections of amphetamine into the anterior dorsal and ventromedial neostriatum can produce similar effects [254].

It is striking that incentive behavior for *positive* conditioned reinforcers as well as conditioning of *negative* stimuli that evoke fearful responses should be modulated together and in the same way by manipulations of dopamine activity in the accumbens or striatum. This does not negate a role for dopamine in reward. It does highlight the possibility, however, that dopamine's psychological role in reward may have common elements with its role in aversive situations—possibly involving a similar psychological 'core process' as well as a similar neural substrate [35,198,298,366,380].

13.2. Beyond the dopamine synapse

The focus of this paper has been on the motivational role of dopamine projections from the midbrain to targets in the dorsal and ventral striatum. It would be misleading, however, to simply identify incentive salience with the *activation of mesolimbic dopamine neurons, or the release of dopamine in a striatal target*. Even to the extent that dopamine neurons are the critical substrate for incentive salience, it is possible that dopamine projections to different targets mediate the incentive properties of different rewards. For example, whereas projections from the ventral tegmentum to the nucleus accumbens are clearly crucial for amphetamine reward, Gong et al. [190] have recently suggested that dopamine projections to the ventral pallidum are more important for cocaine reward. Following a similar theme, it has been reported that food may activate different neurons in the ventral striatum than cocaine even in the same monkey [55], and that cocaine and heroin may also produce neuronal patterns of activation in the nucleus accumbens that differ from each other [80]. Thus, different rewards may activate different subpopulations of dopamine/accumbens neurons.

To complicate matters more, it has been suggested that a single dopamine neuron may form different types of chemical synapses, with different morphologies, which release different neurotransmitters [453]. For example,

dopamine neurons form both symmetrical synapses that are tyrosine hydroxylase-positive and asymmetrical synapses that release glutamate [221,453]. Thus, dopamine-containing neurons that project to the nucleus accumbens and neostriatum may co-release dopamine and glutamate differently at spatially-distinct sites [453]. And even the question of whether the primary action of dopamine itself is excitatory or inhibitory on post-synaptic neurons remains the subject of controversy [191]. It remains unclear what implication these issues have for the psychological functions of dopamine neurons discussed in this paper, but the interactions will surely be complex.

Further, despite our emphasis on dopamine, we caution that dopamine neurons need not be the *sole substrate* or even *chief substrate* for attributions of incentive salience to neural representations of conditioned stimuli. Other neural systems, both presynaptic and postsynaptic to dopamine neurons, may eventually prove to be even more directly related to the attribution of incentive salience than are dopamine projection systems. For example, Carlezon and Wise have suggested that the critical effect of dopamine in reward is inhibition of medium spiny neurons in the nucleus accumbens, and this may be achieved in ways other than by increasing synaptic dopamine [79]. Kelley et al. [255,256] have suggested the rewarding effects of amphetamine in the nucleus accumbens depend upon NMDA glutamate receptors there. Sarter et al. [387,388] suggest that accumbens dopamine might mediate incentive salience attribution via a GABAergic link to the basal forebrain, by triggering acetylcholine release in the neocortex.

In short, it is too simple to conclude that dopamine neurons themselves mediate incentive salience. More accurately, one can assert that the attribution of incentive salience appears to coincide with the activation of dopamine neurons, and that *incentive salience is the reward component most directly altered by manipulations of dopamine systems* (e.g., by 6-OHDA lesions, dopamine antagonist drugs, lateral hypothalamic stimulation, etc.). These manipulations reveal dissociations between 'wanting' rewards and 'liking' them, but they do not directly reveal the full nature of the psychological process or of its neurobiological substrate.

A final caveat is that it remains possible that dopamine neurons might participate in an *auxiliary* way even in reward functions we've rejected, such as associative learning or even hedonic impact. Our demonstration that dopamine-depleted rats show normal hedonics and reward learning simply means that dopamine projections are not *necessary* for normal mediation of these functions. It does not exclude the possibility that dopamine neurons normally *participate* in the neural processing of those psychological functions, as part of a neurally redundant system (providing feedback, monitoring for conveyance to other systems, etc.). Dopamine systems might participate, but we stress that these psychological functions can continue without them.

14. General conclusion

It is generally accepted that normal motivation and reward require the integrity of mesolimbic/mesostriatal dopamine systems. Some have interpreted the apparent primacy of dopamine systems to mean that these neutrons are a 'common neural currency' for pleasant rewards, mediating the *hedonic impact or pleasure of reinforcers*. Others have instead posited dopamine systems to mediate *reward learning or prediction*. But our results and those reviewed above indicate that dopamine's role in reward is not to mediate hedonic impact, nor to mediate most forms of learning about the predictive relationships between reward-relevant stimuli and their hedonic consequences. Suppression of dopamine function by massive 6-OHDA lesions does not alter the ability of rats to make hedonic evaluations, as reflected in affective taste reactivity patterns, despite obliterating the incentive value of food, water, and other rewards. Nor do 6-OHDA lesions suppress the learning of new hedonic relationships between conditioned and unconditioned stimuli, or the translating of those new reward associations into the generation of appropriate conditioned affective reactions.

We have demonstrated a dissociation between aphagia and other motivational deficits produced by 6-OHDA lesions, on one hand, and the lack of anhedonia or learning deficits on the other. We suggest this may best be explained by the hypothesis that normal reward is a multiplex process, which comprises at least three psychological components: 1) hedonic activation, 2) associative learning of the relationship between neutral events and their hedonic consequences, and 3) subsequent attribution of incentive salience to those events or their representations. Dopamine projections are not needed for either the hedonic or the associative prediction components. Instead we suggest that loss of dopamine from the nucleus accumbens and neostriatum impairs only the final component of reward, namely, the attribution of incentive salience to motivational stimuli and their representations. Lacking incentive salience attribution, dopamine-depleted rats cannot use their hedonic and associative competence to transform the perception or representation of a reward into a target incentive that is attractive and 'wanted'. Dopamine-depleted rats still 'like' rewards, and still know the rewards they 'like'. They simply fail to 'want' rewards they 'like'.

15. Addendum 1: Taste reactivity patterns as a measure of 'liking'

We do not mean to suggest that the subjective experience of pleasure is measured by the taste reactivity test. Instead, it measures a behavioral *affective reaction* [35,109,144,273]. A subjective experience need not even accompany a behavioral affective response (and almost

certainly does not in some cases; for example, in the case of affective reaction patterns emitted by decerebrate animals or anencephalic human infants [211,441]). But *hedonic* and *aversive* patterns of affective reactions may still reflect a brain's underlying core evaluation of 'liking' or 'disliking' for a taste even if an evaluation is not registered by neural mechanisms of conscious awareness (for discussion of relationship between subjective pleasure and affective reactions to taste, see [34,35]).

For present purposes, our concern is whether taste reactivity patterns indeed can be used to measure the affective hedonic impact ('liking') or aversive impact ('disliking') of a stimulus. Evidence for the affective nature of hedonic/aversive taste reactivity patterns comes chiefly from the many correlations that have been found between them and the subjective ratings of taste palatability given by humans to tastes that are liked or disliked [34,206]. Human subjective reports and rat affective reactions reflect similar 'likes' and 'dislikes', and changes in their 'liking' for tastes are caused by the same manipulations.

- The sensory pleasure of sweetness to humans is enhanced by hunger and suppressed by caloric satiety [70,71,270]. Similarly, hedonic reaction patterns of rats to sweet tastes are enhanced by hunger and are suppressed by caloric satiety [33,73,74,212].
- The palatability of salt for humans is selectively enhanced by physiological sodium deficiency (salt appetite) [15,397]. Similarly, hedonic reactions of rats to NaCl are selectively increased, and aversive reactions decreased, by sodium depletion [38,178,213].
- By associative aversion conditioning procedures, taste pleasure for humans can be abolished and replaced with subjective aversion by associative pairing of a palatable food with gastrointestinal illness [377]. Similarly, hedonic reactions of rats to sweetness are abolished and replaced by aversive behavioral reactions by pairings of taste with LiCl or certain other noxious agents [30,64,209,327,329].
- Conversely, associative pairing of a palatable food with a neutral stimulus transfers the food's capacity to elicit hedonic responses to that conditioned stimulus; equivalent transfer of aversion can be obtained by pairing the stimulus with a bitter taste [42,63,113]. Similar conditioned preferences and aversions may occur for humans after associative taste pairings [377].

15.1. Insufficiency of alternative interpretations of affective taste reactivity

A reader may be tempted to reject the claim that affective patterns of taste reactivity reflect hedonic or aversive core evaluations. Instead, one might argue, taste reactivity only measures something simpler, such as a brainstem reflex, a decision whether to ingest, a consummatory phase of a behavior sequence, or a motor concomitant of swallowing or rejection. Each of these conceptual categories does apply to some aspect of reactions elicited by taste stimuli, and taste reactivity measures legitimately have been used to study each [171,205,209,210,249, 251,437]. But measurement of *hedonic vs. aversive patterns* of taste reactivity, as used here, cannot be reduced to any of those simpler categories, either alone or in combination. Since our conclusion about the role of dopamine in reward depends upon this argument regarding taste reactivity, it seems worthwhile to make clear why alternative interpretations of hedonic/aversive taste reactivity patterns are inadequate. The remark of Section 15 reviews the inadequacy of alternative interpretations, and our basis for concluding that this measure does indeed reflect core affective processes of 'liking' and 'disliking'.

15.1.1. Not mere reflex

Does taste reactivity reflect a mere brainstem reflex, or a rigid response to a sensory stimulus? No. Although the basic motor components are generated by the brainstem [211], under ordinary conditions the forebrain controls the affective pattern of response [34,206]. Evidence that the forebrain controls affective reactions comes from demonstrations that neural manipulations restricted to the forebrain produce dramatic changes in affective patterns of taste reactivity. Hedonic reaction patterns are enhanced, for example, by microinjection of an opioid agonist into the forebrain ventricles or nucleus accumbens [336,338]. Conversely, aversive reactions are enhanced by ablation lesions of the ventral pallidum and rostral structures [211], or by electrolytic or excitotoxin lesions limited to the lateral hypothalamic and ventral pallidal areas [36, 106,393,446,455]. The ability of forebrain manipulations to alter hedonic/aversive response patterns shows that forebrain neural systems control the affective pattern of response to a taste. Evidence that affective reaction patterns are not rigid S–R reflexes to a stimulus comes from demonstrations that a particular taste stimulus can elicit *opposite* affective reaction patterns if associative or physiological conditions change. Associatively conditioned aversions switch the response to sweet sucrose from hedonic to aversive [209], and conditioned preferences switch the response to a bitter taste from aversive to hedonic [42,63,530]. Similarly, changes in physiological sodium balance can switch the reaction to concentrated NaCl from aversive to hedonic, and back again with physiological state [38,42,173,178].

An alternative 'sensory reflex' interpretation of taste reactivity, offered by Nader et al. [310], attempts to account for shifts in affective reactions within a fixed (S–R) reflex framework, by positing changes in the stimulus (S). Nader et al. [310] suggest that the ''taste reactivity paradigm is a better measure of the food's subjective sensory, as opposed to hedonic, properties'' (p.100, [310]).

They posit taste reactivity patterns to reflect the 'discriminative properties of stimuli', or 'simply subjective sensory events' (p.101, [310]), rather than hedonic or motivational properties of the stimulus. Additionally, they suggest that conditioned *changes* in taste reactivity, such as aversion learning, are essentially a kind of conditioned *sensory illusion*. For example, an 'aversive' saccharin CS, which has been previously paired with illness, is recognized when ''the first few licks will produce the normal representation of the saccharin taste'' (p. 101, [310]). But its memory ''will elicit conditioned aversive effects that will decrease consumption, as well as other conditioned responses such as the oro-facial behaviors that taste reactivity measures'' (p. 101–102, [310]). In other words, the sweet conditioned stimulus elicits a bitter or otherwise unpleasant sensory illusion. A *conditioned hedonic enhancement* could be explained by this 'sensory reflex' interpretation as a sensory illusion of sweetness, triggered by the conditioned stimulus. Conditioned illusions cannot be invoked to explain *direct changes* in taste reactivity patterns produced either by *physiological state* (e.g., hedonic enhancement by hunger or sodium appetite) or by *pharmacological or neural manipulations* (e.g., hedonic enhancement by intracranial morphine or benzodiazepines). But presumably Nader et al. might argue that these manipulations *directly alter the 'discriminative sensory properties' of a taste*, so that the *sensation of sweetness* is enhanced by hunger, salt appetite, morphine, etc.

There are several implausibilities concerning this 'sensory reflex' interpretation as a sufficient explanation of hedonic and aversive taste reactivity patterns. First, for associative changes in affective reaction patterns, the posited sequence of 'normal representation' followed by a conditioned sensory illusion does not seem to fit the observations. Rats respond *immediately* with conditioned aversive reactions to even an isolated 50 μl squirt of the conditioned taste (about the amount ingested in a single ordinary lick) [30,209] and do not appear to require several 'normal representation' licks to recognize it [217]. More to the point, humans who have developed a conditioned taste aversion for a sweet food or drink do not report that the food subsequently has a bitter taste or otherwise changed *sensation*. Instead, the food tastes as sweet as it did before —but now they perceive it as unpleasant [376,377]. Second, regarding hunger, humans report enhanced hedonic ratings but no increase in sweetness intensity during hunger [71,270]. Unless rats experience a sensory shift during hunger or aversion learning that humans lack, these states seems more likely to alter hedonic, rather than sensory, properties of food perception. By contrast, physiological sodium depletion may indeed alter the sensory intensity coding of salty taste [91,389,418,454]. However, it is difficult for a 'sensory interpretation' to explain the dramatic shift of rats to *high* NaCl concentrations from aversive to hedonic reaction patterns on that basis (humans experience salt as *more* intense during sodium depletion [15], and a similar story is suggested for the rat in sodium depletion states by electrophysiological studies of taste sensory intensity coding in the gustatory nucleus of the solitary tract [454]), and even more difficult to explain on a 'sensory discriminative' basis why sodium deficiency also enhances hedonic reactions to a *sour or bitter taste that has been associatively paired* with salt [42]. Third, morphine and other pharmacological enhancement of hedonic taste reactivity patterns appears to similarly reflect a specific 'liking' change, since evidence indicates that opioid manipulations do *not* change the sensory discriminative properties of taste. For example, naloxone does not alter human subjective ratings of sensory sweetness intensity or of other sensory qualities of food [132], nor does it alter the ability of rats to perform a sensory discrimination task that requires them to recognize the taste of sucrose [319]. Yet opioid agonists and antagonists do alter hedonic subjective ratings in humans [132,133,520,521], and they alter hedonic/aversive taste reactivity patterns and other measures of palatability in rats [86,87,131,332,336,360]. In conclusion, evidence fails to indicate that massive shifts in taste sensory discriminative properties are caused by appetite states or conditioned food preferences/aversions, of the type sufficient to explain changes in taste reactivity patterns. It seems reasonable to conclude that taste reactivity patterns therefore do *not* reflect the *sensory discriminative* properties of a taste stimulus. Instead, hedonic and aversive reaction patterns reflect the *affective* properties of that stimulus.

15.1.2. Not mere intake

Wise has suggested that ''the taste reactivity paradigm simply measures the consummatory responses of ingestion or rejection and adds little to what we can infer from other consummatory measures as to the hedonic impact of rewarding stimuli'' (p. 252, [504]). Hedonic reaction patterns have often been considered as 'ingestive' [171, 205,207,209,249,406]. But on closer scrutiny, to equate taste reactivity patterns with ingestion will not stand. Although intake measures and taste reactivity patterns often change together, they can be pulled completely apart from each other and therefore must measure different processes [40]. For example, Galaverna et al. [178,412] found that the increased consumption of salt produced by physiological sodium depletion was abolished by lesions of the central nucleus of the amygdala, but this lesion had no effect on affective taste reactivity shifts. Rats failed to drink salt voluntarily from a spout after the lesion, even though they had been hormonally depleted of sodium [178]. Similarly, the rats failed to increase even their passive intake of salt solution when it was infused into their mouths [412]. Yet the same rats showed a normal increase in hedonic taste reactivity patterns to salt infusions, and reduced their aversive taste reactivity patterns [178]. In other words, after a central amygdala lesion, the

rats still 'like' salt when sodium deprived, but do not seem to 'want' it. [17]

The dissociation by Galaverna et al. shows that taste reactivity patterns are separable from measures of ingestion or intake. A similar dissociation between intake and affective reaction patterns occurs naturally (even without brain damage) in the case of natural satiation at the end of a meal. After eating a certain amount, a rat refuses to ingest any more food. Its refusal is reflected both in voluntary intake tests and in passive swallowing intra-oral intake tests. However, the rejection of food caused by caloric satiation, although accompanied by reduced hedonic reactions, is *not accompanied by increased aversive reaction patterns*, even after 'super-satiation' (after the rat swallows up to 10% of its body-weight of a palatable and calorie-rich solution) [33]. Finally, in the present study, a further dissociation between affective taste reactivity patterns and intake was found: dopamine depletion reduces voluntary intake of all food and water to zero. But taste reactivity patterns remain positive to sweet tastes, negative to bitter tastes, and can be further modulated in a normal fashion by aversion learning or benzodiazepine administration. This dissociation between voluntary intake measures and taste reactivity is generally true for all neural manipulations that produce aphagia without producing aversive taste reactivity patterns [211,393].

15.1.3. Not mere consummatory behavior

Concepts of ingestion (consumption) and consummatory behavior (applied to feeding) are often combined, as in the quote from Wise above. Conceptually, however, they are not necessarily identical. 'Consummatory behavior' originally was a term introduced by the early ethologist, Craig [102], to describe the terminal phase of motivated behavior, and distinguish it from preceding phases. Is 'consummatory behavior' an adequate label to apply to taste reactivity patterns—even if consumption is not? Dopamine suppression has been suggested to disrupt appetitive but not consummatory behavior by a number of investigators [50,51,108,152,157,205,239,325,343–345]. Taste reactivity patterns have been called 'consummatory' by a number of authors (including one of us) [30,205,412]. However, there are serious difficulties with the notion that 'taste reactivity is just consummatory behavior'.

In Craig's original sense, the terms 'appetitive' and 'consummatory' refer to *temporal* phases of motivated behavior: *appetitive* behavior occurs *prior* to capture of the goal object, whereas *consummatory* behavior occurs *after* it [102]. Taken merely as a temporal label, consummatory can be applied legitimately to taste reactivity patterns, since the reactions occur after food is obtained. But as an explanatory category of brain-behavior relations (in the sense that 'consummatory behavior is mediated by neural system X'), 'consummatory' is woefully inadequate. 'Consummatory behavior' as a category includes too many different types of behavior to be changed coherently by a single brain manipulation.

Regarding eating, there are at least three types of consummatory behavior. First, consummatory ingestive behavior in Craig's original sense included the actual *licks and bites of voluntary eating* [102]. Second, the *hedonic / aversive taste reactivity patterns* studied here occur during the consummatory phase [30,205–207,210,248, 249,251,353]. Third, the act of swallowing a substance, as opposed to spitting or spilling it out of the mouth, is a form of consummatory behavior. In that sense, the consummatory label has often been used to refer to *intraoral intake*, that is, the amount passively swallowed of a solution infused into a rat's mouth via cannula by the experimenter [171,205,207,208,213,406,413]. In many cases, these various senses of 'consummatory' have been taken by their authors explicitly or implicitly to be interchangeable [30,204–207,214,249,251,406]. But it is now clear that these various types of 'consummatory behavior' are not interchangeable. They often dissociate in different directions and therefore cannot possibly be measures of the same underlying process. A few examples will suffice.

- The case of amygdala lesion-induced impairment of salt appetite discussed above provides one example of a dissociation among different 'consummatory' behaviors. Amygdala lesions disrupted the first and third senses of 'consummatory (voluntary licking of salt and intra-oral intake) but not the second sense (affective taste reactivity)' [178,412]. In the same way, caloric satiety produces rejection of food in the first sense (voluntary intake) and third sense (passive intra-oral intake) of consummatory behavior, as described above, but not in the second sense of aversive affective reaction patterns.
- Administration of bombesin and gastrin-releasing-peptide, two putative satiety peptides, has been found by Flynn and Robillard [165–170,172] to produce a similar dissociation among types of consummatory behavior. Bombesin microinjections into the 4th ventricle suppress the first sense of consummatory behavior (voluntary licking for sucrose or salt solutions) and also suppress the third sense (passive intra-oral intake [even in decerebrate rats]). However, bombesin fails to shift the second sense of consummatory behavior (hedonic or aversive taste reactivity patterns) [167,169]. Flynn concludes that these satiety peptides ''inhibit intake without affecting the gustatory

[17] Electrolytic lesions of the central amygdala were used by Galaverna et al. [178,412], which destroyed both amygdala neurons and fibers of passage. Dunn and Everitt [137] have shown that taste aversion learning deficits after electrolytic amygdala lesions, once ascribed to amygdala loss, are actually due to loss of cortical fibers of passage (because they are not caused by excitotoxin amygdala lesions). It is presently unclear whether cortex or amygdala damage causes the salt appetite deficit reported by Galaverna et al. But the point remains valid that this deficit illustrates the independence of taste reactivity patterns from measures of intake or consumption, regardless of whether the dissociation is caused by destruction of amygdala neurons or of cortical fibers.

reinforcing properties of the food'' (p. 113, [169]), an interpretation similar to the 'liking' vs. 'wanting' framework we have presented.

• Even intra-oral intake (the third sense of consummatory behavior) can be detached from voluntary intake (the first sense) and from affective taste reactivity (the second sense). The intraventricular administration of neuropeptide Y is known to promote voluntary food intake, but it does not enhance the amount of a nutritive solution that rats swallow when they are fed directly by intra-oral infusion [414]. Neuropeptide Y also fails to produce strong shifts in hedonic/aversive patterns of taste reactivity to caloric solutions (R.J. Seeley, personal communication; Peciña and Berridge, personal observations).

• Disruption of dopamine neurotransmission can also dissociate the different types of consummatory behavior. After extensive 6-OHDA lesions rats fail to initiate voluntary licking or chewing even if food is placed immediately before them (loss of first sense of consummatory behavior) [471]. Dopamine antagonists can slow the rate and amount of voluntary eating for rats given food pellets [512] and suppress the duration and microstructure of bouts of voluntary licking for rats given sucrose solution [395,396,429] (effects that stand in contrast to the view that dopamine is important to appetitive but not consummatory behavior). All of these effects apply only to the voluntary chewing/licking sense of consummatory behavior (first sense), and not to the other two senses of affective reactions or passive swallowing. Dopamine antagonists do not shift consummatory behavior in the sense of hedonic/aversive patterns of taste reactivity [339,465] (although they do suppress the capacity to sustain a vigorous bout of consummatory behavior even in this sense if the eliciting stimulus is prolonged over several minutes) [339]. And consummatory behavior in the sense of intra-oral intake, or passive swallowing of an infused solution, is similarly resistant to dopamine antagonists. Tyrka and Smith [469] found that raclopride and SCH 23990, preferential D2 receptor antagonists, had no effect on the intra-oral sucrose intake of rat pups who had the solution infused directly into their mouths via an implanted cannulae. However, dopamine antagonists suppressed the free intake of sucrose if the rat pups were laid in the sucrose solution, and needed to lower their head and lap in order to ingest [468,469]. What was the difference between these two forms of consummatory behavior? Smith notes that in the free-intake test, ''pups do not make continuous contact'' with sucrose but instead ''must repeatedly initiate contact'' in order to ingest (p. 119, [429]). The need to actively re-engage an external source of sucrose, rather than respond passively to what is delivered to the mouth appears to make a crucial difference. In our view, active re-engagement with the external food requires the attribution of incentive salience to that food. The recurrence of 'wanting' is required to initiate each successive bout or lick, and is dopamine-dependent. In order to claim that consummatory behavior is not dopamine-dependent, one would have to posit that the individual fluctuates rapidly during a meal back and forth between appetitive and consummatory phases, as many times as there are bites in a meal. Although that revision is arguable, it destroys Wallace Craig's original concept of a linear progression from an appetitive to a consummatory phase of motivated behavior.

• Even the effect of dopamine manipulations on a single sense of consummatory behavior may vary, depending how it is measured. For example, Qian et al. [353] have found that the third sense of consummatory behavior (intra-oral intake) is unimpaired by 6-OHDA lesions, at least by one criterion. The aphagic rats still swallowed enough of thrice-daily infusions sufficient to maintain their body weight. However, by other criteria, the rats had a consummatory deficit even for this type of consummatory behavior. They failed to increase passive intake after food deprivation, and they generally failed to swallow as much as normal rats [353]. Such variable effects mean that it cannot be conclusively stated whether 6-OHDA rats have a consummatory behavior deficit, even in this single sense of the term. Further distinctions would need to be made in order to arrive at an answer. Clearly, consummatory behavior is not a sufficient explanatory category either to place taste reactivity in or to explain the effects of dopamine lesions. [18]

In summary, the term 'consummatory behavior' actually refers to a number of different types of behavior that follow contact with a goal. It is not a coherent single category in which to classify a response. The term can no longer be used, therefore, as an *explanation* or even as a sufficient *description* for the effects of any brain manipulation.

15.2. Conclusion: Affective reaction patterns reflect hedonic impact of 'liked' stimulus

We therefore conclude that taste reactivity patterns cannot be dismissed as an *intake* or *ingestion* measure, or as a *brainstem sensorimotor reflex*, or as a piece of homogeneous *consummatory behavior*. Although taste elicited responses partake of each of these categories, they are not reducible to any one, nor to any combination of them. These considerations can be coupled to the close relationship, summarized earlier, that rat taste reactivity patterns show to human measures of taste pleasantness or

[18] Further evidence for a role of dopamine systems in the intra-oral intake type of consummatory behavior comes from Kaplan and Södersten's [250] finding that the dopamine agonist apomorphine suppresses the consummatory intra-oral intake of an orally-infused sucrose solution by decerebrate rats. In that case, the relevant dopamine neurons must be intrinsic to the brainstem, since decerebration would eliminate the role of ascending projections to accumbens or neostriatum.

unpleasantness after many psychological and physiological manipulations. In conclusion, this compels the verdict that taste *reactivity patterns must be regarded as true affective reactions*, which connote core processes of *affective 'liking'* vs. 'disliking'.

16. Addendum 2: Measuring cognitive expectations of reward in animals (studies of incentive learning by Dickinson and Balleine)

A cognitive expectation of reward is not merely elicitation of an affective or motivational response by a conditioned stimulus. It must also, Dickinson et al. [125–127] suggest, be accompanied by the recognition by the animal that the to-be-obtained reward is *obtained by its own action*, and a *representation of the to-be-obtained reward* must be accessed to guide behavior to the goal. In other words, for an animal to have a cognitive expectation of a reward, it must *know what reward it is working for* (i.e., that it will gain a particular reward), and *understand that it is working for it* (i.e., that the reward will be the final outcome of its actions). A cognitive expectation of reward, according to Dickinson and Balleine [128] is what gives the representation of a stimulus *incentive value*. The representation of a stimulus has these properties if ''instrumental behavior is mediated not only by a representation of the action-outcome relation, but also by a representation of the incentive value of the outcome, or what in common parlance would be referred to as the desire for the outcome'' (p. 163, Dickinson and Balleine [128]). If dopamine systems mediated 'incentive value' in the sense of Dickinson and Balleine then dopamine must mediate learning the explicit relation between actions and specific outcomes.

It is important to stress that 'incentive learning' in Dickinson's sense implies much more than is meant by the other senses of 'expectation of reward'. It is more than a procedural associative representation of the correlation between two events. It is more than hedonic re-valuation of a conditioned stimulus based on its association with an unconditioned stimulus. It is more than the attribution of incentive salience to a stimulus that makes it motivationally attractive, or able to elicit approach. It differs from these in that it requires the expectation to be explicitly represented in a way that gives the animal prior access to features of the future reward and to the causal relations among events that predict the reward. Dickinson's use of the phrase 'incentive learning' is different from the way the term is used by other motivational theorists such as Bindra [48,49] or Toates [460–463], and is different from our use [34,366]. For Bindra or Toates, and for us, 'incentive learning' can be a simpler construct, referring merely to the process by which a Pavlovian conditioned stimulus acquires new hedonic or motivational value (i.e., it can be procedural rather than declarative, implicit rather than explicit).

In a typical experiment, Dickinson and Balleine and colleagues have assessed whether an animal has a cognitive representation of a reward by asking whether it can act appropriately when it is suddenly placed in a new motivational state. For example, if a rat had learned while hungry to perform two instrumental responses, one for sucrose solution and another for food pellets, it might be tested in a state of thirst or in a state of caloric satiety, or after one food had been associatively paired (in a different setting) with LiCl illness to induce a taste aversion. Two features of the 'new state' test are particularly important to the experiments of Dickinson and Balleine. First, the rat is tested in extinction, so that operant responses no longer earn the actual food rewards. The rat must therefore choose to work based solely on its *representation* of the rewards, since the foods themselves are not present. Second, Dickinson and Balleine take pains to arrange the experimental situation so that potential Pavlovian conditioned stimuli predict both foods equally well. This obviates control of behavior by Pavlovian-related motivational processes, which otherwise could guide behavior to one goal or the other (and which would be more related to *our* sense of incentive salience and to the Bindra/Toates sense of incentive learning).

Under these conditions, Dickinson and Balleine have shown that rats quite often fail to appropriately modify their instrumental behavior for the revalued food. If a rat had worked vigorously for a food when it was trained, it often continues to work hard in the test—even if the food would now have reduced hedonic value (e.g., because now the food would evoke a conditioned aversion). If a rat had not worked vigorously before, because the food did not have great value during training, it still does not work harder during the test, even though the food would now have enhanced hedonic value (e.g., because now the rat is hungrier). If the two foods now have different values, rats often seem not to recognize that difference, and work similarly for both (although see Rescorla [357] for instances in which the specific inference transfers successfully to behavior; these, however, may be at least partly accounted for by noncognitive factors [12,127]). In such cases, Dickinson's and Balleine's rats, at any rate, appear to behave based on the 'predicted reward value' of the food. That is, the rats behave as if the food's value is *equivalent to the value it last had when it was previously experienced*. The rat's 'expectation of reward' apparently is that the reward will be the same as before—even though it won't. In these situations a rat can be said to have a 'cognitive expectation of reward' in one sense, but it is an incorrect one. The rat has not yet fully learned about the new value of the food (its cognitive representation is not updated), and its behavior is not guided by an accurate representation of the food at that moment. In the strict Dickinsonian sense, therefore, its behavior does not reflect the incentive value of the reward: it lacks incentive learning.

There are two ways Dickinson et al. have found in which a rat can be provided with information sufficient to correct its mistake, allowing it to change its instrumental behavior appropriate to the new incentive value of the food or water.

The primary way is to let a rat experience the changed hedonic value of the reward while it is in the changed state. [19] This would ordinarily happen naturally if the test were not conducted under extinction conditions. If it was not tested in extinction the rat would simply sample both rewards, and quickly experience which was better in the new state, and modify its behavior accordingly. But the same outcome is obtained, Dickinson and Balleine show, by simply allowing a rat to taste the revalued reward elsewhere (while the rat is in the state to be tested later), and thus to experience its new hedonic value prior to the instrumental extinction test. Armed with that information, a rat will later employ the now-known value of the food in the cognitive representation it has of the food's value, and of the food's causal relationship to the two different actions. It then modifies its instrumental response in the extinction test appropriate to the re-valued food. Other instrumental responses, used to obtain another reward that was not re-valued, are not altered. For Dickinson, Balleine and colleagues this selective and intelligent change in behavior demonstrates true 'incentive learning'. It demonstrates that a rat knows what it is working for, and how to get it. Anything else falls short. Future studies of dopamine systems regarding the learning and prediction of reward stimuli will need to incorporate this distinction in order to parse among the multiple possible meanings of 'reward learning'.

[19] The second way is to provide during extinction testing a simple *Pavlovian conditioned stimulus* that had previously been paired with the re-valued food specifically. For example, Dickinson and Dawson [130] presented a conditioned stimulus for a sucrose solution to thirsty rats while they performed two responses in extinction. The two responses had previously delivered sucrose solution or food pellets when they had been hungry. Presentation of the conditioned stimulus for sucrose solution caused the rats to work harder on both responses: it energized their motivation. A conditioned stimulus for dry food pellets, by contrast, did not energize performance. This is especially relevant to the Bindra/Toates account of incentive motivation theory, by which the sucrose conditioned stimulus evoked the same hedonic and incentive processes that the watery sucrose solution would have evoked if it had been present. In a sense, it called to mind the properties of sucrose solution more vividly, and the rats responded to the conditioned stimulus as they would have to the sucrose itself. This kind of effect is both *associative* in a Pavlovian sense and *motivational*, in the sense that the stimulus has hedonic and incentive impact. It is essentially what is meant by 'incentive learning' in theories of motivation such as Bindra's [47–49] and Toates' [460,463]. It is also what we have meant by 'learned incentive salience' [44,45,366]. But the classically-conditioned motivational process is not *cognitive*, and Dickinson and Dawson [130] conclude that it does not convey information about the *differential relation between sucrose solution and the two responses*. For this reason, the energized rats could—in a sense—be said not to know what they were working for.

17. Note added in proof

An important review was published after this article went to press: W. Schultz, Predictive reward signals of dopamine neurons. J. Neurophysiol. 80 (1998) 1–27. In it, Schultz provides an excellent overview and adds substantial detail to the 'reward learning' hypothesis of dopamine function. However, the theory remains similar in its essential points to that outlined in earlier reviews by Schultz and colleagues, and so we stand by our comments regarding the 'dopamine reward learning' hypothesis.

Acknowledgements

Without implying acquiescence to the ideas presented here, we thank Drs. J. Wayne Aldridge, Steven Cooper, Howard (Casey) Cromwell, Anthony Dickinson, Susana Peciña, Per Södersten, Roland Suri, and Frederick Toates for helpful comments on earlier versions of this manuscript. We also thank Drs. Antoine Bechara, Karim Nader, and Derek van der Kooy for stimulating discussion of their reward hypothesis, and Gaetano Di Chiara for supplying an advance copy of a manuscript. Finally, we thank Dr. Diane Camp for assistance with the dopamine assay, and Darlene Tansil for assistance with the taste reactivity experiments.

References

[1] E. Acquas, E. Carboni, P. Leone, G. Dichiara, SCH 23390 blocks drug-conditioned place-preference and place- aversion—anhedonia (lack of reward) or apathy (lack of motivation) after dopamine-receptor blockade, Psychopharmacology 99 (1989) 151–155.

[2] A. Agmo, A. Galvan, B. Talamantes, Reward and reinforcement produced by drinking sucrose: two processes that may depend on different neurotransmitters, Pharmacol. Biochem. Behav. 52 (1995) 403–414.

[3] T. Aosaki, A.M. Graybiel, M. Kimura, Effect of the nigrostriatal dopamine system on acquired neural responses in the striatum of behaving monkeys, Science 265 (1994) 412–415.

[4] T. Aosaki, M. Kimura, A.M. Graybiel, Temporal and spatial characteristics of tonically active neurons of the primate's striatum, J. Neurophysiol. 73 (1995) 1234–1252.

[5] P. Apicella, T. Ljungberg, E. Scarnati, W. Schultz, Responses to reward in monkey dorsal and ventral striatum, Exp. Brain Res. 85 (1991) 491–500.

[6] J.M. Arnold, D.C. Roberts, A critique of fixed and progressive ratio schedules used to examine the neural substrates of drug reinforcement, Pharmacol. Biochem. Behav. 57 (1997) 441–447.

[7] C.S. Bailey, S. Hsiao, J.E. King, Hedonic reactivity to sucrose in rats: modification by pimozide, Physiol. Behav. 38 (1986) 447–452.

[8] B. Balleine, J. Ball, A. Dickinson, Benzodiazepine-induced outcome revaluation and the motivational control of instrumental action in rats, Behav. Neurosci. 108 (1994) 573–589.

[9] B. Balleine, A. Dickinson, Instrumental performance following reinforcer devaluation depends upon incentive learning, Q. J. Exp. Psychol. [B] 45B (1991) 285–301.

[10] B. Balleine, S. Killcross, Effects of ibotenic acid lesions of the nucleus accumbens on instrumental action, Behav. Brain Res. 65 (1994) 181–193.
[11] B.W. Balleine, A. Dickinson, The role of incentive learning in instrumental outcome revaluation by sensory-specific satiety, Anim. Learn and Behav. 26 (1998) 46–59.
[12] B.W. Balleine, A. Dickinson, Goal-directed instrumental action: contingency and incentive learning and their cortical substrates, Neuropharmacol. (in press).
[13] M.T. Bardo, Neuropharmacological mechanisms of drug reward: Beyond dopamine in the nucleus accumbens, Crit. Rev. Neurobiol. 12 (1998) 37–67.
[14] V. Bassareo, G. Di Chiara, Differential influence of associative and nonassociative learning mechanisms on the responsiveness of prefrontal and accumbal dopamine transmission to food stimuli in rats fed ad libitum, J. Neurosci. 17 (1997) 851–861.
[15] G.K. Beauchamp, M. Bertino, D. Burke, K. Engelman, Experimental sodium depletion and salt taste in normal human volunteers, Am. J. of Clinical Nutrition 51 (1990) 881–889.
[16] A. Bechara, H. Damasio, D. Tranel, A.R. Damasio, Deciding advantageously before knowing the advantageous strategy, Science 275 (1997) 1293–1295.
[17] A. Bechara, F. Harrington, K. Nader, D. van der Kooy, Neurobiology of motivation: double dissociation of two motivational mechanisms mediating opiate reward in drug-naive versus drug-dependent animals, Behav. Neurosci. 106 (1992) 798–807.
[18] A. Bechara, K. Nader, D. van der Kooy, Neurobiology of withdrawal motivation: evidence for two separate aversive effects produced in morphine-naive versus morphine-dependent rats by both naloxone and spontaneous withdrawal, Behav. Neurosci. 109 (1995) 91–105.
[19] A. Bechara, K. Nader, D. Van der Kooy, A two-separate-motivational-systems hypothesis of opioid addiction, Pharmacol. Biochem. Behav. 59 (1998) 1–17.
[20] A. Bechara, D. Tranel, H. Damasio, R. Adolphs, C. Rockland, A.R. Damasio, Double dissociation of conditioning and declarative knowledge relative to the amygdala and hippocampus in humans, Science 269 (1995) 1115–1118.
[21] A. Bechara, D. van der Kooy, The tegmental pedunculopontine nucleus: a brain-stem output of the limbic system critical for the conditioned place preferences produced by morphine and amphetamine, J. Neurosci. 9 (1989) 3400–3409.
[22] A. Bechara, D. van der Kooy, A single brain stem substrate mediates the motivational effects of both opiates and food in nondeprived rats but not in deprived rats, Behav. Neurosci. 106 (1992) 351–363.
[23] R.J. Beninger, The role of dopamine in locomotor activity and learning, Brain Res. 287 (1983) 173–196.
[24] R.J. Beninger, C.M. D'Amico, R. Ranaldi, Microinjections of flupenthixol into the caudate putamen of rats produce intrasession declines in food-rewarded operant responding, Pharmacol. Biochem. Behav. 45 (1993) 343–350.
[25] R.J. Beninger, S.T. Mason, A.G. Phillips, H.C. Fibiger, The use of conditioned suppression to evaluate the nature of neuroleptic-induced avoidance deficits, J. Pharmacol. Exp. Ther. 213 (1980) 623–627.
[26] R.J. Beninger, R. Miller, Dopamine D-1 like receptors and reward-related incentive learning, Neurosci. and Biobehav. Rev. 22 (1998) 335–345.
[27] J. Benjamin, L. Li, C. Patterson, B.D. Greenberg, D.L. Murphy, D.H. Hamer, Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking, Nature Genet. 12 (1996) 81–84.
[28] S.P. Berger, S. Hall, J.D. Mickalian, M.S. Reid, C.A. Crawford, K. Delucchi, K. Carr, S. Hall, Haloperidol antagonism of cue-elicited cocaine craving, Lancet 347 (1996) 504–508.
[29] C.W. Berridge, T.L. Stratford, S.L. Foote, A.E. Kelley, Distribution of dopamine beta-hydroxylase-like immunoreactive fibers within the shell subregion of the nucleus accumbens, Synapse 27 (1997) 230–241.
[30] K. Berridge, H.J. Grill, R. Norgren, Relation of consummatory responses and preabsorptive insulin release to palatability and learned taste aversions, J. Comp. Physiol. Psychol. 95 (1981) 363–382.
[31] K.C. Berridge, Brainstem systems mediate the enhancement of palatability by chlordiazepoxide, Brain Res. 447 (1988) 262–268.
[32] K.C. Berridge, Substantia nigra 6-OHDA lesions mimic striatopallidal disruption of syntactic grooming chains: a neural systems analysis of sequence control, Psychobiology 17 (1989) 377–385.
[33] K.C. Berridge, Modulation of taste affect by hunger, caloric satiety, and sensory-specific satiety in the rat, Appetite 16 (1991) 103–120.
[34] K.C. Berridge, Food reward: brain substrates of wanting and liking, Neurosci. Biobehav. Rev. 20 (1996) 1–25.
[35] K.C. Berridge, Pleasure, pain, desire, and dread: Hidden core processes of emotion, in: D. Kahneman, E. Diener, N. Schwarz, (Eds.), Foundations of Hedonic Psychology: Scientific Understanding of Enjoyment and Suffering, Russell Sage Foundation, New York, in press.
[36] K.C. Berridge, H.C. Cromwell, Motivational-sensorimotor interaction controls aphagia and exaggerated treading after striatopallidal lesions, Behav. Neurosci. 104 (1990) 778–795.
[37] K.C. Berridge, J.C. Fentress, Trigeminal-taste interaction in palatability processing, Science 228 (1985) 747–750.
[38] K.C. Berridge, F.W. Flynn, J. Schulkin, H.J. Grill, Sodium depletion enhances salt palatability in rats, Behav. Neurosci. 98 (1984) 652–660.
[39] K.C. Berridge, H.J. Grill, Isohedonic tastes support a two-dimensional hypothesis of palatability, Appetite 5 (1984) 221–231.
[40] K.C. Berridge, S. Peciña, Benzodiazepines, appetite, and taste palatability, Neurosci. Biobehav. Rev. 19 (1995) 121–131.
[41] K.C. Berridge, T.E. Robinson, The mind of an addicted brain: sensitization of wanting versus liking, Cur. Dir. Psychol. Sci. 4 (1995) 71–76.
[42] K.C. Berridge, J. Schulkin, Palatability shift of a salt-associated incentive during sodium depletion, Q. J. Exp. Psychol. [B] 41 (1989) 121–138.
[43] K.C. Berridge, D. Treit, Chlordiazepoxide directly enhances positive ingestive reactions in rats, Pharmacol. Biochem. Behav. 24 (1986) 217–221.
[44] K.C. Berridge, E.S. Valenstein, What psychological process mediates feeding evoked by electrical stimulation of the lateral hypothalamus?, Behav. Neurosci. 105 (1991) 3–14.
[45] K.C. Berridge, I.L. Venier, T.E. Robinson, Taste reactivity analysis of 6-hydroxydopamine-induced aphagia: implications for arousal and anhedonia hypotheses of dopamine function, Behav. Neurosci. 103 (1989) 36–45.
[46] K.P. Bhatia, C.D. Marsden, The behavioural and motor consequences of focal lesions of the basal ganglia in man, Brain 117 (1994) 859–876.
[47] D. Bindra, A unified interpretation of emotion and motivation, Ann New York Acad. Sci. 159 (1969) 1071–1083.
[48] D. Bindra, A motivational view of learning, performance, and behavior modification, Psychol. Rev. 81 (1974) 199–213.
[49] D. Bindra, How adaptive behavior is produced: a perceptual-motivation alternative to response reinforcement, Behav. Brain Sci. 1 (1978) 41–91.
[50] J.R. Blackburn, J.G. Pfaus, A.G. Phillips, Dopamine functions in appetitive and defensive behaviours, Prog. Neurobiol. 39 (1992) 247–279.
[51] J.R. Blackburn, A.G. Phillips, H.C. Fibiger, Dopamine and preparatory behavior: I Effects of pimozide, Behav. Neurosci. 101 (1987) 352–360.

[52] J.R. Blackburn, A.G. Phillips, A. Jakubovic, H.C. Fibiger, Dopamine and preparatory behavior: II A neurochemical analysis, Behav. Neurosci. 103 (1989) 15–23.
[53] R.C. Bolles, Reinforcement, expectancy, and learning, Psychol. Rev. 79 (1972) 394–409.
[54] T.B. Borowski, L. Kokkinidis, Contribution of ventral tegmental area dopamine neurons to expression of conditional fear: effects of electrical stimulation, excitotoxin lesions, and quinpirole infusion on potentiated startle in rats, Behav. Neurosci. 110 (1996) 1349–1364.
[55] E.M. Bowman, T.G. Aigner, B.J. Richmond, Neural signals in the monkey ventral striatum related to motivation for juice and cocaine rewards, J. Neurophysiol. 75 (1996) 1061–1073.
[56] M.A. Bozarth, R.A. Wise, Heroin reward is dependent on a dopaminergic substrate, Life Sci. 29 (1981) 1881–1886.
[57] M.A. Bozarth, R.A. Wise, Anatomically distinct opiate receptor fields mediate reward and physical dependence, Science 224 (1984) 516–517.
[58] L.H. Brauer, H. de Wit, Subjective responses to D-amphetamine alone and after pimozide pretreatment in normal, healthy volunteers, Biol. Psychiatry 39 (1996) 26–32.
[59] L.H. Brauer, H. De Wit, High dose pimozide does not block amphetamine-induced euphoria in normal volunteers, Pharmacol. Biochem. Behav. 56 (1997) 265–272.
[60] L.H. Brauer, A.J. Goudie, H. de Wit, Dopamine ligands and the stimulus effects of amphetamine: animal models versus human laboratory data, Psychopharmacology 130 (1997) 2–13.
[61] T.S. Braver, J.D. Cohen, An integrated computational model of dopamine function in reinforcement learning and working memory, Journal of Cognitive Neuroscience (1998) 82-82.
[62] H.C. Breiter, R.L. Gollub, R.M. Weisskoff, D.N. Kennedy, N. Makris, J.D. Berke, J.M. Goodman, H.L. Kantor, D.R. Gastfriend, J.P. Riorden, R.T. Mathew, B.R. Rosen, S.E. Hyman, Acute effects of cocaine on human brain activity and emotion, Neuron 19 (1997) 591–611.
[63] P.A. Breslin, T.L. Davidson, H.J. Grill, Conditioned reversal of reactions to normally avoided tastes, Physiol. Behav. 47 (1990) 535–538.
[64] P.A. Breslin, A.C. Spector, H.J. Grill, A quantitative comparison of taste reactivity behaviors to sucrose before and after lithium chloride pairings: a unidimensional account of palatability, Behav. Neurosci. 106 (1992) 820–836.
[65] L. Brown, The New Shorter Oxford English Dictionary on Historical Principles, Clarendon Press: Oxford Univ. Press, Oxford and New York, 1993.
[66] V.J. Brown, P.J. Brasted, E.M. Bowman, The effect of systemic D-amphetamine on motor versus motivational processes in the rat, Psychopharmacology 128 (1996) 171–180.
[67] L.H. Burns, B.J. Everitt, A.E. Kelley, T.W. Robbins, Glutamate-dopamine interactions in the ventral striatum: role in locomotor activity and responding with conditioned reinforcement, Psychopharmacology 115 (1994) 516–528.
[68] L.H. Burns, T.W. Robbins, B.J. Everitt, Differential effects of excitotoxic lesions of the basolateral amygdala, ventral subiculum and medial prefrontal cortex on responding with conditioned reinforcement and locomotor activity potentiated by intra-accumbens infusions of D-amphetamine, Behav. Brain Res. 55 (1993) 167–183.
[69] M.J. Burton, S.J. Cooper, A. Posadas-Andrews, Interactions between chlordiazepoxide and food deprivation determining choice in food-preference test [proceedings], Br. J. Pharmacol. 68 (1980) 157P–158P.
[70] M. Cabanac, Physiological role of pleasure, Science 173 (1971) 1103–1107.
[71] M. Cabanac, Sensory pleasure, Q. Rev. Biol. 54 (1979) 1–29.
[72] M. Cabanac, On the origin of consciousness, a postulate and its corollary, Neurosci. and Biobehav. Rev. 20 (1996) 33–40.
[73] M. Cabanac, L. Lafrance, Postingestive alliesthesia: the rat tells the same story, Physiol. Behav. 47 (1990) 539–543.
[74] M. Cabanac, L. Lafrance, Facial consummatory responses in rats support the ponderostat hypothesis, Physiol. Behav. 50 (1991) 179–183.
[75] M. Cador, T.W. Robbins, B.J. Everitt, Involvement of the amygdala in stimulus-reward associations: interaction with the ventral striatum, Neuroscience 30 (1989) 77–86.
[76] M. Cador, T.W. Robbins, B.J. Everitt, H. Simon, M. Le Moal, L. Stinus, Limbic-striatal interactions in reward-related processes: Modulation by the dopaminergic system, in: P. Willner, J. Scheel-Kruger (Eds.), The Mesolimbic Dopamine System: From Motivation to Action, Wiley, New York, 1991, pp. 225–250.
[77] S.B. Caine, G.F. Koob, L.H. Parsons, B.J. Everitt, J.C. Schwartz, P. Sokoloff, D3 receptor test in vitro predicts decreased cocaine self-administration in rats, Neuroreport 8 (1997) 2373–2377.
[78] D.J. Calcagnetti, M.D. Schechter, Conditioned place aversion following the central administration of a novel dopamine release inhibitor CGS 10746B, Pharmacol. Biochem. Behav. 40 (1991) 255–259.
[79] W.A. Carlezon Jr., R.A. Wise, Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex, J. Neurosci. 16 (1996) 3112–3122.
[80] J.Y. Chang, P.H. Janak, D.J. Woodward, Comparison of mesocorticolimbic neuronal responses during cocaine and heroin self-administration in freely moving rats, J. Neurosci. 18 (1998) 3098–3115.
[81] J.Y. Chang, S.F. Sawyer, R.S. Lee, D.J. Woodward, Electrophysiological and pharmacological evidence for the role of the nucleus accumbens in cocaine self-administration in freely moving rats, J. Neurosci. 14 (1994) 1224–1244.
[82] A.L. Chausmer, A. Ettenberg, A role for D2, but not D1, dopamine receptors in the response-reinstating effects of food reinforcement, Pharmacol. Biochem. Behav. 57 (1997) 681–685.
[83] A.L. Chausmer, C.M. Reals, A. Ettenberg, Comparison of the effects of D1 and D2 dopamine receptor antagonist on the response-reinstating properties of food reinforcement, Soc. Neurosci. 21 (1995) 1674, Abstract.
[84] D. Clark, L.A. Chiodo, Electrophysiological and pharmacological characterization of identified nigrostriatal and mesoaccumbens dopamine neurons in the rat, Synapse 2 (1988) 474–485.
[85] R.E. Clark, L.R. Squire, Classical conditioning and brain systems: The role of awareness, Science 280 (1998) 77–81.
[86] S.N. Clarke, L.A. Parker, Morphine-induced modification of quinine palatability: effects of multiple morphine-quinine trials, Pharmacol. Biochem. Behav. 51 (1995) 505–508.
[87] J. Cleary, D.T. Weldon, E. Hare, C. Billington, A.S. Levine, Naloxone effects on sucrose-motivated behavior, Psychopharmacology 126 (1996) 110–114.
[88] P.G. Clifton, I.N. Rusk, S.J. Cooper, Effects of dopamine D1 and dopamine D2 antagonists on the free feeding and drinking patterns of rats, Behav. Neurosci. 105 (1995) 272–281.
[89] J.D. Cohen, D. Servan-Schreiber, A theory of dopamine function and its role in cognitive deficits in schizophrenia, Schizophrenia Bulletin 19 (1993) 85–104.
[90] K.L. Conover, P. Shizgal, Competition and summation between rewarding effects of sucrose and lateral hypothalamic stimulation in the rat, Behav. Neurosci. 108 (1994) 537–548.
[91] R.J. Contreras, M. Frank, Sodium deprivation alters neural responses to gustatory stimuli, J. General Physiology 73 (1979) 569–594.
[92] S.J. Cooper, Benzodiazepines as appetite-enhancing compounds, Appetite 1 (1980) 7–19.
[93] S.J. Cooper, L.B. Estall, Behavioural pharmacology of food, water and salt intake in relation to drug actions at benzodiazepine receptors, Neurosci. Biobehav. Rev. 9 (1985) 5–19.
[94] S.J. Cooper, J. Francis, D.J. Barber, Selective dopamine D-1

receptor agonists, SK and F 38393 and CY 208-243 reduce sucrose sham-feeding in the rat, Neuropharmacology 32 (1993) 101–102.
[95] S.J. Cooper, S. Higgs, The benzodiazepine agonist midazolam microinjected into the rat parabrachial nucleus produces hyperphagia, Soc. Neurosci. Abst. 20 (1994) 1285.
[96] S.J. Cooper, S. Higgs, Neuropharmacology of appetite and taste preferences, in: C.R. Legg, D.A. Booth, (Eds.), Appetite: Neural and Behavioural Bases, Oxford Univ. Press, New York, 1994, pp. 212–242.
[97] S.J. Cooper, S. Higgs, P.G. Clifton, Behavioral and neural mechanisms for benzodiazepine-induced hyperphagia, Appetite 24 (1995) 78–79.
[98] S.J. Cooper, A. Jackson, R. Morgan, R. Carter, Evidence for opiate receptor involvement in the consumption of a high palatability diet in nondeprived rats, Neuropeptides 5 (1985) 345–348.
[99] M.S. Cousins, A. Atherton, L. Turner, J.D. Salamone, Nucleus accumbens dopamine depletions alter relative response allocation in a T-maze cost/benefit task, Behav. Brain Res. 74 (1996) 189–197.
[100] M.S. Cousins, J.D. Salamone, Nucleus accumbens dopamine depletions in rats affect relative response allocation in a novel cost/benefit procedure, Pharmacol. Biochem. Behav. 49 (1994) 85–91.
[101] M.S. Cousins, W. Wei, J.D. Salamone, Pharmacological characterization of performance on a concurrent lever pressing/feeding choice procedure: effects of dopamine antagonist, cholinomimetic, sedative and stimulant drugs, Psychopharmacology 116 (1994) 529–537.
[102] W. Craig, Appetites and aversions as constituents of instincts, Biological Bulletin of Woods Hole 34 (1918) 91–107.
[103] L.P. Crespi, Quantitative variation of incentive and performance in the white rat, Am. J. Psychol. 55 (1942) 467–517.
[104] A. Crider, P.R. Solomon, M.A. McMahon, Disruption of selective attention in the rat following chronic D-amphetamine administration: relationship to schizophrenic attention disorder, Biol. Psychiatry. 17 (1982) 351–361.
[105] D. Crippens, T.E. Robinson, Withdrawal from morphine or amphetamine: Different effects on dopamine in the ventral–medial striatum studied with microdialysis, Brain Res. 650 (1994) 56–62.
[106] H.C. Cromwell, K.C. Berridge, Where does damage lead to enhanced food aversion: the ventral pallidum/substantia innominata or lateral hypothalamus?, Brain Res. 624 (1993) 1–10, [published erratum appears in Brain Res 1994 Apr 11;642(1–2):355].
[107] C.A. Dackis, M.S. Gold, New concepts in cocaine addiction: the dopamine depletion hypothesis, Neurosci. Biobehav. Rev. 9 (1985) 469–477.
[108] G. Damsma, J.G. Pfaus, D. Wenkstern, A.G. Phillips, H.C. Fibiger, Sexual behavior increases dopamine transmission in the nucleus accumbens and striatum of male rats: comparison with novelty and locomotion, Behav. Neurosci. 106 (1992) 181–191.
[109] C. Darwin, P. Ekman, The Expression of the Emotions in Man and Animals, Harper Collins—Oxford Univ. Press, Oxford, 1998 (originally published 1872).
[110] M. Davis, J.M. Hitchcock, M.B. Bowers, C.W. Berridge, K.R. Melia, R.H. Roth, Stress-induced activation of prefrontal cortex dopamine turnover: blockade by lesions of the amygdala, Brain Res. 664 (1994) 207–210.
[111] M. de Ryck, P. Teitelbaum, The postures of catecholamine-depletion catalepsy: their possible adaptive value in thermoregulation, Physiol. Behav. 21 (1978) 817–820.
[112] H. De Wit, R.A. Wise, Blockade of cocaine reinforcement in rats with the dopamine receptor blocker pimozide, but not with the noradrenergic blockers phentolamine or phenoxybenzamine, Can. J. Psychol. 31 (1977) 195–203.
[113] A.R. Delamater, V.M. LoLordo, K.C. Berridge, Control of fluid palatability by exteroceptive Pavlovian signals, J. Exp. Psychol. [Anim. Behav.] 12 (1986) 143–152.
[114] R.Y. Depoortere, D.H. Li, J.D. Lane, M.W. Emmett-Oglesby, Parameters of self-administration of cocaine in rats under a progressive-ratio schedule, Pharmacol. Biochem. Behav. 45 (1993) 539–548.
[115] R.A. Depue, Collins P.F., Neurobiology of the structure of personality: dopamine, facilitation, and extraversion, Behav. Brain Sci. (in press).
[116] G. Di Chiara, The role of dopamine in drug abuse viewed from the perspective of its role in motivation, Drug Alcohol Depend. 38 (1995) 95–137.
[117] G. Di Chiara, A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use, J. Psychopharmacol. 12 (1998) 54–67.
[118] G. Di Chiara, A. Imperato, Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats, Proc. Natl. Acad. Sci. U.S.A. 85 (1988) 5274–5278.
[119] G. Di Chiara, G. Tanda, Blunting of reactivity of dopamine transmission to palatable food: a biochemical marker of anhedonia in the CMS model?, Psychopharmacology 134 (1997) 351–353, discussion 371-377.
[120] P. Di Ciano, C.D. Blaha, A.G. Phillips, Conditioned changes in dopamine oxidation currents in the nucleus accumbens of rats by stimuli paired with self-administration or yoked-administration of d-amphetamine, Euro. J. Neurosci. 10 (1998) 1121–1127.
[121] P.M. Di Lorenzo, S. Monroe, Corticofugal input to taste-responsive units in the parabrachial pons, Brain Res. Bull. 29 (1992) 925–930.
[122] P.M. Di Lorenzo, S. Monroe, Corticofugal influence on taste responses in the nucleus of the solitary tract in the rat, J. Neurophysiol. 74 (1995) 258–272.
[123] A. Dickinson, Intentionality in animal conditioning, in: L. Weiskrantz (Ed.), Thought Without Language: A Fyssen Foundation Symposium., Clarendon Press/Oxford Univ. Press, Oxford, England, 1988, pp. 305–325.
[124] A. Dickinson, Expectancy theory in animal conditioning, in: R.R.M. Stephen, B. Klein (Eds.), Contemporary Learning Theories: Pavlovian Conditioning and the Status of Traditional Learning Theory., Lawrence Erlbaum Associates, Hillsdale, NJ, USA, 1989, pp. 279–308.
[125] A. Dickinson, Instrumental conditioning, in: N.J. Mackintosh (Ed.), Animal Learning and Cognition, Academic Press, New York, 1994, pp. 45–79.
[126] A. Dickinson, B. Balleine, Motivational control of instrumental performance following a shift from thirst to hunger, Q. J. Exp. Psychol. [B] 42 (1990) 413–431.
[127] A. Dickinson, B. Balleine, Motivational control of goal-directed action, Anim. Learn. and Behav. 22 (1994) 1–18.
[128] A. Dickinson, B. Balleine, Motivational control of instrumental action, Cur. Dir. Psychol. Sci. 4 (1995) 162–167.
[129] A. Dickinson, J. Campos, Z.I. Varga, B. Balleine, Bidirectional instrumental conditioning, Q. J. Exp. Psychol. [B] 49 (1996) 289–306.
[130] A. Dickinson, G.R. Dawson, Pavlovian processes in the motivational control of instrumental performance, Q. J. Exp. Psychol. [B] B (1987) 201–213.
[131] T.G. Doyle, K.C. Berridge, B.A. Gosnell, Morphine enhances hedonic taste palatability in rats, Pharmacol. Biochem. Behav. 46 (1993) 745–749.
[132] A. Drewnowski, D.D. Krahn, M.A. Demitrack, K. Nairn, B.A. Gosnell, Taste responses and preferences for sweet high-fat foods: evidence for opioid involvement, Physiol. Behav. 51 (1992) 371–379.
[133] A. Drewnowski, D.D. Krahn, M.A. Demitrack, K. Nairn, B.A. Gosnell, Naloxone, an opiate blocker, reduces the consumption of sweet high-fat foods in obese and lean female binge eaters, Am. J. Clin. Nutr. 61 (1995) 1206–1212.
[134] A.J. Dunn, Stress-related activation of cerebral dopaminergic systems, Ann. New York Acad. Sci. 537 (1988) 188–205.

[135] A.J. Dunn, J.E. Alpert, S.D. Iversen, Dopamine denervation of frontal cortex or nucleus accumbens does not affect ACTH-induced grooming behaviour, Behav. Brain Res. 12 (1984) 307–315.
[136] A.J. Dunn, C.W. Berridge, Physiological and behavioral-responses to corticotropin-releasing factor administration—Is CRF a mediator of anxiety or stress responses, Brain Res. Rev. 15 (1990) 71–100.
[137] L.T. Dunn, B.J. Everitt, Double dissociations of the effects of amygdala and insular cortex lesions on conditioned taste aversion, passive avoidance, and neophobia in the rat using the excitotoxin ibotenic acid, Behav. Neurosci. 102 (1988) 3–23.
[138] S.B. Dunnett, I.Q. Whishaw, G.H. Jones, S.T. Bunch, Behavioural, biochemical and histochemical effects of different neurotoxic amino acids injected into nucleus basalis magnocellularis of rats, Neuroscience 20 (1987) 653–669.
[139] C.L. Duvauchelle, M. Levitin, L.A. MacConell, L.K. Lee, A. Ettenberg, Opposite effects of prefrontal cortex and nucleus accumbens infusions of flupenthixol on stimulant-induced locomotion and brain stimulation reward, Brain Res. 576 (1992) 104–110.
[140] P. Ekman, An argument for basic emotions, Cognition and Emotion 6 (1992) 169–200.
[141] P.C. Ellsworth, Levels of thought and levels of emotion, in: P. Ekman, R.J. Davidson (Eds.), The Nature of Emotion: Fundamental Questions, Oxford Univ. Press, New York, 1994, pp. 192–196.
[142] Epictetus, E. Carter, All the works of Epictetus, which are now extant; consisting of his Discourses, preserved by Arrian, in four books, the Enchiridion, and fragments, J. and F. Rivington, London, 1768.
[143] Epictetus, T.W. Higginson, The works of Epictetus. Consisting of his Discourses, in four books, the Enchiridion, and Fragments, Little Brown, Boston, 1897.
[144] A.N. Epstein, Instinct and motivation as explanations for complex behavior, in: D.W. Pfaff (Ed.), The Physiology of Motivation, Springer-Verlag, New York, 1982, pp. 25–58.
[145] A. Ettenberg, Dopamine, neuroleptics and reinforced behavior, Neurosci. and Biobehav. Rev. 13 (1989) 105–111.
[146] A. Ettenberg, C.H. Camp, Haloperidol induces a partial reinforcement extinction effect in rats: implications for a dopamine involvement in food reward, Pharmacol. Biochem. Behav. 15 (1986) 813–821.
[147] A. Ettenberg, G.F. Koob, F.E. Bloom, Response artifact in the measurement of neuroleptic-induced anhedonia, Science 213 (1981) 357–359.
[148] A. Ettenberg, L.A. MacConell, T.D. Geist, Effects of haloperidol in a response-reinstatement model of heroin relapse, Psychopharmacology 124 (1996) 205–210.
[149] A. Ettenberg, H.O. Pettit, F.E. Bloom, G.F. Koob, Heroin and cocaine intravenous self-administration in rats: mediation by separate neural systems, Psychopharmacology 78 (1982) 204–209.
[150] K.R. Evans, F.J. Vaccarino, Intra-nucleus accumbens amphetamine: dose-dependent effects on food intake, Pharmacol. Biochem. Behav. 25 (1986) 1149–1151.
[151] K.R. Evans, F.J. Vaccarino, Amphetamine- and morphine-induced feeding: evidence for involvement of reward mechanisms, Neurosci. Biobehav. Rev. 14 (1990) 9–22.
[152] B.J. Everitt, Sexual motivation: a neural and behavioural analysis of the mechanisms underlying appetitive and copulatory responses of male rats, Neurosci. Biobehav. Rev. 14 (1990) 217–232.
[153] B.J. Everitt, M. Cador, T.W. Robbins, Interactions between the amygdala and ventral striatum in stimulus-reward associations: studies using a second-order schedule of sexual reinforcement, Neuroscience 30 (1989) 63–75.
[154] B.J. Everitt, K.A. Morris, O.B. A, T.W. Robbins, The basolateral amygdala-ventral striatal system and conditioned place preference: further evidence of limbic-striatal interactions underlying reward-related processes, Neuroscience 42 (1991) 1–18.
[155] B.J. Everitt, T.W. Robbins, Amygdala-ventral striatal interactions and reward-related processes, in: J.P. Aggleton (Ed.), The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction, Wiley, New York, 1992, pp. 401–429.
[156] M.B. Feigin, A. Sclafani, S.R. Sunday, Species differences in polysaccharide and sugar taste preferences, Neurosci. Biobehav. Rev. 11 (1987) 231–240.
[157] H.C. Fibiger, A.G. Phillips, Reward, motivation, cognition: Psychobiology of mesotelencephalic systems, Handbook of Physiology —The Nervous System, 4 (1986) 647–675.
[158] H.C. Fibiger, A.G. Phillips, E.E. Brown, The neurobiology of cocaine-induced reinforcement, Ciba Found. Symp. 166 (1992) 96–111, discussion 111-24.
[159] D.F. Fiorino, A. Coury, A.G. Phillips, Dynamic changes in nucleus accumbens dopamine efflux during the Coolidge effect in male rats, J. Neurosci. 17 (1997) 4849–4855.
[160] L.L. Firestone, F. Gyulai, M. Mintun, L.J. Adler, K. Urso, P.M. Winter, Human brain activity response to fentanyl imaged by positron emission tomography, Anesth. Analg. 82 (1996) 1247–1251.
[161] M.W. Fischman, Relationship between self-reported drug effects and their reinforcing effects: studies with stimulant drugs, NIDA Res. Monogr. 92 (1989) 211–230.
[162] C.F. Flaherty, Incentive Relativity, Cambridge Univ. Press, New York, 1996.
[163] P.J. Fletcher, Dopamine receptor blockade in nucleus accumbens or caudate nucleus differentially affects feeding induced by 8-OH-DPAT injected into dorsal or median raphe, Brain Res. 552 (1991) 181–189.
[164] S.J. Fluharty, H.J. Grill, Taste reactivity of lateral hypothalamic lesioned rats: effects of deprivation and tube feeding, Neurosci. Abstr. 7 (1981) 29.
[165] F.W. Flynn, Fourth ventricle bombesin injection suppresses ingestive behaviors in rats, Am. J. Physiol. 256 (1989) R590–R596.
[166] F.W. Flynn, Effects of fourth ventricle bombesin injection on meal-related parameters and grooming behavior, Peptides 12 (1991) 761–765.
[167] F.W. Flynn, Caudal brain stem systems mediate effects of bombesin-like peptides on intake in rats, Am. J. Physiol. 262 (1992) R37–R44.
[168] F.W. Flynn, Fourth ventricular injection of selective bombesin receptor antagonists facilitates feeding in rats, Am. J. Physiol. 264 (1993) R218–R221.
[169] F.W. Flynn, Applications of taste reactivity to the study of the neural-hormonal controls of ingestive behavior, Neurosci. Biobehav. Rev. 19 (1995) 109–120.
[170] F.W. Flynn, Mammalian bombesin-like peptides suppress sham drinking of salt by sodium-deficient rats, Peptides 17 (1996) 951–956.
[171] F.W. Flynn, H.J. Grill, Intraoral intake and taste reactivity responses elicited by sucrose and sodium chloride in chronic decerebrate rats, Behav. Neurosci. 102 (1988) 934–941.
[172] F.W. Flynn, L. Robillard, Inhibition of ingestive behavior following fourth ventricle bombesin injection in chronic decerebrate rats, Behav. Neurosci. 106 (1992) 1011–1014.
[173] F.W. Flynn, J. Schulkin, M. Havens, Sex differences in salt preference and taste reactivity in rats, Brain Res. Bull. 32 (1993) 91–95.
[174] G. Fouriezos, P. Hansson, R.A. Wise, Neuroleptic-induced attenuation of brain stimulation reward in rats, J. Comp. Physiol. Psychol. 92 (1978) 661–671.
[175] G. Fouriezos, R.A. Wise, Pimozide-induced extinction of intracranial self-stimulation: response patterns rule out motor or performance deficits, Brain Res. 103 (1976) 377–380.
[176] K.B.J. Franklin, S.N. McCoy, Pimozide-induced extinction in rats: stimulus control of responding rules out motor deficits, Pharmacol. Biochem. Behav. 11 (1979) 71–75.
[177] N.H. Frijda, A. Tcherkassof, Facial expressions as modes of action readiness, in: J.A. Russell, J.M. Fernández-Dols (Eds.), The Psy-

chology of Facial Expression, Cambridge Univ. Press, Cambridge, 1997, pp. 78–102.
[178] O.G. Galaverna, R.J. Seeley, K.C. Berridge, H.J. Grill, A.N. Epstein, J. Schulkin, Lesions of the central nucleus of the amygdala. I: Effects on taste reactivity, taste aversion learning and sodium appetite, Behav. Brain Res. 59 (1993) 11–17.
[179] C.R. Gallistel, M. Boytim, Y. Gomita, L. Klebanoff, Does pimozide block the reinforcing effect of brain stimulation?, Pharmacol. Biochem. Behav. 17 (1982) 769–781.
[180] E.L. Gardner, Brain reward mechanisms, in: J.H. Lowinson, P. Ruiz, R.B. Millman, J.G. Langrod (Eds.), Substance Abuse: A Comprehensive Textbook, Williams and Wilkin, Baltimore, 1997, pp. 51–85.
[181] E.L. Gardner, J.H. Lowinson, Drug craving and positive–negative hedonic brain substrates activated by addicting drugs, Sem. Neurosci. 5 (1993) 359–368.
[182] N. Geary, G.P. Smith, Pimozide decreases the positive reinforcing effect of sham fed sucrose in the rat, Pharmacol. Biochem. Behav. 22 (1985) 787–790.
[183] T.D. Geist, A. Ettenberg, Concurrent positive and negative goalbox events produce runway behaviors comparable to those of cocaine-reinforced rats, Pharmacol. Biochem. Behav. 57 (1997) 145–150.
[184] A.N. Gilbert, A.J. Fridlund, J. Sabini, Hedonic and social determinants of facial displays to odors., Chem. Senses 12 (1987) 355–363.
[185] D.B. Gilbert, S.J. Cooper, 7-OH-DPAT injected into the accumbens reduces locomotion and sucrose ingestion: D3 autoreceptor-mediated effects?, Pharmacol. Biochem. Behav. 52 (1995) 275–280.
[186] S.Q. Giraudo, M.K. Grace, C.C. Welch, C.J. Billington, A.S. Levine, Naloxone's anorectic effect is dependent upon the relative palatability of food, Pharmacol. Biochem. Behav. 46 (1993) 917–921.
[187] B.K. Giza, T.R. Scott, A. Sclafani, R.F. Antonucci, Polysaccharides as taste stimuli: their effect in the nucleus tractus solitarius of the rat, Brain Res. 555 (1991) 1–9.
[188] S.E. Glickman, B.B. Schiff, A biological theory of reinforcement, Psychol. Rev. 74 (1967) 81–109.
[189] W. Gong, D. Neill, J.B. Justice Jr., Conditioned place preference and locomotor activation produced by injection of psychostimulants into ventral pallidum, Brain Res. 707 (1996) 64–74.
[190] W. Gong, D. Neill, J.B. Justice Jr., 6-Hydroxydopamine lesion of ventral pallidum blocks acquisition of place preference conditioning to cocaine, Brain Res. 754 (1997) 103–112.
[191] F. Gonon, Prolonged and extrasynaptic excitatory action of dopamine mediated by D1 receptors in the rat striatum in vivo, J. Neurosci. 17 (1997) 5972–5978.
[192] A.A. Grace, Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia, Neuroscience 41 (1991) 1–24.
[193] A.A. Grace, B.S. Bunney, The control of firing pattern in nigral dopamine neurons: burst firing, J. Neurosci. 4 (1984) .
[194] A. Gratton, R.A. Wise, Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous cocaine self-administration in rats, J. Neurosci. 14 (1994) 4130–4146.
[195] J.A. Gray, Elements of a Two-Process Theory of Learning, Academic Press, New York, 1975.
[196] J.A. Gray, Dopamine release in the nucleus accumbens: the perspective from aberrations of consciousness in schizophrenia, Neuropsychologia 33 (1995) 1143–1153.
[197] J.A. Gray, P.M. Moran, G. Grigoryan, S.L. Peters, A.M. Young, M.H. Joseph, Latent inhibition: the nucleus accumbens connection revisited, Behav. Brain Res. 88 (1997) 27–34.
[198] J.A. Gray, A.M. Young, M.H. Joseph, Dopamine's role [letter], Science 278 (1997) 1548–1549.
[199] R.W. Gray, S.J. Cooper, Benzodiazepines and palatability: taste reactivity in normal ingestion, Physiol. Behav. 58 (1995) 853–859.
[200] A.M. Graybiel, Building action repertoires: memory and learning functions of the basal ganglia, Cur. Opin. Neurobiol. 5 (1995) 733–741.
[201] A.M. Graybiel, T. Aosaki, A.W. Flaherty, M. Kimura, The basal ganglia and adaptive motor control, Science 265 (1994) 1826–1831.
[202] A.M. Graybiel, E.C. Hirsch, Y. Agid, The nigrostriatal system in Parkinson's disease, Adv. Neurol. 53 (1990) 17–29.
[203] A.M. Graybiel, M. Kimura, Adaptive neural networks in the basal ganglia, in: J.C. Houk, J.L. Davis, D.G. Beiser (Eds.), Models of Information Processing in the Basal Ganglia, MIT, Cambridge, 1995, pp. 103–116.
[204] P.S. Grigson, J.M. Kaplan, M.F. Roitman, R. Norgren, H.J. Grill, Reward comparison in chronic decerebrate rats, Am. J. Physiol. 273 (1997) R479–R486.
[205] H.J. Grill, Production and regulation of ingestive consummatory behavior in the chronic decerebrate rat, Brain Res. Bull. 5 (1980) 79–87.
[206] H.J. Grill, K.C. Berridge, Taste reactivity as a measure of the neural control of palatability, in: J.M. Sprague, A.N. Epstein (Eds.), Progress in Psychobiology and Physiological Psychology, Vol. 11, Academic Press, Orlando, 1985, pp. 1–61.
[207] H.J. Grill, J.M. Kaplan, Caudal brainstem participates in the distributed neural control of feeding, in: E.M. Stricker (Ed.), Neurobiology of Food and Fluid Intake, Vol. 10, Plenum, New York, 1990, pp. 125–149.
[208] H.J. Grill, R.R. Miselis, Lack of ingestive compensation to osmotic stimuli in chronic decerebrate rats, Am. J. Physiol. 240 (1981) R81–R86.
[209] H.J. Grill, R. Norgren, Chronically decerebrate rats demonstrate satiation but not bait shyness, Science 201 (1978) 267–269.
[210] H.J. Grill, R. Norgren, The taste reactivity test: I. Mimetic responses to gustatory stimuli in neurologically normal rats, Brain Res. 143 (1978) 263–279.
[211] H.J. Grill, R. Norgren, The taste reactivity test: II. Mimetic responses to gustatory stimuli in chronic thalamic and chronic decerebrate rats, Brain Res. 143 (1978) 281–297.
[212] H.J. Grill, M.F. Roitman, J.M. Kaplan, A new taste reactivity analysis of the integration of taste and physiological state information, Am. J. Physiol. 271 (1996) R677–R687.
[213] H.J. Grill, J. Schulkin, F.W. Flynn, Sodium homeostasis in chronic decerebrate rats, Behav. Neurosci. 100 (1986) 536–543.
[214] H.J. Grill, A.C. Spector, G.J. Schwartz, J.M. Kaplan, F.W. Flynn, Evaluating taste effects on ingestive behavior, in: F.M. Toates, N.R. Rowland (Eds.), Feeding and Drinking, Vol. 1, Elsevier, Amsterdam, 1987, pp. 151–188.
[215] A. Hajnal, G.P. Mark, P.V. Rada, L. Lenard, B.G. Hoebel, Norepinephrine microinjections in the hypothalamic paraventricular nucleus increase extracellular dopamine and decrease acetylcholine in the nucleus accumbens: Relevance to feeding reinforcement, J. Neurochem. 68 (1997) 667–674.
[216] S. Hall, T. Schallert, Striatal dopamine and the interface between orienting and ingestive functions, Physiol. Behav. 44 (1988) 469–471.
[217] B.P. Halpern, D.N. Tapper, Taste stimuli: quality coding time, Science 171 (1971) 1256–1258.
[218] S.B. Hamann, L. Cahill, L.R. Squire, Emotional perception and memory in amnesia, Neuropsychology 11 (1997) 104–113.
[219] M. Haney, R.W. Foltin, M.W. Fischman, Effects of pergolide on intravenous cocaine self-administration in men and women, Psychopharmacology 137 (1998) 15–24.
[220] S. Hansen, A.H. Bergvall, S. Nyiredi, Interaction with pups enhances dopamine release in the ventral striatum of maternal rats—a microdialysis study, Pharmacol. Biochem. Behav. 45 (1993) 673–676.
[221] T. Hattori, Conceptual history of the nigrostriatal dopamine system, Neurosci. Res. 16 (1993) 239–262.
[222] T.G. Heffner, J.A. Hartman, L.S. Seider, A rapid method for the

regional dissection of the rat brain, Pharmacol. Biochem. Behav. 13 (1980) 453–456.
[223] L. Heimer, D.S. Zahm, L. Churchill, P.W. Kalivas, C. Wohltmann, Specificity in the projection patterns of accumbal core and shell in the rat, Neuroscience 41 (1991) 89–125.
[224] S.E. Hemby, C. Co, T.R. Koves, J.E. Smith, S.I. Dworkin, Differences in extracellular dopamine concentrations in the nucleus accumbens during response-dependent and response-independent cocaine administration in the rat, Psychopharmacology 133 (1997) 7–16.
[225] L. Hernandez, B.G. Hoebel, Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis, Life Sci. 42 (1988) 1705–1712.
[226] S. Higgs, S.J. Cooper, Midazolam-induced rapid changes in licking behaviour: evidence for involvement of endogenous opioid peptides, Psychopharmacology 131 (1997) 278–286.
[227] K.G. Hill, S.W. Kiefer, Naltrexone treatment increases the aversiveness of alcohol for outbred rats, Alcohol Clin. Exp. Res. 21 (1997) 637–641.
[228] P.K. Hitchcott, C.M. Bonardi, G.D. Phillips, Enhanced stimulus-reward learning by intra-amygdala administration of a D3 dopamine receptor agonist, Psychopharmacology 133 (1997) 240–248.
[229] W. Hodos, Progressive ratio as a measure of reward strength, Science 134 (1961) 943–944.
[230] W.H. Hodos, E.S. Valenstein, An evaluation of response rate as a measure of rewarding intracranial stimulation, J. Comp. Physiol. Psychol. 55 (1962) 80–84.
[231] B.G. Hoebel, Brain-stimulation reward in relation to behavior, in: A. Waquier, E.T. Rolls (Eds.), Brain-Stimulation Reward, Elsevier, New York, 1976, pp. 335–372.
[232] B.G. Hoebel, Neuroscience and motivation: pathways and peptides that define motivational systems, in: R.C. Atkinson, R.J. Herrnstein, G. Lindzey, R.D. Luce (Ed.), Stevens' Handbook of Experimental Psychology, Vol. 1, Wiley, New York, 1988, pp. 547–626.
[233] B.G. Hoebel, G.P. Mark, H.L. West, Conditioned release of neurotransmitters as measured by microdialysis, Clin. Neuropharmacol. 15 (Suppl 1) (1992) 704A–705A, Pt A.
[234] J.C. Horvitz, A. Ettenberg, Haloperidol blocks the response-reinstating effects of food reward: a methodology for separating neuroleptic effects on reinforcement and motor processes, Pharmacol. Biochem. Behav. 31 (1988) .
[235] J.C. Horvitz, A. Ettenberg, Conditioned incentive properties of a food-paired conditioned stimulus remain intact during dopamine receptor blockade, Behav. Neurosci. 105 (1991) 536–541.
[236] S. Hsiao, G.P. Smith, Raclopride reduces sucrose preference in rats, Pharmacol. Biochem. Behav. 50 (1995) 121–125.
[237] C.L. Hull, Essentials of Behavior, Yale Univ. Press, New Haven, 1951.
[238] C.L. Hull, A. Amsel, M.E. Rashotte, Mechanisms of Adaptive Behavior: Clark L. Hull's Theoretical Papers, with Commentary, Columbia Univ. Press, New York, 1984.
[239] S. Ikemoto, J. Panksepp, Dissociations between appetitive and consummatory responses by pharmacological manipulations of reward-relevant brain regions, Behav. Neurosci. 110 (1996) 331–345.
[240] M.F. Jacquin, H.P. Zeigler, Trigeminal orosensation and ingestive behavior in the rat, Behav. Neurosci. 97 (1983) 62–97.
[241] W. James, What is an emotion, Mind 9 (1884) 188–205.
[242] S.A. Josselyn, R.J. Beninger, Neuropeptide Y: intraaccumbens injections produce a place preference that is blocked by *cis*-flupenthixol, Pharmacol. Biochem. Behav. 46 (1993) 543–552.
[243] D. Kahneman, Assessments of individual well-being: a bottom-up approach, in: D. Kahneman, E. Diener, N. Schwartz (Eds.), Foundations of Hedonic Psychology: Scientific Perspectives on Enjoyment and Suffering, Russel Sage Foundation, New York, in press.
[244] D. Kahneman, B.L. Fredrickson, C.A. Schreiber, D.A. Redelmeier, When more pain is preferred to less: adding a better end, Psychological Science 4 (1993) 401–405.
[245] D. Kahneman, P.P. Wakker, R. Sarin, Back to Bentham? Explorations of experienced utility, Q. J. Econ. 112 (1997) 375–405.
[246] P.W. Kalivas, Interactions between dopamine and excitatory amino acids in behavioral sensitization to psychostimulants, Drug and Alcohol Dependence 37 (1995) 95–100.
[247] P.W. Kalivas, P. Duffy, Selective activation of dopamine transmission in the shell of the nucleus accumbens by stress, Brain Res. 675 (1995) 325–328.
[248] J.M. Kaplan, I. Bednar, P. Södersten, Simultaneous display of sexual and ingestive behaviour by rats, J. Neuroendocrin. 4 (1993) 381–392.
[249] J.M. Kaplan, M.F. Roitman, H.J. Grill, Ingestive taste reactivity as licking behavior, Neurosci. Biobehav. Rev. 19 (1995) 89–98.
[250] J.M. Kaplan, P. Södersten, Apomorphine suppresses ingestive behaviour in chronic decerebrate rats, Neuroreport 5 (1994) 1839–1840.
[251] J.M. Kaplan, A.C. Spector, H.J. Grill, Ingestion rate as an independent variable in the behavioral analysis of satiation, Am. J. Physiol. 258 (1990) R662–R671.
[252] A. Katoh, T. Nabeshima, A. Kuno, M. Wada, R. Ukai, T. Kameyama, Changes in striatal dopamine release in stress-induced conditioned suppression of motility in rats, Behav. Brain Res. 77 (1996) 219–221.
[253] A.E. Kelley, E.P. Bless, C.J. Swanson, Investigation of the effects of opiate antagonists infused into the nucleus accumbens on feeding and sucrose drinking in rats, J. Pharmacol. Exp. Ther. 278 (1996) 1499–1507.
[254] A.E. Kelley, J.M. Delfs, Dopamine and conditioned reinforcement: I. Differential effects of amphetamine microinjections into striatal subregions, Psychopharmacology 103 (1991) 187–196.
[255] A.E. Kelley, S.L. Smith-Roe, M.R. Holahan, Response-reinforcement learning is dependent on *N*-methyl-D-aspartate receptor activation in the nucleus accumbens core, Proc. Natl. Acad. Sci. U.S.A. 94 (1997) 12174–12179.
[256] A.E. Kelley, L.C. Throne, NMDA receptors mediate the behavioral effects of amphetamine infused into the nucleus accumbens, Brain Res. Bull. 29 (1992) 247–254.
[257] T.H. Kelly, R.W. Foltin, L. King, M.W. Fischman, Behavioral response to diazepam in a residential laboratory, Biol. Psychiatry 31 (1992) 808–822.
[258] S.W. Kiefer, M.R. Orr, Taste avoidance, but not aversion, learning in rats lacking gustatory cortex, Behav. Neurosci. 106 (1992) 140–146.
[259] E.A. Kiyatkin, Functional significance of mesolimbic dopamine, Neurosci. Biobehav. Rev. 19 (1995) 573–598.
[260] E.A. Kiyatkin, A. Gratton, Electrochemical monitoring of extracellular dopamine in nucleus accumbens of rats lever-pressing for food, Brain Res. 652 (1994) 225–234.
[261] E.A. Kiyatkin, G.V. Rebec, Activity of presumed dopamine neurons in the ventral tegmental area during heroin self-administration, Neuroreport 8 (1997) 2581–2585.
[262] E.A. Kiyatkin, E.A. Stein, Conditioned changes in nucleus accumbens dopamine signal established by intravenous cocaine in rats, Neurosci. Lett. 211 (1996) 73–76.
[263] E.A. Kiyatkin, R.A. Wise, A. Gratton, Drug- and behavior-associated changes in dopamine-related electrochemical signals during intravenous heroin self-administration in rats, Synapse 14 (1993) 60–72.
[264] M.A. Klitenick, A.Y. Deutch, L. Churchill, P.W. Kalivas, Topography and functional role of dopaminergic projections from the ventral mesencephalic tegmentum to the ventral pallidum, Neuroscience 50 (1992) 371–386.
[265] M.J. Koepp, R.N. Gunn, A.D. Lawrence, V.J. Cunningham, A.

Dagher, T. Jones, D.J. Brooks, C.J. Bench, P.M. Grasby, Evidence for striatal dopamine release during a video game, Nature 393 (1998) 266–268.
[266] G.F. Koob, Neural mechanisms of drug reinforcement, Ann. New York Acad. Sci. 654 (1992) 171–191.
[267] G.F. Koob, S.B. Caine, L. Parsons, A. Markou, F. Weiss, Opponent process model and psychostimulant addiction, Pharmacol. Biochem. Behav. 57 (1997) 513–521.
[268] G.F. Koob, M. Le Moal, Drug abuse: hedonic homeostatic dysregulation, Science 278 (1997) 52–58.
[269] A.E. Kosobud, G.C. Harris, J.K. Chapin, Behavioral associations of neuronal activity in the ventral tegmental area of the rat, J. Neurosci. 14 (1994) 7117–7129.
[270] B. Laeng, K.C. Berridge, C.M. Butter, Pleasantness of a sweet taste during hunger and satiety: effects of gender and 'sweet tooth', Appetite 21 (1993) 247–254.
[271] R.J. Lamb, K.L. Preston, C.W. Schindler, R.A. Meisch, F. Davis, J.L. Katz, J.E. Henningfield, S.R. Goldberg, The reinforcing and subjective effects of morphine in post-addicts: a dose-response study, J. Pharmacol. Exp. Ther. 259 (1991) 1165–1173.
[272] S. Laviolette, D. van der Kooy, GABA-A receptor signalling in the ventral tegmental area dissociates separate dopamine-dependent and dopamine-independent motivational systems, Neurosci. Abstr, 24 (in press).
[273] J. LeDoux, The Emotional Brain: The Mysterious Underpinnings of Emotional Life, Simon and Schuster, New York, 1996.
[274] K. Leeb, L. Parker, R. Eikelboom, Effects of pimozide on the hedonic properties of sucrose: analysis by the taste reactivity test, Pharmacol. Biochem. Behav. 39 (1991) 895–901.
[275] P. Leone, D. Pocock, R.A. Wise, Morphine–dopamine interaction —ventral tegmental morphine increases nucleus-accumbens dopamine release, Pharmacol. Biochem. Behav. 39 (1991) 469–472.
[276] A.S. Levine, D.T. Weldon, M. Grace, J.P. Cleary, C.J. Billington, Naloxone blocks that portion of feeding driven by sweet taste in food-restricted rats, Am. J. Physiol. 268 (1995) R248–R252.
[277] T. Ljungberg, P. Apicella, W. Schultz, Responses of monkey midbrain dopamine neurons during delayed alternation performance, Brain Res. 567 (1991) 337–341.
[278] T. Ljungberg, P. Apicella, W. Schultz, Responses of monkey dopamine neurons during learning of behavioral reactions, J. Neurophysiol. 67 (1992) 145–163.
[279] Y. Lu, J.L. Peters, A.C. Michael, Direct comparison of the response of voltammetry and microdialysis to electrically evoked release of striatal dopamine, J. Neurochem. 70 (1998) 584–593.
[280] W.B. Mackey, D. van der Kooy, Neuroleptics block the positive reinforcing effects of amphetamine but not of morphine as measured by place conditioning, Pharmacol. Biochem. Behav. 22 (1985) 101–105.
[281] C.S. Maldonado-Irizarry, C.J. Swanson, A.E. Kelley, Glutamate receptors in the nucleus accumbens shell control feeding behavior via the lateral hypothalamus, J. Neurosci. 15 (1995) 6779–6788.
[282] G.P. Mark, D.S. Blander, B.G. Hoebel, A conditioned stimulus decreases extracellular dopamine in the nucleus accumbens after the development of a learned taste aversion, Brain Res. 551 (1991) 308–310.
[283] G.P. Mark, S.E. Smith, P.V. Rada, B.G. Hoebel, An appetitively conditioned taste elicits a preferential increase in mesolimbic dopamine release, Pharmacol. Biochem. Behav. 48 (1994) 651–660.
[284] A. Markou, G.F. Koob, Postcocaine anhedonia. An animal model of cocaine withdrawal, Neuropsychopharmacology 4 (1991) 17–26.
[285] C.D. Marsden, Which motor disorder in Parkinson's disease indicates the true motor function of the basal ganglia? in: D. Evered, M. O'Conner (Eds.), Functions of the Basal Ganglia, Pitman, London, 1984, pp. 225–237.
[286] C.D. Marsden, Dopamine and basal ganglia disorders in humans, Semin. Neurosci. 4 (1992) 171–178.
[287] J.F. Marshall, J.S. Richardson, P. Teitelbaum, Nigrostriatal bundle damage and the lateral hypothalamic syndrome, J. Comp. Physiol. Psychol. 87 (1974) 808–830.
[288] J.F. Marshall, B.H. Turner, P. Teitelbaum, Compulsive, abnormal walking caused by anticholinergics in akinetic, 6-hydroxydopamine-treated rats, Science 199 (1978) 1461–1463.
[289] P. Martel, M. Fantino, Influence of the amount of food ingested on mesolimbic dopaminergic system activity: a microdialysis study, Pharmacol. Biochem. Behav. 55 (1996) 297–302.
[290] P. Martel, M. Fantino, Mesolimbic dopaminergic system activity as a function of food reward: a microdialysis study, Pharmacol. Biochem. Behav. 53 (1996) 221–226.
[291] K. McFarland, A. Ettenberg, Haloperidol differentially affects reinforcement and motivational processes in rats running an alley for intravenous heroin, Psychopharmacology 122 (1995) 346–350.
[292] K. McFarland, A. Ettenberg, Reinstatement of drug-seeking behavior produced by heroin-predictive environmental stimuli, Psychopharmacology 131 (1997) 86–92.
[293] A. McGregor, G. Baker, D.C. Roberts, Effect of 6-hydroxydopamine lesions of the amygdala on intravenous cocaine self-administration under a progressive ratio schedule of reinforcement, Brain Res. 646 (1994) 273–278.
[294] A. McGregor, D.C. Roberts, Dopaminergic antagonism within the nucleus accumbens or the amygdala produces differential effects on intravenous cocaine self-administration under fixed and progressive ratio schedules of reinforcement, Brain Res. 624 (1993) 245–252.
[295] W.M. Meil, M.D. Schechter, Olanzapine attenuates the reinforcing effects of cocaine, Eur. J. Pharmacol. 340 (1997) 17–26.
[296] R.L. Meisel, D.M. Camp, T.E. Robinson, A microdialysis study of ventral striatal dopamine during sexual behavior in female Syrian hamsters, Behav. Brain Res. 55 (1993) 151–157.
[297] A. Mendrek, C.D. Blaha, A.G. Phillips, Pre-exposure of rats to amphetamine sensitizes self-administration of this drug under a progressive ratio schedule, Psychopharmacology 135 (1998) 416–422.
[298] Z. Merali, J. McIntosh, P. Kent, D. Michaud, H. Anisman, Aversive and appetitive events evoke the release of corticotropin-releasing hormone and bombesin-like peptides at the central nucleus of the amygdala, J. Neurosci. 18 (1998) 4758–4766.
[299] P.G. Mermelstein, J.B. Becker, Increased extracellular dopamine in the nucleus accumbens and striatum of the female rat during paced copulatory behavior, Behav. Neurosci. 109 (1995) 354–365.
[300] J. Mirenowicz, W. Schultz, Importance of unpredictability for reward responses in primate dopamine neurons, J. Neurophysiol. 72 (1994) 1024–1027.
[301] J. Mirenowicz, W. Schultz, Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli, Nature 379 (1996) 449–451.
[302] J.G. Modell, J.M. Mountz, F.B. Glaser, J.Y. Lee, Effect of haloperidol on measures of craving and impaired control in alcoholic subjects, Alcohol Clin. Exp. Res. 17 (1993) 234–240.
[303] G.J. Mogenson, C.R. Yang, The contribution of basal forebrain to limbic-motor integration and the mediation of motivation to action, Adv. Exp. Med. Biol. 295 (1991) 267–290.
[304] P.R. Montague, P. Dayan, T.J. Sejnowski, A framework for mesencephalic dopamine systems based on predictive Hebbian learning, J. Neurosci. 16 (1996) 1936–1947.
[305] F. Mora, G.J. Mogenson, E.T. Rolls, Activity of neurons in the region of the substantia nigra during feeding in the monkey, Brain Res. 133 (1977) 267–276.
[306] P.J. Morgane, Alterations in feeding and drinking behavior of rats with lesions of the globus pallidi, Am. J. Physiol. 201 (1961) 420–428.
[307] S.T. Murphy, R.B. Zajonc, Affect, cognition, and awareness: affective priming with optimal and suboptimal stimulus exposures, J. Pers. Soc. Psychol. 64 (1993) 723–739.

[308] E. Murzi, L. Hernandez, T. Baptista, Lateral hypothalamic sites eliciting eating affect medullary taste neurons in rats, Physiol. Behav. 36 (1986) 829–834.
[309] K. Nader, A. Bechara, D.C. Roberts, D. van der Kooy, Neuroleptics block high- but not low-dose heroin place preferences: further evidence for a two-system model of motivation, Behav. Neurosci. 108 (1994) 1128–1138.
[310] K. Nader, A. Bechara, D. van der Kooy, Neurobiological constraints on behavioral models of motivation, An. Rev. Psychol. 48 (1997) 85–114.
[311] K. Nader, D. van der Kooy, Deprivation state switches the neurobiological substrates mediating opiate reward in the ventral tegmental area, J. Neurosci. 17 (1997) 383–390.
[312] S. Nakajima, R.L. Patterson, The involvement of dopamine D2 receptors, but not D3 or D4 receptors, in the rewarding effect of brain stimulation in the rat, Brain Res. 760 (1997) 74–79.
[313] K. Nakamura, R. Norgren, Taste response of neurons in the nucleus of the solitary tract of awake rats: an extended stimulus array, J. Neurophysiol. 70 (1993) 879–891.
[314] M.J. Nash, Addicted: Why do people get hooked? Mounting evidence points to a powerful brain chemical called dopamine, Time, 1997, pp. 68–76.
[315] R.M. Nesse, K.C. Berridge, Psychoactive drug use in evolutionary perspective, Science 278 (1997) 63–66.
[316] R.W. Nisbett, T.D. Wilson, Telling more than we can know: verbal reports on mental processes, Psychol. Rev. 84 (1978) 231–259.
[317] R. Norgren, Gustatory system, in: G. Paxinos (Ed.) The Rat Nervous System, Academic Press, San Diego, 1995, pp. 751–771.
[318] R. Norgren, P.S. Grigson, The role of the central gustatory system in learned taste aversions, in: T. Onon, B.L. McNaughton, S. Molotchnikoff, E.T. Rolls, H. Nishijo (Eds.), Perception, Memory, and Emotion: Frontiers in Neuroscience. Eds., Pergamon, Oxford, UK, 1996, pp. 479–497.
[319] E. O'Hare, J. Cleary, P.J. Bartz, D.T. Weldon, C.J. Billington, A.S. Levine, Naloxone administration following operant training of sucrose/water discrimination in the rat, Psychopharmacology 129 (1997) 289–294.
[320] D.C. Ohuoha, J.A. Maxwell, L.E. Thomson 3rd, J.L. Cadet, R.B. Rothman, Effect of dopamine receptor antagonists on cocaine subjective effects: a naturalistic case study, J. Subst. Abuse Treat. 14 (1997) 249–258.
[321] P.G. Overton, D. Clark, Burst firing in midbrain dopaminergic neurons, Brain Res. Rev. 25 (1997) 312–334.
[322] J. Panksepp, The anatomy of emotions, in: R. Plutchik, H. Kellerman (Eds.), Emotion: Theory, Research, and Experience., Vol. 3: Biological Foundation of Emotions, Academic Press, New York, 1986, pp. 91–124.
[323] J. Panksepp, The neurochemistry of behavior, An. Rev. Psychol. 37 (1986) 77–107.
[324] J. Panksepp, Brain emotional circuits and psychopathologies, in: J.P. Manfred Clynes (Ed.), Emotions and Psychopathology., Plenum, New York, NY, US, 1988, pp. 37–76.
[325] J. Panksepp, Affective Neuroscience: the Foundations of Human and Animal Emotions, Oxford Univ. Press, Oxford, U.K., 1998.
[326] L. Parker, K. Leeb, Amphetamine-induced modification of quinine palatability: Analysis by the taste reactivity test, Pharmacol. Biochem. Behav. 47 (1994) 413–420.
[327] L.A. Parker, Behavioral conditioned responses across multiple conditioning/testing trials elicited by lithium- and amphetamine-paired flavors, Behav. Neural. Biol. 41 (1984) 190–199.
[328] L.A. Parker, Chlordiazepoxide enhances the palatability of lithium-, amphetamine-, and saline-paired saccharin solution, Pharmacol. Biochem. Behav. 50 (1995) 345–349.
[329] L.A. Parker, Rewarding drugs produce taste avoidance, but not taste aversion, Neurosci. Biobehav. Rev. 19 (1995) 143–151.
[330] L.A. Parker, T. Carvell, Orofacial and somatic responses elicited by lithium-, nicotine- and amphetamine-paired sucrose solution, Pharmacol. Biochem. Behav. 24 (1986) 883–887.
[331] L.A. Parker, N. Lopez Jr., Pimozide enhances the aversiveness of quinine solution, Pharmacol. Biochem. Behav. 36 (1990) 653–659.
[332] L.A. Parker, S. Maier, M. Rennie, J. Crebolder, Morphine- and naltrexone-induced modification of palatability: analysis by the taste reactivity test, Behav. Neurosci. 106 (1992) 999–1010.
[333] I.P. Pavlov, Conditioned reflexes; an Investigation of the Physiological Activity of the Cerebral Cortex, Oxford Univ. Press: Humphrey Milford, [London], 1927.
[334] S. Pecina, K. Berridge, Opioid feeding site objectively mapped within shell of nucleus accumbens, Neurosci. Abstr. 23 (1997) 529.
[335] S. Peciña, K.C. Berridge, Comparison of systemic and intracranial administration of morphine: effects on hedonic taste reactivity (in rats), Neurosci. Abstr. 19 (1993) 1820.
[336] S. Peciña, K.C. Berridge, Central enhancement of taste pleasure by intraventricular morphine, Neurobiology 3 (1995) 269–280.
[337] S. Peciña, K.C. Berridge, Brainstem mediates benzodiazepine enhancement of taste palatability: comparison of diazepam microinjections into fourth versus lateral ventricles, Brain Res. 727 (1996) 22–30.
[338] S. Peciña, K.C. Berridge, Morphine microinjections enhance feeding and palatability in the shell but not core of nucleus accumbens, Neurosci. Abstr. 22 (1996) 1408.
[339] S. Peciña, K.C. Berridge, L.A. Parker, Pimozide does not shift palatability: separation of anhedonia from sensorimotor effects, Pharmacol. Biochem. Behav. 58 (1997) 801–811.
[340] S.M. Pellis, V.C. Pellis, R.M. Chesire, N. Rowland, P. Teitelbaum, Somnolence, akinesia, and sensory activation of motivated behavior in the lateral hypothalamic syndrome, Proc. Natl. Acad. Sci. U.S.A. 72 (1975) 2819–2823.
[341] C.M. Pennartz, The ascending neuromodulatory systems in learning by reinforcement: comparing computational conjectures with experimental findings, Brain Res. Rev. 21 (1996) 219–245.
[342] J.L. Peters, A.C. Michael, Modeling voltammetry and microdialysis of striatal extracellular dopamine: The impact of dopamine uptake on extraction and recovery ratios, J. Neurochem. 70 (1998) 594–603.
[343] J.G. Pfaus, Homologies of animal and human sexual behaviors, Horm. Behav. 30 (1996) 187–200.
[344] J.G. Pfaus, G. Damsma, D. Wenkstern, H.C. Fibiger, Sexual activity increases dopamine transmission in the nucleus accumbens and striatum of female rats, Brain Res. 693 (1995) 21–30.
[345] A.G. Phillips, J.G. Pfaus, C.D Blaha, Dopamine and motivated behavior: insights provided by in vivo analyses, in: P. Willner, J. Scheel-Kruger, (Ed.), The Mesolimbic Dopamine System: From Motivation to Action, Wiley, Chichester, 1991, pp. 199–224.
[346] A.G. Phillips, L.J. Atkinson, J.R. Blackburn, C.D. Blaha, Increased extracellular dopamine in the nucleus accumbens of the rat elicited by a conditional stimulus for food: an electrochemical study, Can. J. Physiol. Pharmacol. 71 (1993) 387–393.
[347] A.G. Phillips, C.D. Blaha, J.G. Pfaus, J.R. Blackburn, Neurobiological correlates of positive emotional states: Dopamine, anticipation, and reward, in: K.T. Strongman (Ed.), International Review of Studies on Emotion, Vol. 2, Wiley, New York, 1992, pp. 31–50.
[348] A.G. Phillips, R.S. Nikaido, Disruption of brain stimulation-induced feeding by dopamine receptor blockade, Nature 258 (1975) 750–751.
[349] G.D. Phillips, T.W. Robbins, B.J. Everitt, Mesoaccumbens dopamine-opiate interactions in the control over behaviour by a conditioned reinforcer, Psychopharmacology 114 (1994) 345–359.
[350] R.C. Pierce, P.W. Kalivas, A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants, Brain Res. Rev. 25 (1997) 192–216.
[351] E.N. Pothos, I. Creese, B.G. Hoebel, Restricted eating with weight loss selectively decreases extracellular dopamine in the nucleus

accumbens and alters dopamine response to amphetamine, morphine, and food intake, J. Neurosci. 15 (1995) 6640–6650.
[352] M.T. Price, H.C. Fibiger, Discriminated escape learning and response to electric shock after 6-hydroxydopamine lesions of the nigro-neostriatal dopaminergic projection, Pharmacol. Biochem. Behav. 3 (1975) 285–290.
[353] M. Qian, A.E. Johnson, P. Södersten, CCK-8 inhibits ingestive behaviour in rats with lateral hypothalamic 6-OHDA lesions, Neuroreport (in press).
[354] P.V. Rada, P.M.G., G.H.B., Dopamine release in the nucleus accumbens by hypothalamic stimulation-escape behavior, Brain Res. 782 (1998) 228–234.
[355] R.A. Rescorla, Behavioral studies of Pavlovian conditioning, Ann. Rev. Neurosci. 11 (1988) 329–352.
[356] R.A. Rescorla, Pavlovian conditioning. It's not what you think it is, Am. Psychol. 43 (1988) 151–160.
[357] R.A. Rescorla, Control of instrumental performance by Pavlovian and instrumental stimuli, J. Exp. Psychol. Anim. Behav. Process 20 (1994) 44–50.
[358] R.A. Rescorla, R.L. Solomon, Two-process learning theory: Relationships between Pavlovian conditioning and instrumental learning, Psychol. Rev. 74 (1967) 151–182.
[359] N.R. Richardson, A. Gratton, Behavior-relevant changes in nucleus accumbens dopamine transmission elicited by food reinforcement: an electrochemical study in rat, J. Neurosci. 16 (1996) 8160–8169.
[360] H.J. Rideout, L.A. Parker, Morphine enhancement of sucrose palatability: analysis by the taste reactivity test, Pharmacol. Biochem. Behav. 53 (1996) 731–734.
[361] F.O. Risinger, S.D. Dickinson, C.L. Cunningham, Haloperidol reduces ethanol-induced motor activity stimulation but not conditioned place preference, Psychopharmacology 107 (1992) 453–456.
[362] T.W. Robbins, M. Cador, J.R. Taylor, B.J. Everitt, Limbic-striatal interactions in reward-related processes, Neurosci. Biobehav. Rev. 13 (1989) 155–162.
[363] T.W. Robbins, B.J. Everitt, Neurobehavioural mechanisms of reward and motivation, Curr. Opin. Neurobiol. 6 (1996) 228–236.
[364] D.C. Roberts, E.A. Loh, G. Vickers, Self-administration of cocaine on a progressive ratio schedule in rats: dose–response relationship and effect of haloperidol pretreatment, Psychopharmacology 97 (1989) 535–538.
[365] T.E. Robinson, A.L. Angus, J.B. Becker, Sensitization to stress: the enduring effects of prior stress on amphetamine-induced rotational behavior, Life Sci. 37 (1985) 1039–1042.
[366] T.E. Robinson, K.C. Berridge, The neural basis of drug craving: an incentive-sensitization theory of addiction, Brain Res. Rev. 18 (1993) 247–291.
[367] T.E. Robinson, K.C. Berridge, The psychology and neurobiology of addiction: an incentive sensitization view, Addiction, in press (1998).
[368] T.E. Robinson, D.M. Camp, The effects of 4 days of continuous striatal microdialysis on indexes of dopamine and serotonin neurotransmission in rats, J. Neurosci. Meth. 40 (1991) 211–222.
[369] B.A. Rocha, K. Scearce-Levie, J.J. Lucas, N. Hiroi, N. Castanon, J.C. Crabbe, E.J. Nestler, R. Hen, Increased vulnerability to cocaine in mice lacking the serotonin-1B receptor, Nature 393 (1998) 175–178.
[370] E.T. Rolls, The neurophysiology of feeding, Proc. Nutr. Soc. 40 (1981) 361–362.
[371] R. Romo, W. Schultz, Dopamine neurons of the monkey midbrain: contingencies of responses to active touch during self-initiated arm movements, J. Neurophysiol. 63 (1990) 592–606.
[372] J.B. Rosen, J. Schulkin, From normal fear to pathological anxiety, Psychol. Rev. 105 (1998) 325–350.
[373] Z.L. Rossetti, Y. Hmaidan, G.L. Gessa, Marked inhibition of mesolimbic dopamine release: a common feature of ethanol, morphine, cocaine and amphetamine abstinence in rats, Eur. J. Pharmacol. 221 (1992) 227–234.
[374] R.B. Rothman, J.R. Glowa, A review of the effects of dopaminergic agents on humans, animals, and drug-seeking behavior, and its implications for medication development—focus on GBR-12909, Molecular Neurobiology 11 (1995) 1–19.
[375] N. Rowland, D.M. Marques, A.E. Fisher, Comparison of the effects of brain dopamine-depleting lesions upon oral behaviors elicited by tail pinch and electrical brain stimulation, Physiol. Behav. 24 (1980) 273–281.
[376] P. Rozin, A. Fallon, The acquisition of likes and dislikes for foods., What is America Eating?: Proceedings of a Symposium. (National Research Council), National Academy Press, Washington, DC, US, 1986, pp. 58–71.
[377] P.N. Rozin, J. Schulkin, Food selection, in: E.M. Stricker (Ed.), Neurobiology of Food and Fluid Intake, Vol. 10, Plenum, New York, 1990, pp. 297–328.
[378] J.D. Salamone, Behavioral pharmacology of dopamine systems: a new synthesis, in: P. Willner, J. Scheel-Kruger (Eds.), The Mesolimbic dopamine system: from motivation to action, Wiley, New York, 1991, pp. 599–611.
[379] J.D. Salamone, Complex motor and sensorimotor functions of striatal and accumbens dopamine: involvement in instrumental behavior processes, Psychopharmacology 107 (1992) 160–174.
[380] J.D. Salamone, The involvement of nucleus accumbens dopamine in appetitive and aversive motivation, Behav. Brain Res. 61 (1994) 117–133.
[381] J.D. Salamone, The behavioral neurochemistry of motivation: methodological and conceptual issues in studies of the dynamic activity of nucleus accumbens dopamine, J. Neurosci. Meth. 64 (1996) 137–149.
[382] J.D. Salamone, M.S. Cousins, S. Bucher, Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure, Behav. Brain. Res. 65 (1994) 221–229.
[383] J.D. Salamone, M.S. Cousins, B.J. Snyder, Behavioral functions of nucleus accumbens dopamine: empirical and conceptual problems with the anhedonia hypothesis, Neurosci. Biobehav. Rev. 21 (1997) 341–359.
[384] J.D. Salamone, K. Mahan, S. Rogers, Ventrolateral striatal dopamine depletions impair feeding and food handling in rats, Pharmacol. Biochem. Behav. 44 (1993) 605–610.
[385] J.D. Salamone, R.E. Steinpreis, L.D. McCullough, P. Smith, D. Grebel, K. Mahan, Haloperidol and nucleus accumbens dopamine depletion suppress lever pressing for food but increase free food consumption in a novel food choice procedure, Psychopharmacology 104 (1991) 515–521.
[386] J.D. Salamone, M.J. Zigmond, E.M. Stricker, Characterization of the impaired feeding behavior in rats given haloperidol or dopamine-depleting brain lesions, Neuroscience 39 (1990) 17–24.
[387] M. Sarter, G.G. Berntson, J.T. Cacioppo, Brain imaging and cognitive neuroscience. Toward strong inference in attributing function to structure, Am. Psychol. 51 (1996) 13–21.
[388] M. Sarter, J.P. Bruno, Dopamine role [letter], Science 278 (1997) 1549–1550.
[389] G. Scalera, P.S. Grigson, R. Norgren, Gustatory functions, sodium appetite, and conditioned taste aversion survive excitotoxic lesions of the thalamic taste area, Behav. Neurosci. 111 (1997) 633–645.
[390] G.E. Schafe, R.J. Seeley, I.L. Bernstein, Forebrain contribution to the induction of a cellular correlate of conditioned taste aversion in the nucleus of the solitary tract, J. Neurosci. 15 (1995) 6789–6796.
[391] T. Schallert, S. Hall, 'Disengage' sensorimotor deficit following apparent recovery from unilateral dopamine depletion, Behav. Brain Res. 30 (1988) 15–24.
[392] T. Schallert, M. Upchurch, N. Lobaugh, S.B. Farrar, W.W. Spirduso, P. Gilliam, D. Vaughn, R.E. Wilcox, Tactile extinction: distinguishing between sensorimotor and motor asymmetries in rats with unilateral nigrostriatal damage, Pharmacol. Biochem. Behav. 16 (1982) 455–462.

[393] T. Schallert, I.Q. Whishaw, Two types of aphagia and two types of sensorimotor impairment after lateral hypothalamic lesions: observations in normal weight, dieted, and fattened rats, J. Comp. Physiol. Psychol. 92 (1978) 720–741.
[394] T. Schallert, I.Q. Whishaw, V.D. Ramirez, P. Teitelbaum, Neurotransmitters and the regulation of food intake, Prog. Brain Res. 42 (1975) 235–249.
[395] L.H. Schneider, J.D. Davis, C.A. Watson, G.P. Smith, Similar effect of raclopride and reduced sucrose concentration on the microstructure of sucrose sham feeding, Eur. J. Pharmacol. 186 (1990) 61–70.
[396] L.H. Schneider, C.A. Watson, J.D. Davis, J. Gibbs, G.P. Smith, Microstructural analysis of the inhibition of sucrose sham feeding by SCH 23390, Appetite 12 (1989) 122–124.
[397] J. Schulkin, Sodium Hunger: the Search for a Salty Taste, Cambridge Univ. Press, New York, 1991.
[398] W. Schultz, Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey, J. Neurophysiol. 56 (1986) 1439–1461.
[399] W. Schultz, Activity of dopamine neurons in the behaving primate, Sem. Neurosci. 4 (1992) 129–138.
[400] W. Schultz, Dopamine neurons and their role in reward mechanisms, Cur. Opin. Neurobio. 7 (1997) 191–197.
[401] W. Schultz, P. Apicella, T. Ljungberg, Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task, J. Neurosci. 13 (1993) 900–913.
[402] W. Schultz, P. Apicella, T. Ljungberg, R. Romo, Activity of monkey striatal and dopamine neurons during the performance of delayed response tasks, in: G. Percheron, J.S. McKenzie, J. Feger (Eds.), The Basal Ganglia IV, Plenum, New York, 1995, pp. 305–316.
[403] W. Schultz, P. Apicella, T. Ljungberg, R. Romo, E. Scarnati, Reward-related activity in the monkey striatum and substantia nigra, Prog. Brain Res. 99 (1993) 227–235.
[404] W. Schultz, P. Apicella, E. Scarnati, T. Ljungberg, Neuronal activity in monkey ventral striatum related to the expectation of reward, J. Neurosci. 12 (1992) 4595–4610.
[405] W. Schultz, P. Dayan, P.R. Montague, A neural substrate of prediction and reward, Science 275 (1997) 1593–1599.
[406] G.J. Schwartz, H.J. Grill, Relationships between taste reactivity and intake in the neurologically intact rat, Chem. Senses 9 (1984) 249–272.
[407] M. Schwartz, P. Teitelbaum, Nigrostriatal bundle damage and the lateral hypothalamic syndrome, J. Comp. Physiol. Psychol. 87 (1974) 808–830.
[408] A. Sclafani, L.T. Einberg, J.W. Nissenbaum, Influence of saccharin on Polycose, sucrose, and glucose intake and preference in rats, Neurosci. Biobehav. Rev. 11 (1987) 223–229.
[409] A. Sclafani, J.W. Nissenbaum, M. Vigorito, Starch preference in rats, Neurosci. Biobehav. Rev. 11 (1987) 253–262.
[410] T.R. Scott, The effect of physiological need on taste, in: E.D. Capaldi, T.L. Powley (Eds.), Taste, Experience, and Feeding, American Psychological Association, Washington, DC, 1990, pp. 45–61.
[411] T.R. Scott, S. Yaxley, Z.J. Sienkiewicz, E.T. Rolls, Gustatory responses in the nucleus tractus solitarius of the alert cynomolgus monkey, J. Neurophysiol. 55 (1986) 182–200.
[412] R.J. Seeley, O. Galaverna, J. Schulkin, A.N. Epstein, H.J. Grill, Lesions of the central nucleus of the amygdala: II. Effects on intraoral NaCl intake, Behav. Brain Res. 59 (1993) 19–25.
[413] R.J. Seeley, J.M. Kaplan, H.J. Grill, Effects of interrupting an intraoral meal on meal size and meal duration in rats, Appetite 20 (1993) 13–20.
[414] R.J. Seeley, C.J. Payne, S.C. Woods, Neuropeptide Y fails to increase intraoral intake in rats, Am. J. Physiol. 268 (1995) R423–R427.
[415] D.W. Self, W.J. Barnhart, D.A. Lehman, E.J. Nestler, Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists, Science 271 (1996) 1289–1586.
[416] D. Servan-Schreiber, R.M. Bruno, C.S. Carter, J.D. Cohen, Dopamine and the mechanisms of cognition: Part I. A neural network model predicting dopamine effects on selective attention, Biological Psychiatry 43 (1998) 713–722.
[417] M. Shidara, T.G. Aigner, B.J.R., Neuronal signals in the monkey ventral striatum related to progress through a predictable series of trials, J. Neurosci. 16 (1998) 2613–2625.
[418] T. Shimura, M. Komori, T. Yamamoto, Acute sodium deficiency reduces gustatory responsiveness to NaCl in the parabrachial nucleus of rats, Neurosci. Lett. 236 (1997) 33–36.
[419] T.S. Shippenberg, R. Bals-Kubik, A. Huber, A. Herz, Neuroanatomical substrates mediating the aversive effects of D-1 dopamine receptor antagonists, Psychopharmacology 103 (1991) 209–214.
[420] T.S. Shippenberg, A. Herz, Motivational effects of opioids: influence of D-1 versus D-2 receptor antagonists, Eur. J. Pharmacol. 151 (1988) 233–242.
[421] P. Shizgal, Neural basis of utility estimation, Cur. Opin. Neurobio. 7 (1997) 198–208.
[422] P. Shizgal, On the neural computation of utility: implications from studies of brain stimulation reward, in: D. Kahneman, E. Deiner, N. Schwartz (Eds.), Foundations of Hedonic Psychology: Scientific Perspectives on Enjoyment and Suffering, Russel Sage Foundation, New York, in press.
[423] P. Shizgal, K. Conover, On the neural computation of utility, Cur. Dir. Psychol. Sci. 5 (1996) 37–43.
[424] T.L. Sills, J.P. Baird, F.J. Vaccarino, Individual differences in the feeding effects of amphetamine: role of nucleus accumbens dopamine and circadian factors, Psychopharmacology 112 (1993) 211–218.
[425] K.J. Simansky, K.A. Bourbonais, G.P. Smith, Food-related stimuli increase the ratio of 3,4-dihydroxyphenylacetic acid to dopamine in the hypothalamus, Pharmacol. Biochem. Behav. 23 (1985) 253–258.
[426] L.C. Simbayi, R.A. Boakes, M.J. Burton, Effects of basolateral amygdala lesions on taste aversions produced by lactose and lithium chloride in the rat, Behav. Neurosci. 100 (1986) 455–465.
[427] B.F. Skinner, The Behavior of Organisms: An Experimental Analysis, D. Appleton-Century Company incorporated, New York, London, 1938.
[428] B.F. Skinner, Cumulative Record: A Selection of Papers, 3rd edn., Appleton-Century-Crofts, New York, 1972.
[429] G.P. Smith, Dopamine and food reward, in: A.M. Morrison, S.J. Fluharty (Eds.), Progress in Psychobiology and Physiological Psychology, Vol. 15, Academic Press, New York, 1995, pp. 83–144.
[430] G.P. Smith, L.H. Schneider, Relationships between mesolimbic dopamine function and eating behavior, Ann. New York Acad. Sci. 537 (1988) 254–261.
[431] A.H.V. Söderpalm, S. Hansen, Benzodiazepines enhance the consumption and palatability of alcohol in the rat, Psychopharmacology 137 (1998) 215–222.
[432] J.D. Sokolowski, J.D. Salamone, The role of accumbens dopamine in lever pressing and response allocation: Effects of 6-OHDA injected into core and dorsomedial shell, Pharmacol. Biochem. Behav. 59 (1998) 557–566.
[433] P.R. Solomon, A. Crider, J.W. Winkelman, A. Turi, R.M. Kamer, L.J. Kaplan, Disrupted latent inhibition in the rat with chronic amphetamine or haloperidol-induced supersensitivity: relationship to schizophrenic attention disorder, Biol. Psychiatry 16 (1981) 519–537.
[434] R.L. Solomon, Addiction: An opponent-process theory of acquired motivation: The affective dynamics of addiction, in: M.E.P.S. Jack, D. Maser (Eds.), Psychopathology: Experimental Models, W. H. Freeman, Publishers, San Francisco, CA, US, 1977, pp. 66–103.

[435] R.L. Solomon, J.D. Corbit, An opponent-process theory of motivation: I Temporal dynamics of affect, Psychol. Rev. 81 (1974) 119–145.
[436] R. Soussignan, B. Schall, Children's facial responsiveness to odors: Influences of hedonic valence of odor, gender, age, and social presence, Developmental Psychology 32 (1996) 367–379.
[437] A.C. Spector, P. Breslin, H.J. Grill, Taste reactivity as a dependent measure of the rapid formation of conditioned taste aversion: a tool for the neural analysis of taste-visceral associations, Behav. Neurosci. 102 (1988) 942–952.
[438] A.C. Spector, R. Norgren, H.J. Grill, Parabrachial gustatory lesions impair taste aversion learning in rats, Behav. Neurosci. 106 (1992) 147–161.
[439] L.R. Squire, S.M. Zola, Structure and function of declarative and nondeclarative memory systems, Proc. Natl. Acad. Sci. U.S.A. 93 (1996) 13515–13522.
[440] T.L. Stefurak, D. van der Kooy, Tegmental pedunculopontine lesions in rats decrease saccharin's rewarding effects but not its memory-improving effect, Behav. Neurosci. 108 (1994) 972–980.
[441] J.E. Steiner, The gustofacial response: observation on normal and anencephalic newborn infants, Symp. Oral Sens. Percept. 4 (1973) 254–278.
[442] J.E. Steiner, Human facial expressions in response to taste and smell stimulation, Adv. Child Dev. Behav. 13 (1979) 257–295.
[443] J.E. Steiner, D. Glaser, Differential behavioral responses to taste stimuli in non-human primates, J. Human Evol. 13 (1984) 709–723.
[444] J.E. Steiner, D. Glaser, Taste-induced facial expressions in apes and humans, Human Evol. 10 (1995) 97–105.
[445] J.E. Steiner, D. Glaser, M.E. Hawilo, K.C. Berridge, Evolutionary continuum of facial expression: human newborn versus nonhuman primate reaction to sensory pleasure, Manuscript in preparation. (1998).
[446] J.R. Stellar, F.H. Brooks, L.E. Mills, Approach and withdrawal analysis of the effects of hypothalamic stimulation and lesions in rats, J. Comp. Physiol. Psychol. 93 (1979) 446–466.
[447] J.R. Stellar, D. Corbett, Regional neuroleptic microinjections indicate a role for nucleus accumbens in lateral hypothalamic self-stimulation reward, Brain Res. 477 (1989) 126–143.
[448] J.R. Stellar, E. Stellar, The Neurobiology of Motivation and Reward, Springer-Verlag, New York, 1985.
[449] J. Stewart, Normal hedonic reactions to sucrose by 6-OHDA rats may reflect 'functional decerebration'. Communicated at Society for Neuroscience meeting, New Orleans, 1991.
[450] R.E. Strecker, G.F. Steinfels, B.L. Jacobs, Dopaminergic unit activity in freely moving cats: lack of relationship to feeding, satiety, and glucose injections, Brain Res. 260 (1983) 317–321.
[451] E.M. Stricker, M.J. Zigmond, Brain catecholamines and the lateral hypothalamic syndrome, in: D. Novin, W. Wyrwicka, G. Bray (Eds.), Hunger: Basic Mechanisms and Clinical Implications, Raven Press, New York, 1976, pp. 19–32.
[452] E.M. Stricker, M.J. Zigmond, Brain monoamines, homeostasis, and adaptive behavior., Handbook of Physiology: Intrinsic Regulatory Systems of the Brain, Vol. 4, American Physiological Society, Bethesda, MD, 1986, pp. 677–696.
[453] D. Sulzer, M.P. Joyce, L. Lin, D. Geldwert, S.N. Haber, T. Hattori, S. Rayport, Dopamine neurons make glutamatergic synapses in vitro, J. Neurosci. 18 (1998) 4588–4602.
[454] R. Tamura, R. Norgren, Repeated sodium depletion affects gustatory neural responses in the nucleus of the solitary tract of rats, Am. J. Physiol. 273 (1997) R1381–R1391.
[455] P. Teitelbaum, A.N. Epstein, The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions, Psychol. Rev. 69 (1962) 74–90.
[456] P. Teitelbaum, D.L. Wolgin, Abnormal gait sequence in locomotion after atropine treatment of catecholamine-deficient akinetic rats, Proc. Natl. Acad. Sci. U.S.A. 84 (1987) 8750–8753.
[457] P. Terry, Dopamine receptor subtypes and ingestive behavior, in: S.J. Cooper, P.G. Clifton (Eds.), Drug Receptor Subtypes and Ingestive Behavior, Academic Press, San Diego, 1995.
[458] P. Terry, D.B. Gilbert, S.J. Cooper, Dopamine receptor subtype agonists and feeding behavior, Obesity Res. 3 (1995) 515S–523S.
[459] E.L. Thorndike, Animal Intelligence: An Experimental Study of the Associative Processes in Animals, Macmillan, New York, 1898.
[460] F. Toates, Motivational Systems, Cambridge Univ. Press, Cambridge, 1986.
[461] F. Toates, The interaction of cognitive and stimulus-response processes in the control of behaviour, Neurosci. Biobehav. Rev. 22 (1998) 59–83.
[462] F.M. Toates, The control of ingestive behaviour by internal and external stimuli—a theoretical review, Appetite 2 (1981) 35–50.
[463] F.M. Toates, Comparing motivational systems—an incentive motivation perspective, in: C.R. Legg, D.A. Booth (Eds.), Appetite: Neural and Behavioural Bases, Oxford Univ. Press, New York, 1994, pp. 305–327.
[464] J.B. Travers, L.R. Akey, S.C. Chen, S. Rosen et al., Taste preferences in Parkinson's disease patients, Chem. Senses 18 (1993) 47–55.
[465] D. Treit, K.C. Berridge, A comparison of benzodiazepine, serotonin, and dopamine agents in the taste-reactivity paradigm, Pharmacol. Biochem. Behav. 37 (1990) 451–456.
[466] D. Treit, K.C. Berridge, C.E. Schultz, The direct enhancement of positive palatability by chlordiazepoxide is antagonized by Ro 15-1788 and CGS 8216, Pharmacol. Biochem. Behav. 26 (1987) 709–714.
[467] M.E. Trulson, D.W. Preussler, Dopamine-containing ventral tegmental area neurons in freely moving cats: activity during the sleep–waking cycle and effects of stress, Exp. Neurol. 83 (1984) 367–377.
[468] A. Tyrka, C. Gayle, G.P. Smith, Raclopride decreases sucrose intake of rat pups in independent ingestion tests, Pharmacol. Biochem. Behav. 43 (1992) 863–869.
[469] A. Tyrka, G.P. Smith, Potency of SCH 23390 for decreasing sucrose intake in rat pups depends on mode of ingestion, Pharmacol. Biochem. Behav. 39 (1991) 955–961.
[470] U. Ungerstedt, Is interruption of the nigro-striatal dopamine system producing the 'lateral hypothalamus syndrome'?, Acta Physiol. Scand. 80 (1970) 35A–36A.
[471] U. Ungerstedt, Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system, Acta Physiol. Scand. Suppl. 367 (1971) 95–122.
[472] F.J. Vaccarino, B.B. Schiff, S.E. Glickman, Biological view of reinforcement, in: S.B. Klein, R.R. Mowrer (Eds.), Contemporary Learning Theories: Instrumental Conditioning Theory and the Impact of Biological Constraints on Learning, Lawrence Erlbaum Associates, Hillsdale, NJ, 1989, pp. 111–142.
[473] E.S. Valenstein, Problems of measurement and interpretation with reinforcing brain stimulation, Psychol. Rev. 71 (1964) 415–437.
[474] E.S. Valenstein, The interpretation of behavior evoked by brain stimulation, in: A. Wauquier, E.T. Rolls (Eds.), Brain-Stimulation Reward, Elsevier, New York, 1976, pp. 557–575.
[475] D. van der Kooy, K. Nader, A. Bechara, Role of dopamine in reward. Personal communication (email discussion), 1998.
[476] P. Vezina, Sensitization by prior drug exposure increases break point for self-administration of drug reward by rats, Personal Communication, 1998.
[477] N.D. Volkow, G.J. Wang, J.S. Fowler, J. Logan, S.J. Gatley, R. Hitzemann, A.D. Chen, S.L. Dewey, N. Pappas, Decreased striatal dopaminergic responsiveness in detoxified cocaine-dependent subjects, Nature 386 (1997) 830–833.
[478] C.T. Wang, R.L. Huang, M.Y. Tai, Y.F. Tsai, M.T. Peng, Dopamine release in the nucleus accumbens during sexual behavior in prenatally stressed adult male rats, Neurosci. Lett. 200 (1995) 29–32.

[479] E.M. Wasserman, Y. Gomita, C.R. Gallistel, Pimozide blocks reinforcement but not priming from MFB stimulation in the rat, Pharmacol. Biochem. Behav. 17 (1982) 783–787.
[480] F. Weiss, A. Markou, M.T. Lorang, G.F. Koob, Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration, Brain Res. 593 (1992) 314–318.
[481] C.C. Welch, E.M. Kim, M.K. Grace, C.J. Billington, A.S. Levine, Palatability-induced hyperphagia increases hypothalamic Dynorphin peptide and mRNA levels, Brain Res. 721 (1996) 126–131.
[482] B.H. Westerink, A. Teisman, J.B. de Vries, Increase in dopamine release from the nucleus accumbens in response to feeding: a model to study interactions between drugs and naturally activated dopaminergic neurons in the rat brain, Naunyn-Schmiedeberg's Arch. Pharmacol. 349 (1994) 230–235.
[483] I.Q. Whishaw, S.B. Dunnett, Dopamine depletion, stimulation or blockade in the rat disrupts spatial navigation and locomotion dependent upon beacon or distal cues, Behav. Brain Res. 18 (1985) 11–29.
[484] I.Q. Whishaw, W.T. O'Connor, S.B. Dunnett, Disruption of central cholinergic systems in the rat by basal forebrain lesions or atropine: effects on feeding, sensorimotor behaviour, locomotor activity and spatial navigation, Behav. Brain Res. 17 (1985) 103–115.
[485] I.Q. Whishaw, W.T. O'Connor, S.B. Dunnett, The contributions of motor cortex, nigrostriatal dopamine and caudate-putamen to skilled forelimb use in the rat, Brain 109 (1986) 805–843.
[486] F.J. White, Cocaine and the serotonin saga, Nature 393 (1998) 118–119.
[487] N.M. White, Control of sensorimotor function by dopaminergic nigrostriatal neurons: influence on eating and drinking, Neurosci. Biobehav. Rev. 10 (1986) 15–36.
[488] N.M. White, Reward or reinforcement: what's the difference?, Neurosci. Biobehav. Rev. 13 (1989) 181–186.
[489] N.M. White, Addictive drugs as reinforcers: multiple partial actions on memory systems, Addiction 91 (1996) 921–949, discussion 951-965.
[490] N.M. White, M.G. Packard, N. Hiroi, Place conditioning with dopamine D1 and D2 agonists injected peripherally or into nucleus accumbens, Psychopharmacology 103 (1991) 271–276.
[491] I. Wickelgren, Getting the brain's attention [news], Science 278 (1997) 35–37.
[492] G.V. Williams, E.T. Rolls, C.M. Leonard, C. Stern, Neuronal responses in the ventral striatum of the behaving macaque, Behav. Brain Res. 55 (1993) 243–252.
[493] C. Wilson, G.G. Nomikos, M. Collu, H.C. Fibiger, Dopaminergic correlates of motivated behavior: importance of drive, J. Neurosci. 15 (1995) 5169–5178.
[494] T.D. Wilson, J.W. Schooler, Thinking too much: introspection can reduce the quality of preferences and decisions, J. Pers. Soc. Psychol. 60 (1991) 181–192.
[495] P. Winkielman, R.B. Zajonc, N. Schwarz, Subliminal affective priming resists attributional interventions, Cognition and Emotion 11 (1997) 433–465.
[496] P. Winn, The lateral hypothalamus and motivated behavior: an old syndrome reassessed and a new perspective gained, Cur. Dir. Psychol. Sci. 4 (1995) 182–187.
[497] R.A. Wise, The dopamine synapse and the notion of 'pleasure centers' in the brain, Trends Neurosci. 3 (1980) 91–95.
[498] R.A. Wise, Common neural basis for brain stimulation reward, drug reward, and food reward, in: B.G. Hoebel, D. Novin (Eds.), The Neural Basis of Feeding and Reward, Haer Institute for Electrophysiological Research, Brunswick, Maine, 1982, pp. 445–454.
[499] R.A. Wise, Neuroleptics and operant behavior: the anhedonia hypothesis, Behav. Brain Sci. 5 (1982) 39–87.
[500] R.A. Wise, The anhedonia hypothesis: Mark III, Behav. Brain Sci. 8 (1985) 178–186.
[501] R.A. Wise, Sensorimotor modulation and the variable action pattern (VAP): Toward a noncircular definition of drive and motivation, Psychobiology 15 (1987) 7–20.
[502] R.A. Wise, The brain and reward, in: J.M. Liebman, S.J. Cooper (Eds.), The Neuropharmacological Basis of Reward, Clarendon Press, Oxford, U.K., 1989, pp. 377–424.
[503] R.A. Wise, Neuroleptic-induced anhedonia: Recent studies, in: C.A. Tamminga, C.S. Schulz (Eds.), Schizophrenia Research. Advances in Neuropsychiatry and Psychopharmacology, Vol. 1., Raven Press, Publishers, New York, NY, US, 1991, pp. 323–331.
[504] R.A. Wise, A brief history of the anhedonia hypothesis, in: C.R. Legg, D. Booth (Eds.), Appetite: Neural and Behavioural Bases, Oxford Univ. Press, New York, 1994, pp. 243–263.
[505] R.A. Wise, Addictive drugs and brain stimulation reward, An. Rev. Neurosci. 19 (1996) 140–319.
[506] R.A. Wise, Neurobiology of addiction, Cur. Opin. Neurobio. 6 (1996) 243–251.
[507] R.A. Wise, M.A. Bozarth, Brain mechanisms of drug reward and euphoria, Psychiat. Med. 3 (1985) 445–460.
[508] R.A. Wise, M.A. Bozarth, A psychomotor stimulant theory of addiction, Psychol. Rev. 94 (1987) 469–492.
[509] R.A. Wise, V. Dawson, Diazepam-induced eating and lever pressing for food in sated rats, J. Comp Physiol. Psychol. 86 (1974) 930–941.
[510] R.A. Wise, P. Leone, R. Rivest, K. Leeb, Elevations of nucleus accumbens dopamine and DOPAC levels during intravenous heroin self-administration, Synapse 21 (1995) 140–148.
[511] R.A. Wise, P. Newton, K. Leeb, B. Burnette, D. Pocock, J.B. Justice Jr., Fluctuations in nucleus accumbens dopamine concentration during intravenous cocaine self-administration in rats, Psychopharmacology 120 (1995) 10–20.
[512] R.A. Wise, L. Raptis, Effects of naloxone and pimozide on initiation and maintenance measures of free feeding, Brain Res. 368 (1986) 62–68.
[513] R.A. Wise, P.-P. Rompre, Brain dopamine and reward, An. Rev. Psychol. 40 (1989) 191–225.
[514] R.A. Wise, J. Spindler, H. deWit, G.J. Gerberg, Neuroleptic-induced 'anhedonia' in rats: pimozide blocks reward quality of food, Science 201 (1978) 262–264.
[515] D.L. Wolgin, J. Cytawa, P. Teitelbaum, Sensory neglect produced by lateral hypothalamic damage, Science 174 (1971) 523–525.
[516] P.L. Wood, T.S. Rao, Morphine stimulation of mesolimbic and mesocortical but not nigrostriatal dopamine release in the rat as reflected by changes in 3-methoxytyramine levels, Neuropharmacology 30 (1991) 399–401.
[517] S. Xenakis, A. Sclafani, The effects of pimozide on the consumption of a palatable saccharin-glucose solution in the rat, Pharmacol. Biochem. Behav. 15 (1981) 435–442.
[518] S. Xenakis, A. Sclafani, The dopaminergic mediation of a sweet reward in normal and VMH hyperphagic rats, Pharmacol. Biochem. Behav. 16 (1982) 293–302.
[519] J.S. Yeomans, A. Mathur, M. Tampakeras, Rewarding brain stimulation: role of tegmental cholinergic neurons that activate dopamine neurons, Behav. Neurosci. 107 (1993) 1077–1087.
[520] M.R. Yeomans, R.W. Gray, Effects of naltrexone on food intake and changes in subjective appetite during eating: evidence for opioid involvement in the appetizer effect, Physiol. Behav. 62 (1997) 15–21.
[521] M.R. Yeomans, P. Wright, H.A. Macleod, J.A. Critchley, Effects of nalmefene on feeding in humans. Dissociation of hunger and palatability, Psychopharmacology 100 (1990) 426–432.
[522] R.A. Yokel, R.A. Wise, Increased lever pressing for amphetamine after pimozide in rats: implications for a dopamine theory of reward, Science 187 (1975) 547–549.
[523] R.A. Yokel, R.A. Wise, Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats, Psychopharmacology 48 (1976) 311–318.

[524] M. Yoshioka, M. Matsumoto, H. Togashi, H. Saito, Effect of conditioned fear stress on dopamine release in the rat prefrontal cortex, Neurosci. Lett. 209 (1996) 201–203.
[525] A.M. Young, R.G. Ahier, R.L. Upton, M.H. Joseph, J.A. Gray, Increased extracellular dopamine in the nucleus accumbens of the rat during associative learning of neutral stimuli, Neuroscience 83 (1998) 1175–1183.
[526] A.M. Young, M.H. Joseph, J.A. Gray, Latent inhibition of conditioned dopamine release in rat nucleus accumbens, Neuroscience 54 (1993) 5–9.
[527] P.T. Young, The role of affective processes in learning and motivation, Psychol. Rev. 66 (1959) 1104–1125.
[528] R.B. Zajonc, Feeling and thinking: preferences need no inferences, Am. Psychol. 35 (1980) 151–175.
[529] H.P. Zeigler, M.F. Jacquin, M.G. Miller, Trigeminal sensorimotor mechanisms and ingestive behavior, Neurosci. Biobehav. Rev. 8 (1984) 415–423.
[530] D.A. Zellner, K.C. Berridge, H.J. Grill, J.W. Ternes, Rats learn to like the taste of morphine, Behav. Neurosci. 99 (1985) 290–300.
[531] M.J. Zigmond, E.M. Stricker, Deficits in feeding behavior after intraventricular injection of 6-hydroxydopamine in rats, Science 177 (1972) 1211–1214.