ELSEVIER

Brain Research Reviews 31 (1999) 6–41

BRAIN RESEARCH REVIEWS

www.elsevier.com/locate/bres

Full-length review

The role of nucleus accumbens dopamine in motivated behavior: a unifying interpretation with special reference to reward-seeking

Satoshi Ikemoto [a,*], Jaak Panksepp [b]

[a] *Behavioral Neuroscience Branch, Intramural Research Program, National Institute on Drug Abuse, Baltimore, MD 21224, USA*
[b] *Department of Psychology, Bowling Green State University, Bowling Green, OH 43402, USA*

Accepted 7 September 1999

Abstract

Studies addressing behavioral functions of dopamine (DA) in the nucleus accumbens septi (NAS) are reviewed. A role of NAS DA in reward has long been suggested. However, some investigators have questioned the role of NAS DA in rewarding effects because of its role in aversive contexts. As findings supporting the role of NAS DA in mediating aversively motivated behaviors accumulate, it is necessary to accommodate such data for understanding the role of NAS DA in behavior. The aim of the present paper is to provide a unifying interpretation that can account for the functions of NAS DA in a variety of behavioral contexts: (1) its role in appetitive behavioral arousal, (2) its role as a facilitator as well as an inducer of reward processes, and (3) its presently undefined role in aversive contexts. The present analysis suggests that NAS DA plays an important role in sensorimotor integrations that facilitate flexible approach responses. Flexible approach responses are contrasted with fixed instrumental approach responses (habits), which may involve the nigro-striatal DA system more than the meso-accumbens DA system. Functional properties of NAS DA transmission are considered in two stages: unconditioned behavioral invigoration effects and incentive learning effects. (1) When organisms are presented with salient stimuli (e.g., novel stimuli and incentive stimuli), NAS DA is released and invigorates flexible approach responses (invigoration effects). (2) When proximal exteroceptive receptors are stimulated by unconditioned stimuli, NAS DA is released and enables stimulus representations to acquire incentive properties within specific environmental context. It is important to make a distinction that NAS DA is a critical component for the conditional *formation* of incentive representations but not the *retrieval* of incentive stimuli or behavioral expressions based on over-learned incentive responses (i.e., habits). Nor is NAS DA essential for the cognitive perception of environmental stimuli. Therefore, even without normal NAS DA transmission, the habit response system still allows animals to perform instrumental responses given that the tasks take place in fixed environment. Such a role of NAS DA as an incentive-property constructor is not limited to appetitive contexts but also aversive contexts. This dual action of NAS DA in invigoration and incentive learning may explain the rewarding effects of NAS DA as well as other effects of NAS DA in a variety of contexts including avoidance and unconditioned/conditioned increases in open-field locomotor activity. Particularly, the present hypothesis offers the following interpretation for the finding that both conditioned and unconditioned aversive stimuli stimulate DA release in the NAS: NAS DA invigorates approach responses toward 'safety'. Moreover, NAS DA modulates incentive properties of the environment so that organisms emit approach responses toward 'safety' (i.e., avoidance responses) when animals later encounter similar environmental contexts. There may be no obligatory relationship between NAS DA release and positive subjective effects, even though these systems probably interact with other brain systems which can mediate such effects. The present conceptual framework may be valuable in understanding the dynamic interplay of NAS DA neurochemistry and behavior, both normal and pathophysiological.

Keywords: Learning; Operant; Pavlovian; Arousal; Aversion; Novelty; Self-stimulation; Feeding; Sexual behavior; Conditioned reinforcement; Locomotion; Avoidance; Latent inhibition; Incentive motivation

* Corresponding author. Behavioral Neuroscience Branch, Intramural Research Program, National Institute on Drug Abuse, 5500 Nathan Shock Drive, Baltimore, MD 21224, USA. Fax: +1-410-550-1612; e-mail: sikemoto@intra.nida.nih.gov

0165-0173/99/$ - see front matter
PII: S0165-0173(99)00023-5

Contents

1. Introduction

Brain dopamine (DA) has been linked to rewarding processes in the brain for three decades. Two decades ago, Wise [299] and Wise et al. [304] suggested a pleasure or hedonic role for brain DA. Since then, extensive research on the functions of DA has refined such ideas, and our thinking about DA functions has evolved substantially [16,21,68,136,162,181,208,219,290,303]. Although there is no robust evidence to support direct involvement of DA in hedonic effects, which resemble the consummatory aspects of reward phenomena, many lines of evidence suggest that the DA neurons from the ventral tegmental area (VTA) that innervate the nucleus accumbens septi (NAS), referred to as the meso-accumbens DA system, play an important role in mediating reward-seeking effects by presently unknown mechanisms.

However, some workers have questioned such a role of NAS DA because of its involvement in other functions, especially aversive functions. For example, Gray et al. [88] stated that ''We believe... that there is no special relationship between dopamine release in the nucleus accumbens and positive reinforcement'' (p. 1548). Hence, an essential question is whether or not NAS DA is involved in both reward-seeking effects as well as other effects in negative contexts that seem apparently incompatible with the former effects. The aim of the present paper is to review findings regarding the behavioral functions of NAS DA and to examine whether a unified conception of NAS DA in both reward-seeking and yet unidentified functions in aversive contexts can be constructed. The present paper shall focus on the functions of DA in the NAS as clarified primarily through research on laboratory rats.

Studies employing systemic manipulations of DA systems are not comprehensively reviewed in the present paper. Obviously, systemic manipulations can modify activity not only in the meso-accumbens DA system but in other systems as well, particularly the physically more robust DA system of the nigro-striatal continuum. Although DA synapses in the NAS (a portion of the ventral striatum) and caudate–putamen (the dorsal striatum) share similarities in cytoarchitectural organizations, these regions receive distinct afferent inputs and send distinct efferent projections [91]. Such differential anatomical connections reflect functional differences between the NAS and caudate–putamen (e.g., Refs. [7,8,39,40,47,59,127,210,220, 273]), including reward-related effects being clearly elaborated by NAS circuitry but not so in various other DA terminal regions [31,32,34,37,126,247,260].

The major aim of this paper is to focus on the specific functions of NAS DA, cultivating the emerging recognition that different components of ascending DA systems may govern quite different aspects of psychobehavioral integration within the brain, while not denying that such diverse functions may all be subsumed under the broad conceptual umbrella that all brain DA systems promote widespread sensory–motor arousal and competence within the brain. The major claim of this paper is that available evidence indicates that NAS DA is an essential neurochemical system for animals to flexibly approach various rewards, both positive as well as avoidance of negative states, and to construct learned incentive structures in the brain. Our goal is also to provide an extensive literature review embedded in relevant historical perspectives to allow new investigators to become conversant with the many lines of work and those that are relevant for this rich field of inquiry. However, before discussing specific functional issues, we shall provide a brief summary of relevant methodological and anatomical considerations.

1.1. Methodological and conceptual background issues

Several behavioral test procedures provide major methodological frameworks for modern neurobiological investigations of DA function. These methodologies allow investigators to quantify behavioral responses and to define responses in relation to specific environmental changes. Of course, existing conceptual frameworks constrain the ways in which empirical findings are interpreted.

Pavlov [180] developed an ingenious experimental protocol that enabled investigators to study the learning of stimulus–response association using a simplified methodology. In the Pavlovian (or classical) conditioning procedure, biologically important stimuli are defined as *unconditioned stimuli* because they can trigger *unconditioned responses*, that are 'inborn' or 'species-typical' reflexes [180]. Examples of unconditioned stimuli are food, water, and various noxious stimuli. When other comparatively neutral sensory stimuli precede the presentation of such unconditional stimuli, and this pairing is repeated, conditioning occurs. *Conditioned responses* that were not present prior to such pairings can be now observed when the previously neutral sensory stimuli are presented alone. The sensory stimuli are now referred to as *conditioned stimuli*. An important feature of this paradigm is that the resulting learned responses of organisms (i.e., conditioned responses) have no consequence on the presentation of unconditioned stimuli (even though they may have consequences on how organisms cope with such stimuli). This paradigm can be used to study factors and neural mechanisms involved in the formation of central states that anticipate future events [102] (i.e., even subjectively experienced causal relationships among environmental stimuli).

Another important methodology is the operant procedure. Reinforcers are those stimuli or events that increase the future probability of the occurrence of responses, when those responses are associated with the presentation or removal of some biologically important stimuli (i.e., unconditioned stimuli in the Pavlovian procedure). For example, animals increase responses that result in the presentation of incentive stimuli such as food and sexual stimuli (positive reinforcers), as well as responses that result in the

removal of noxious stimuli (negative reinforcers). Skinner [237] made a distinction between responses that are *elicited by stimuli* (i.e., the Pavlovian procedure) and responses that are *emitted by organisms* (as measured by the operant or instrumental procedure). Skinner refers to the former as respondents and the latter as operants, with both yielding conditioned responses. On this foundation, Skinner created a rigorous methodology to study operant or instrumental responses, which, to this day, are contrasted with conditioned responses of the Pavlovian variety (see Ref. [204]).

Still another procedure that has been utilized frequently for studying neural mechanisms of rewarding effects is the place-conditioning paradigm (see Ref. [36,99,223,268]). During the conditioning phase, animals receive a stimulus in one compartment of the place-conditioning chamber, and typically receive a control stimulus in another compartment. For the testing phase, no stimulus is presented and animals are free to go to either compartment. Place-preference can be produced by positive reinforcers such as food, sexual stimuli and drugs of abuse; typically, animals spend more time in the compartment paired with positive reinforcers. Place-avoidance can be obtained by negative reinforcers; animals spend less time in the compartment paired with the aversive events. Thus, the conditioning phase of this procedure appears to be based on long time-frame Pavlovian contingencies, but the responses measured during testing are more akin to instrumental response; thus, this procedure can be viewed as a blend of instrumental and Pavlovian conditioning.

The same stimuli such as food, sexual, and noxious stimuli may be labeled somewhat differently depending on the research paradigm used. To unify related concepts, this paper refers to these biologically relevant stimuli as unconditioned stimuli. Moreover, *those unconditioned stimuli that elicit approach responses are defined as rewards*. The reward concept is useful because NAS DA appears to be involved in the acquisition of Pavlovian conditioning [211,274], operant conditioning (see Section 6.3) and perhaps place conditioning as well. There are, however, some serious concerns in the use of the reward concept. First, the term ‘reward’ has been defined quite differently depending on theoretical positions or phenomena being studied (e.g., Refs. [286,293]). Second, it can carry additional excess meaning for certain subjective effects such as pleasure. In the present paper, reward is simply used to refer to unconditioned stimuli that can evoke approach behavioral effects as defined above, *without necessarily implying any subjective positive hedonic effects*.

1.2. Anatomical considerations

DA in the NAS is released by the neurons whose cell bodies are located in the ventromedial mesencephalon (A10) (Refs. [50,65,77,139,270]; for review, see Ref. [164]), primarily in a zone commonly known as the VTA [193]. Fig. 1A depicts the location of the meso-accumbens DA system in relation to other structures. The NAS can be divided into two major sub-regions: the shell (the ventro-

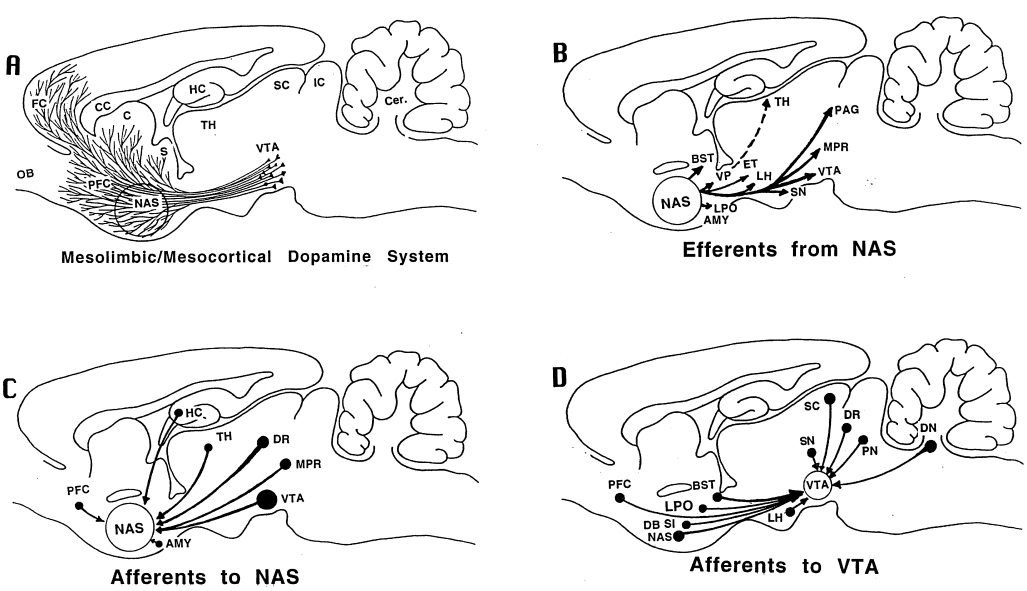

Fig. 1. Schematic diagrams of the rat brain. (A) Ascending projections of A10 DA neurons (localized in the VTA) innervating to limbic regions including the NAS (the mesolimbic DA system) as well as cortical regions (the mesocortical DA system). (B) Major efferent projections of the NAS. (C) Afferent projections to the NAS. (D) Afferent projections to the VTA. Abbreviations — AMY, amygdala; BST, bed nucleus of stria terminalis; C, caudate–putamen; CC, corpus callosum; DB, diagonal band of Broca; DN, dentate nucleus; DR, dorsal raphe; ET, entopeduncular nucleus; FC, frontal cortex; HC, hippocampus; IC, inferior colliculus; LH, lateral hypothalamus; LPO, lateral preoptic area; MPR, mesopontine reticular nuclei; OB, olfactory bulb; PAG, periaqueductal gray; PFC, prefrontal cortex; PN, parabrachial nucleus; SC, superior colliculus; SI, substantia innominata; SN, substantia nigra; TH, thalamus; VP, ventral pallidum.

medial part) and the core (the dorsolateral part) which have different connectivities [92,312]. The shell sends efferent projections to the ventromedial ventral pallidum, extended amygdala (including the bed nucleus of stria terminalis, central amygdaloid nucleus, and interconnecting sublenticular area), lateral preoptic area, lateral hypothalamus, entopeduncular nucleus, VTA, mediodorsal substantia nigra pars compacta, mesopontine reticular formation, and periaqueductal gray. The core sends major efferent projections to the dorsolateral ventral pallidum, entopeduncular nucleus, lateral part of VTA, and substantial nigra. Fig. 1B summarizes efferent projections of the NAS.

The VTA and NAS receive afferent inputs from a variety of regions throughout the brain (see Fig. 1C and D). The inputs from these structures influence the transmission properties of NAS DA circuitry. The VTA [171,192] receives afferent inputs from many forebrain regions: the prefrontal cortex, NAS, bed nucleus of stria terminalis, diagonal band of Broca, substantia innominata, lateral preoptic area, and lateral hypothalamus. The lower brainstem projections to the VTA include the superior colliculus, substantia nigra, dorsal raphe, parabrachial nucleus, and dentate nucleus of cerebellum. The NAS [91] also receives afferent inputs from forebrain structures (including the medial prefrontal cortex, amygdala, hippocampus, thalamus) as well as mesopontine areas (including VTA, dorsal raphe, and mesopontine reticular formation) (see Ref. [157] for differential afferents between the shell and core).

2. A brief overview of empirical findings on NAS DA and behavior

Many lines of evidence support the role of NAS DA in reward-seeking processes. However, we presently need to identify more precisely those psychobehavioral processes in which NAS DA are specifically involved, since emerging evidence indicates that NAS DA is also involved in some types of aversive processes.

2.1. Reward-related functions

The most compelling evidence that supports the role of NAS DA in rewarding effects is that animals self-administer chemicals that mimic DA (i.e., direct DA receptor agonists) or increase extracellular DA (i.e., indirect agonists, e.g., amphetamine) directly into the NAS. In operant procedures, the response contingent delivery of DA agonists directly into the NAS can serve as a reinforcer for that response (i.e., increase its future probability of occurrence or strength of association). Hoebel et al. [98] and Phillips et al. [191] reported that rats self-administer D-amphetamine, which increases extracellular DA, within the NAS. Carlezon et al. [35] showed that rats self-administer nomifensine, a DA reuptake blocker, into the NAS, and Ikemoto et al. [107] found that rats acquire and maintain self-administration of direct DA receptor agonists, a mixture of SKF 38393 (a D1-type agonist) and quinpirole (a D2-type agonist), into the NAS. Within the NAS sub-regions, the shell appears to be responsible for mediating the reinforcing effect of both direct [107] and indirect [35] DA agonists.

Using the place-preference procedure, rewarding effects of D-amphetamine and direct DA agonists have also been shown. Given a choice between environments where animals previously received microinjections of DA agonists (direct or indirect) into the NAS or environments where they received intra-NAS injections of vehicle, animals spend more time in the drug-paired environments [37,38,287]. Such place-preference effects are selective to the NAS. Place-preference conditioning did not occur when the drug was delivered into various other DA terminal regions including the medial prefrontal cortex, caudate–putamen, amygdala or area postrema [37]. Thus, these studies using self-administration and place-conditioning paradigms suggest that facilitation of NAS DA transmission can serve as a reward.

The brain-stimulation reward paradigm played a major role in initiating the idea of brain DA being a central substrate of brain reward (Refs. [49,137,140]; also see the early antecedents of specific DA theories in Refs. [66,295]), which had their origin in the broader catecholamine theory of reward [246]. Briefly, animals can readily learn to make an arbitrary response (e.g., lever-pressing) when a brief electrical stimulation into a discrete region of the brain follows these responses [172] (hence, this is referred to as self-stimulation and the stimulation as brain-stimulation reward). Along the medial forebrain bundle, a major pathway interconnecting the midbrain and forebrain, animals would exhibit remarkably vigorous self-stimulation behavior. Rats readily acquire a response rate of 100 min^{-1} for contingent electrical stimulation and sustain such levels of responding for hours until physical exhaustion.

Systemic manipulations of brain DA receptors have marked effects on self-stimulation behavior [46,72,74–76,248]. DA agonists and antagonists, respectively, facilitate and disrupt self-stimulation behavior. Additional studies indicated that such effects produced by systemic manipulations of DA systems appear to be largely mediated by the NAS. Intra-NAS injections of amphetamine and DA antagonists, respectively, facilitate and disrupt self-stimulation behavior [31,45,247,248], while microinjections of these drugs into the caudate–putamen have little or no effect. These manipulations do not merely effect motoric aspects of self-stimulation. Antagonist-treated animals can exhibit a normal level of responding if the intensity of electrical stimulation is increased. These results are consistent with the role of NAS DA in reward facilitation. It should also be noted that the application of brain stimulation in the medial forebrain bundle results in

increases of NAS DA levels, whether rats administer the stimulation [23,188,189,199,254] or experimenters deliver it non-contingently [84,93,199].

Further support comes from research on substance abuse. Mammalian species readily acquire and maintain self-administration of psychostimulants such as amphetamine and cocaine [231]. Amphetamine and cocaine are known to stimulate DA release and block DA reuptake in the NAS, respectively. Indeed, the meso-accumbens DA system appears to play a critical role in mediating reinforcing effects of these psychomotor-stimulants (for review, see Refs. [133,297]). Depletion of DA by 6-hydroxydopamine (6-OHDA) lesions within the ventral striatum, whose major component is the NAS, abolishes or severely disrupts intravenous self-administration of these drugs [33,145, 183,212,213]. The potential importance of NAS DA in substance abuse is further highlighted by findings that many other drugs of abuse, including ethanol, opioids, nicotine and cannabis, share the ability to selectively stimulate DA release within the ventral striatum (e.g., Refs. [34,115,116,184,259,278,301,308]). In summary, these highly consistent lines of evidence affirm that NAS DA plays an important role in rewarding processes, but its precise nature remains controversial.

2.2. Other functions of NAS DA

Several other recent lines of evidence highlight the need for a more specific conceptualization of NAS DA in the control of behavior. Ikemoto and Panksepp [112] reported results that challenge conventional understandings of the role of NAS DA in specific aspects of rewarding effects. In the experiment, rats were initially trained to traverse a runway in which the opportunity to consume sucrose solution was given in a goal box. In a session, rats were given five trials; each trial consisted of the opportunity to run to the goal box and the opportunity to consume a sucrose solution for 60 s. Running speed and the consumption of sucrose solution were monitored. After establishing a stable baseline of responding, effects of intra-NAS injections of the DA antagonist, *cis*-flupentixol (α-flupenthixol), were examined (see Fig. 2). The highest dose of flupentixol (25 μg/side) severely disrupted the instrumental response for the reward, while having no apparent effect on the sugar consumption. These results raise problems for any simplistic conception of NAS DA involvement in rewarding processes. As is well-established, a distinction between instrumental responding for rewards (conditioned appetitive behaviors) and the consumption of rewards is needed. Similar patterns of results have long been evident after *systemic* administration of DA receptor antagonists, raising the classic concern as to whether the nature of the resulting deficits is related to motoric or rewarding effects (e.g., Refs. [67,72,215,298,305]). Such debates cannot be resolved until the brain dynamics of motoric and rewarding processes has been more clearly distinguished.

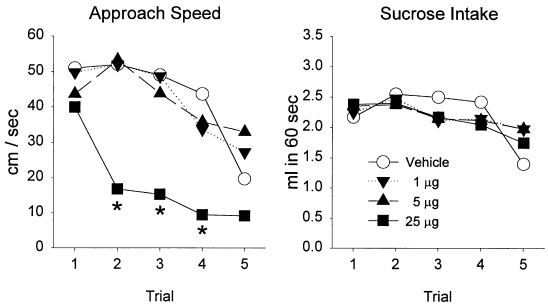

Fig. 2. Effects of DA receptor blockade in the NAS on running speed and consumption of sucrose solution. Rats were trained to traverse on a runway to obtain a reward. After each run, they were permitted to consume sucrose solution from a sipper for 60 s. Five trials were given in a session. Rats received intra-NAS injections of one of pharmacological treatments (1, 5, or 25 μg/side *cis*-flupentixol, a DA receptor antagonist, or vehicle) in each session. Microinjections of 25 μg *cis*-flupentixol markedly decreased running speed for the reward, while having no apparent effect on the consumption of sucrose solution. Figures are based on data [112]. $^{*}p < 0.05$, compared to respective point with vehicle treatment.

Furthermore, the Ikemoto and Panksepp study suggests that intra-NAS injections of DA antagonists have no apparent effect on instrumental responding on the first trial of the session but ever increasing effects on subsequent trials. Similar experience-dependent effects have been long observed with systemic administration of DA antagonists (e.g., Refs. [71,284,304,305]). For example, Fouriezos et al. [71] reported that after systemic treatment of the DA antagonist, pimozide, initial response rates of self-stimulation were not affected; self-stimulation only deteriorated as testing progressed. Using a water-maze escape paradigm, Whishaw et al. [284] found an experience-dependent decrement of water-maze performance between sessions with systemic treatment of DA antagonists. Animals that have been treated with DA antagonists but have not been given the water-maze test do not exhibit any deficit in subsequent sessions in a drug-free state. Although these systemic studies do not indicate the relevant action sites of DA antagonists, the Ikemoto and Panksepp study suggests that the NAS is at least one of the sites mediating experience-dependent performance deficits.

Another line of research that challenges certain traditional ideas regarding NAS DA in reward is that responding for different reinforcers is not uniformly affected by *chronic* destruction of the meso-accumbens DA system. Although acute manipulations of NAS DA by microinjection techniques produce some initial effects on instrumental responses for some rewards, 6-OHDA-induced NAS DA lesions have only transient effects on responding maintained by food reward [141,239], responding maintained by brain-stimulation reward [303], and the self-administration of ethanol [64,109,201] or opioids [58,78,183]. Sustained deficits are not apparent even in cases with depletions of NAS DA of 90% or greater.

Finally, NAS DA also appears to play some functions in aversive contexts (see Refs. [217,219]). First, DA release in the NAS appears to be facilitated by aversive, 'stressful' stimuli such as foot shock and tail pinch [1,17,154,262] and some anxiogenic pharmacological manipulations including beta-CCE and FG 7142 (Refs. [17,152]; but see Ref. [11]). Second, presentations of environmental cues associated with aversive events are also sufficient to trigger NAS DA release [105,222,289, 309,311]. Third, conditioned avoidance behavior is disrupted by DA depletion with intra-NAS 6-OHDA injection [154] as well as by microinjection of the D2 antagonist, sulpiride, into the NAS but not the caudate–putamen [273]. Finally, Ikemoto and Goeders [108] reported that microinjections of DA agonists into the NAS at lower doses than into the caudate–putamen or medial prefrontal cortex produce heightened plasma levels of the 'stress' hormone, corticosterone. How will all of these diverse effects be explained coherently with a single integrative concept? After a brief review of the history of this field, we will develop the idea that this can be achieved by the postulation that NAS DA is essential for invigorating approach behaviors and the formation of incentive representations in the brain.

3. A brief conceptual history of brain DA and behavioral function

The aim of this section is to provide a brief overview of classical literature within which the specific functions of NAS DA will be discussed. In other words, to further clarify the specific role of NAS DA in the control of behavior, it is necessary to specify the types of natural brain functions in which NAS DA normally participates in animals' every-day affairs. We will first review several traditional concepts for the basic functional organization of the central nervous system (CNS) in the mediation of appetitive behaviors. Then the appetitive motivational perspective will be divided into two dominant themes: one emphasizing neuroethology and the other emphasizing learning mechanisms. The former perspective provides a global approach-seeking concept, of which DA neurotransmission in the NAS is one component, and the latter highlights the manner in which brain DA systems interface with learning mechanisms of the brain.

3.1. Appetitive and consummatory concepts, and approach and withdrawal concepts

Sherrington [235], who pioneered research on neural mechanisms of spinal reflexes at the turn of the century, also provided a general conceptual scheme for how the CNS generated adaptive behavior. Specifically, Sherrington categorized behavior globally in terms of *anticipatory* and *consummatory reactions*. Proximal tactile and taste receptors were envisioned to inform organisms about how they should react immediately to enhance their welfare, yielding consummatory reactions such as ingestion of various nutrients and withdrawal from life-threatening events. On the other hand, the visual, auditory, and olfactory receptors — what he called 'distance-receptors' — provide information at a spatiotemporal distance, giving organisms the opportunity to *prepare* for environmental changes (anticipatory reactions). In that scheme, consummatory reactions were roughly equivalent to Pavlov's unconditioned responses, whereas anticipatory reactions included conditioned responses. More recent data [15] suggest that consummatory reactions are largely processed by the sensorimotor integrative systems within the lower levels of the neuroaxis, such as the hindbrain and spinal cord, while higher levels of the CNS, the forebrain and midbrain, are more essential for anticipatory reactions. This is not to suggest that the higher CNS is not involved in consummatory decisions, or the lower CNS is not necessary for the expression of anticipatory reactions. Both of these processes are hierarchically organized through much of the CNS, but the primary focus of control is largely at different levels of the neuroaxis (see also Ref. [95]). In summary, Sherrington's conception yielded initial ideas on how various intrinsic functions of the CNS prepare organisms to cope with for constantly changing, dynamic environments.

In addition to Sherrington's consummatory and anticipatory conceptions, the emergence of approach and withdrawal concepts needs to be mentioned. Schneirla [224] was among the first to argue for two fundamental behavioral processes: one for approach and another for withdrawal that might be completely distinct systems. He stated [224]: ''Much evidence shows that in all animals, the species-typical pattern of behavior is based upon biphasic, functionally opposed mechanisms insuring approach or withdrawal reactions according to whether stimuli of low or high intensity, respectively, are in effect. This is an oversimplified statement; however, in general, what we shall term the *A*-type of mechanisms, underlying approach, favors adjustments such as food-getting, shelter-getting, and mating; the *W*-type, underlying withdrawal, favors adjustments such as defense, huddling, flight, and other protective reactions. Also, through evolution, higher psychological levels have arisen in which through ontogeny such mechanisms can produce new and qualitatively advanced types of adjustment to environmental conditions'' (p. 4).

In sum, it appears that there should be consummatory as well as anticipatory components for both approach and withdrawal brain systems. Indeed, Konorski [132] classified basic organismic activities into four categories: 'preservative preparatory', 'preservative consummatory', 'protective preparatory', and 'protective consummatory'. The term 'preservative' corresponds to approach, while the term 'protective' corresponds to withdrawal. Like Sher-

rington, consummatory refers to terminal responding in both appetitive as well as aversive contexts.

3.2. Discovery of brain self-stimulation phenomena and ethological approach concepts

The discovery of self-stimulation phenomena (mentioned above) by Olds and Milner [173] dramatically advanced our understanding of the neural mechanisms of reward. The additional discovery of some very perplexing behavioral aspects of the arousal that could be achieved by stimulating along the lateral hypothalamic medial forebrain bundle (LH MFB) generated various new theoretical perspectives for conceptualizing brain self-stimulation and related phenomena. Electrical stimulation of the LH MFB can elicit appetitive approach as well as consummatory-related behaviors (e.g., feeding, drinking and gnawing), while stimulation at those site is also reinforcing (i.e., yielding self-stimulation). Glickman and Schiff [79] offered a biological reinforcement theory that makes an explicit connection between approach responses and positive reinforcement, suggesting common underlying neural mechanisms. In their words, ''These species-specific response sequences [approach and withdrawal] are part of the organism's evolutionary heritage. If one accepts the biological wisdom of evolution, it is not circular to suggest that the performance of these approach and withdrawal sequences are, respectively, positively and negatively reinforcing'' (p. 102).

According to Glickman and Schiff's view, each of these approach-type behaviors has its own distinct circuits at the level of the lateral hypothalamic area. Trowill et al. [266] proceeded to argue that self-stimulation could be subsumed under a unitary incentive construct. Indeed, Valenstein et al. [271] demonstrated that various, seemingly specific, goal-directed manifestations of these system during electrical stimulation (e.g., feeding, drinking and gnawing) were, in fact, functionally completely interchangeable with each other. It highlighted how contextual variables could mold the behavioral manifestations induced by artificial arousal of what appeared to be a functionally unitary behavioral control system (for full discussion, see Refs. [177,179], and for a different conception, see Ref. [296]).

Although Valenstein chose not to offer any theoretical resolution of this matter, claiming only that the underlying systems were plastic, others did try to resolve issues in theoretically coherent ways and postulated that the brain contained a coherently operating general-purpose foraging system that aroused unconditional behavioral tendencies to seek out and to anticipate rewards in the environment [174–177,179]. Panksepp [177] wrote ''one of the main functions of transhypothalamic 'reward' circuits may be the elaboration of anticipatory behavior. At the highest cognitive levels, the activity of this system may be expressed in the elaboration of expectancies and the quality of vigilance states. At a lower level of organization, this system may activate an organism's tendency to approach and investigate its environment. At the lowest levels of neural organization, this same system may control the gating of activity within incoming sensory and outgoing motor reflex systems'' (p. 301). In sum, Panksepp [175,177,179] also hypothesized that the ascending DA systems help constitute a general-purpose foraging system, which lies at the core of a postulated 'expectancy sensorimotor command system'.

Ikemoto and Panksepp [113] studied trajectories of LH MFB systems, including prefrontal cortex and mesopontine reticular formation, to examine the relationship between brain-stimulation reward and approach responses, and their findings led to further elaboration of such an approach system concept. One important characteristic of the system is its organization being broadly diffused through much of the brain, including perceptual, attentional, learning, and cognitive processes that have to be coordinated for successful approach responses. In other words, for successful approach, organisms must be able to recognize environmental stimuli and to discriminate distinct forms of exteroceptive input, in addition to the ability to change behavior as a function of experience in order to maximize the probability of obtaining material resources needed for survival. Thus, the overall approach system presumably consists of motoric, attentional, motivational, emotional, memorial and other cognitive sub-processes. Although each one of these sub-processes can be studied separately, we shall argue that in normally functioning organisms, a global system helps coordinate all of the sub-processes needed for adaptive approach toward goals. More recently, from a more psychodynamic perspective, this system has been called the SEEKING system [174,178]. Here we shall continue to advocate the view that the meso-accumbens DA system is a part of such preparatory approach-seeking system.

Across the years, such approach concepts have been applied by various investigators for understanding brain DA functions but only recently has the evidence approached definitive status. Mogenson et al. [162] conceptualized that ''Limbic forebrain structures and the hypothalamus are essential in the initiation of food-seeking, escape [i.e., avoidance] from predators and other behaviors essential for adaptation and survival... the nucleus accumbens is a key component of this neural interface [between limbic and motor systems]'' (p. 91, brackets added). Particularly, DA in the NAS was thought to be the key molecule that coordinated such interface processes. Wise and Bozarth [300] applied the ideas of Glickman and Schiff to drug reinforcement and postulated the meso-accumbens DA system to be a key mechanism.

The views summarized above are the direct intellectual antecedents of the theoretical perspective advocated in this paper. Indeed, we think there is presently a growing consensus on the general point of view that will be described here, even though there are abundant details that

remain controversial and unresolved. In any event, we offer the present theoretical integration as a testament to the emerging synthesis.

3.3. Incentive motivation and brain DA

Another important theoretical line of thought that needs to be incorporated into the present discussion is the behavioral incentive motivational concept elaborated by Bindra [18,19] and Bolles [25]. Incentive motivation concepts arose from traditional learning paradigms (where one had to account for the powerful and systematic effects on behavior of varying the quantity, quality and delay of reward). However, as incentive concepts came to be viewed as potential brain processes, rather than simply the properties of material objects, investigators tried to account for adaptive behavior ever increasingly by emphasizing invisible underlying brain processes that presumably control behavior. As Bindra [18] stated, ''The sway that the response-reinforcement framework (Spencer, Thorndike, Hull, Skinner) has held on the behavioral sciences for nearly a hundred years is finally ending. The strength of this framework lays in providing concepts and methods for studying the effects of hedonic (reinforcing) stimuli on the repetition of specified responses acquired in instrumental training situations of various kinds. Its weakness lays in the invalidity of its central assumptions, stimulus–response association and response-reinforcement, which could not deal with motor equivalence and flexibility (or 'intelligence') in behavior'' (p. 41). Since incentive motivation concepts have been applied to account for the function of brain DA [13] and more specifically for that of the mesolimbic DA system [68], it is important to describe what incentive motivation is (see Ref. [18] for discussion on differences between response-reinforcement vs. incentive motivational perspectives).

The present version of incentive concepts is based on a series of theoretical works by Bindra [18], Bolles [25], Dickinson [57] and Toates [265]. In brief: Incentive motivation is a cognitive and affective state triggered by stimuli associated with the perception of unconditioned stimuli. In other words, incentive motivation is a process in which approach or avoidance responses are generated by stimuli that predict the proximity or availability of unconditioned stimuli (positive or negative). The formation of incentive motivation triggered by a specific environmental stimulus typically results from contingent presentation of a stimulus, detected by distance receptors, just prior to presentation of unconditioned stimuli, typically detected by proximal receptors.

As recently elaborated by White [285], the present paper also seeks to make a clear distinction between incentive learning and two other types of learning. First, animals have the ability to learn the relationship among environmental stimuli without the intervention of unconditioned reward stimuli. This type of learning is referred to as declarative learning (or stimulus–stimulus learning), whose major neural substrates are the hippocampus and anatomically closely related cortical areas [243,244]. It provides a propositional knowledge base for animals concerning the structure of the external world. There are other types of learning systems, and one that is fairly well-documented is habit learning (the traditional stimulus–response learning or R–S* of Bolles [25] may correspond to this process), whose major neural underpinnings may emerge from the caudate–putamen and related neural systems [89,95,131,288].

There are yet other learning systems, but they are beyond the scope of the present paper. In summary, incentive learning or motivation in the present paper refers to processes involving environmental stimuli detected by distance receptors predicting the perception of unconditioned stimuli (usually detected by proximal receptors), which allow animals, on future occasions, to effectively seek out and anticipate various rewards in their environments (both material objects as well as immaterial ones, like safety).

3.3.1. The error signal hypothesis

Supplementing the learning mechanism tradition, a significant related hypothesis concerning brain DA functions has recently been proposed by Schultz [225] and Schultz et al. [228,230]. According to this view [228], DA released by neurons in the substantia nigra and VTA serves as a teaching signal ''to code for a deviation or error between the actual reward received and predictions of the time and magnitude of reward'' (p. 1594). Further, they adapt the Rescorla–Wagner learning model to conceptualize the role of brain DA. Thus, Schultz et al.'s hypothesis concerns the strength of association between conditioned and unconditioned stimuli. As we shall review below, their hypothesis is supported by a great deal of data relating behavioral observations with concurrently harvested electrophysiological data from DA neurons. However, such data are subject to other interpretations (e.g., Ref. [203]).

The Schultz et al. hypothesis concerns us somewhat with respect to its lack of functional specificity for different DA systems; i.e., it does not provide any clear and necessary distinction among ascending DA projection system functions. Indeed, microdialysis data suggest that DA releases in various projection regions of the substantia nigra and VTA respond differentially as a function of the presentation of unconditioned stimuli [1,10,117,289]. In other words, their hypothesis does not deal with possible differences in DA release among the projection regions including the NAS, caudate–putamen, and prefrontal cortex. As mentioned above, various lines of data indicate that NAS DA and caudate–putamen DA [89,131,288] are involved in different aspects of associative learning (incentive learning vs. habit learning in our terms).

The view advocated by Schultz et al. also fails to handle the increasingly large number of findings on the role of brain DA in negative contexts since they claim that

brain DA is solely involved in positive, reward learning. Moreover, the theory does not provide any explanation for the role of DA systems in spontaneous motoric responses. For example, it cannot explain why injections of DA agonists (locally into the brain or systemically) can produce vigorous behavioral activation.

3.4. Synthesis of approach and incentive motivational perspectives

The two perspectives described above, emphasizing distinct aspects of appetitive motivation processes, have recently been explicitly combined by Berridge and Robinson [16] to highlight how brain DA may be involved in rewarding processes. Because the present paper also combines the two theoretical perspectives, it is important to detail the Berridge and Robinson thesis.

According to their view, three psychological processes are postulated to account for motivational and rewarding phenomena: hedonic activation processes (liking), associative learning processes (Pavlovian conditioning), and incentive salience attribution (wanting) processes. By incentive salience, ''they mean processes that transform a perceived and 'liked' stimulus into one that is also 'wanted' and able to elicit voluntary action'' (p. 332, Ref. [16]).

The meso-accumbens and nigro-striatal DA systems are postulated to mediate the attribution of incentive salience but not the other two processes. DA ''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''' (p. 313, Ref. [16]). Thus, Berridge and Robinson clearly delineate not only the process for hedonic evaluation of unconditioned stimuli and the process for incentive salience attribution, but also the associative learning and incentive attribution processes, yielding a variety of explicit predictions. Although we agree with many aspects of their thesis, we do have some concerns. First, their claim that striatal DA is not involved in Pavlovian associative learning is not consistent with empirical findings as far as NAS DA is concerned. Depletion of NAS DA transmission attenuates or abolishes the acquisition of Pavlovian conditioning tasks such as development of displacement responses [211,274] and facilitates latent inhibition, presumably dependent on a Pavlovian conditioning process [86,87,240,275,276]. Their claim, that DA is not involved in Pavlovian conditioning, seems to be based on their finding that animals can still exhibit conditioned taste aversions [16] which, of course, is just one of many possible examples of Pavlovian conditioning and not directly relevant to positively motivated appetitive approach issues. As elaborated below, our interpretation is that Pavlovian conditioning can consist of several distinct associative mechanisms, and NAS DA is only involved in certain ones.

Second, using the results obtained with oral hedonic tests, Berridge and Robinson [16] provide a compelling argument against simple hedonic account of DA function. However, they still try to understand certain behavioral effects of unconditioned stimuli using the framework of certain other positive subjective effects. According to their view, DA is involved in the wanting process, while non-DA processes are responsible for detecting hedonic subjective effects of stimuli (liking), and, in turn, the liking process turns on incentive salience attributions that govern the wanting process. As we will discuss (Section 7.1), it is by no means yet clear whether or how subjective affective effects of unconditioned stimuli exert control over animal actions. In other words, as they themselves emphasize at various points in their discussion, it may be premature to make a causal link between subjective affective effects of stimuli and the types of basic appetitive conditioning that can be studied so effectively in animal models. Although we most certainly remain open to such possibilities, the evaluation of such issues must ultimately include human models based on basic behavioral neuroscience research [174]. In any event, their conception may have difficulty accounting for recent findings on the involvement of DA in aversive situations, which presumably produce negative subjective effects.

Another noteworthy issue is that the incentive salience hypothesis does not make explicit functional distinctions between NAS DA and caudate–putamen DA. Thus, it may be difficult for the incentive attribution hypothesis to explain why animals still exhibit normal instrumental responses for the first couple of trials before exhibiting profound instrumental deficits, when DA transmission is disrupted (e.g., Refs. [71,155,304,305]) particularly in the NAS (see Fig. 2 [112]). According to the incentive salience attribution or 'wanting' view, performance of instrumental responses *should be* affected from the very beginning of a session. Another problematic example is the recent finding by Floresco et al. [70] that intra-NAS injections of haloperidol do not disrupt delayed spatial win-shift foraging task while having severe effects on random foraging. We believe that the incentive salience hypothesis should have predicted that disruption of NAS DA transmission should disrupt a win-shift foraging task as much as random foraging (see Section 6.6 for detailed discussion). In short, even though we believe that the 'incentive salience' hypothesis of DA function is generally on the right track, there is considerable room for refinement of hypotheses, especially as far as the specific functions of the NAS DA system are concerned.

3.5. Other hypotheses on NAS DA

A variety of other recent hypotheses on NAS DA functions do not fit clearly into the intellectual traditions described above. However, they deserve to be briefly mentioned within the present context.

3.5.1. Switching hypotheses

The concept of switching between alternative behaviors was introduced to account for the functions of the ascending DA systems [170,203,208]. As Oades [170] summarized, ''an increase of DA activity promotes the likelihood of switching between alternative sources of information... The effect is likely to be seen either in the change of the temporal patterning of a behavioral sequence or in the initiation of new responses'' (p. 268). This version of the switching hypothesis does not specify what types of responses are being switched by the facilitation of the ascending DA activity. Presumably, it could be anything: Thus, one could imagine that DA release could facilitate switching between feeding and drinking, between eye-lid blinking and sniffing, or between rearing and grooming. Bos et al. [26] and Bos and Cools [27] have further defined the switching hypothesis for the meso-accumbens DA system, stating that NAS DA is involved in switching to cue-directed responses. Although the Bos and Cools version capture some functions of NAS DA, this hypothesis needs to be further defined so that it provides a broad and fundamental framework for analyzing the underlying processes.

3.5.2. The anergia hypothesis

Salamone et al. [219] have characterized the behavioral functions of NAS DA with a variety of techniques and paradigms, and concluded that NAS DA ''is involved in higher-order motor and sensorimotor processes that are important for activational aspects of motivation, response allocation, and responsiveness to conditioned stimuli'' (p. 352). Although this hypothesis also captures many aspects of NAS DA functions, it needs to be further refined so as to provide more specific predictions, as well as incorporating all of the relevant data that exist in this research arena.

4. A unifying interpretation of NAS DA functions

4.1. An updated hypothesis of specific NAS DA functions

Fig. 3 summaries a conceptual model that highlights the role of NAS DA in behavioral control. A key feature of the model is that it has distinct sensorimotor paths for approach and consummatory responses. It is assumed that the same approach response system is engaged when animals escape from negative incentives and develop the ability to avoid such stimuli. Key sub-systems underlying the approach responses include declarative perceptions, habits, and incentive-cue formation systems. The declarative-perception system is a complex assembly of heterogeneous cognitive processes, outside the scope of the present discussion, that represent knowledge about the environment allowing animals to acquire and recall the relationships among environmental objects and events without the essential intervention of unconditioned stimuli (i.e., stimulus–stimulus or declarative learning). It can also detect salience of environmental stimuli (i.e., novel stimuli, conditioned stimuli, and innately salient stimuli) by contrasting present input with previous memories. It is possible that frontal cortical DA systems are important in such brain functions, but that is outside the scope of the present coverage.

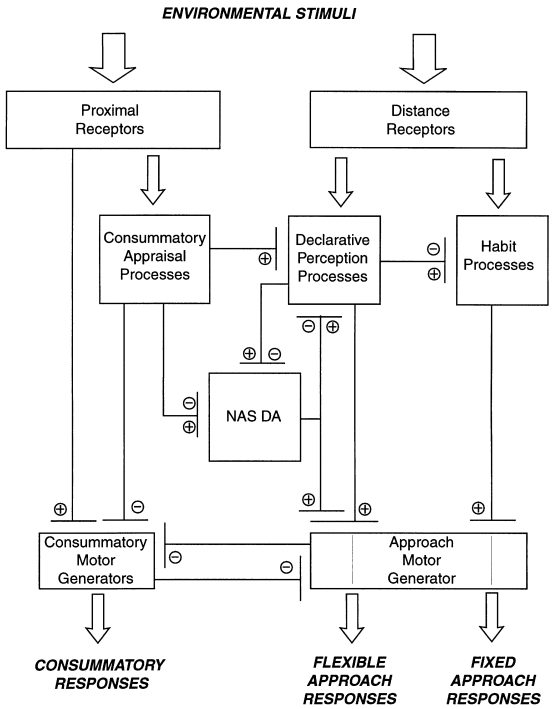

Fig. 3. A conceptual model illustrating the role of NAS DA in incentive motivation modulation. The role of NAS DA is defined in relation to major sub-systems involved in generating conditioned and unconditioned responses. The plus signs in circles indicate excitatory input, while the minus signs indicate inhibitory inputs.

The habit system allows animals to acquire and maintain procedural performance. The nigro-striatal DA system appears to be a key structure involved in habit formation (stimulus–response learning) [89,95,131,288]. Thus, an important feature of the current view is the recognition of two distinct types of approach response systems: a *habit response system* which operates in well-trained animals and a *flexible response system* which operates preferentially when animals are learning about incentive contingencies in their environments. The role of NAS DA is to arouse unconditional appetitive (exploratory-seeking) arousal and to help declarative knowledge gain access to incentive construction processes. In other words, NAS DA can facilitate flexible approach responses in the presence of various salient stimuli (e.g., incentive stimuli and novel stimuli). In summary, the primary role of NAS DA is to facilitate flexible approach responses by modulating incentive motivation processes. Let us develop this idea further by describing two stages of instrumental approach performance.

4.1.1. Invigoration effects

NAS DA transmission plays a critical role in invigorating flexible approach responses when organisms encounter salient stimuli (e.g., incentive and novel stimuli). The declarative-perception system detects various salient stimuli (e.g., arising from all novel events) and arouses NAS DA release, invigorating flexible approach-seeking responses. Fig. 4 highlights proposed routes of control involved in such processes. When NAS DA transmission is artificially enhanced using such methods as local tissue microinjections of various substances (e.g., amphetamine), it would activate a state of incentive motivation and exploratory arousal, thereby generating flexible approach-seeking behaviors toward salient environmental stimuli.

Conversely, the disruption of NAS DA transmission should blunt the ability of organisms to approach salient stimuli. It is not that animals lose the ability to recognize salient stimuli. Their perception and memory-retrieval processes remain intact, even though it is likely that some aspects of their attentional resources are compromised. Such animals simply are not aroused into sustained attentional-investigatory patterns by novel stimuli. It is also not the case that animals lose the physical capacity to perform instrumental tasks or consummatory responses. Clearly, animals lacking NAS DA are not behaviorally incompetent. Rather, their deficits may arise from NAS DA no longer being able to amplify behaviorally energized states of expectancy. In other words, the output of the declarative-perception system to the approach motor system is compromised. Also, there may be deficits of positive feedback between the incentive modulator and the declarative-perception system. On the other hand, well-established conditioned responses in familiar environment contexts (i.e., habits) do not appear to be disrupted by decreased NAS DA transmission. In sum, the NAS DA system is more involved in addressing unfamiliar situations or stimuli which deserve to be investigated and determining whether novel stimuli predict rewards rather than in dealing with familiar situations where organisms already have stable behavioral priorities (i.e., they have habits).

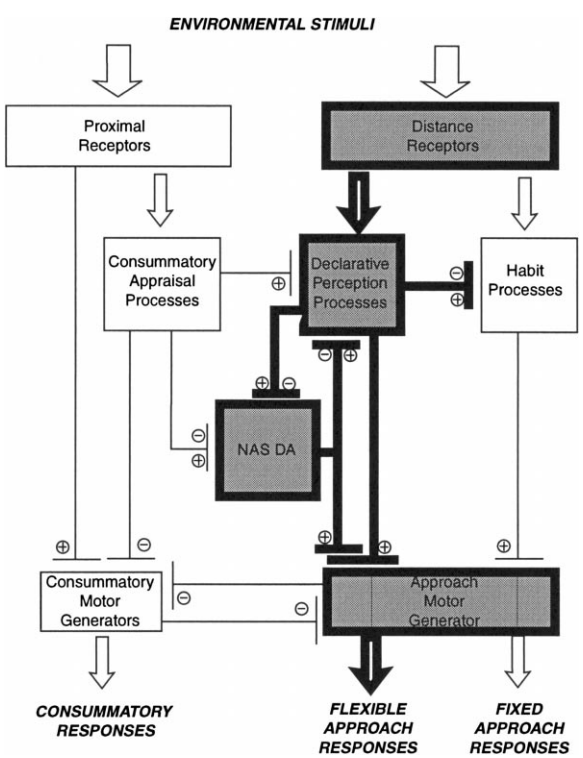

Fig. 4. A conceptual model illustrating the major unit involved in approach responses elicited by salient stimuli.

4.1.2. Incentive learning effects

It appears that the brain is organized in such a way that the detection of unconditioned stimuli can automatically promote learning. The brain is tuned to the appearance of novel stimuli, and NAS DA is aroused especially by those that are associated with beneficial life-sustaining or life-impairing events. Although these associations are not essential to consummatory reactions per se, they do establish an implicit knowledge of situations within which consummatory behaviors can be optimally expressed. NAS DA transmission appears to be critically involved in such incentive learning processes. More specifically, changes in NAS DA transmission may first be involved in investigatory activities and more gradually in signifying the importance of environmental stimuli because of their association with opportunities for consummatory behaviors. This linking of external events with opportunities to stimulate various proximal sensory receptors is here conceptualized as the 'incentive learning effect'. Thus, heightened levels of NAS DA transmission add incentive properties to declarative knowledge so environmental stimuli that are predictive of unconditioned stimuli come to facilitate and energize approach (or avoidance) responses. Normal levels of NAS DA, on the other hand, maintain such incentive motivation; thus, a decrease in NAS DA transmission re-organizes neural mechanisms involved in incentive representations of declarative knowledge so that environmental stimuli that are not predictive of the perception of unconditioned stimuli will no longer activate approach (or avoidance) responses.

Thus, NAS DA plays an important role in integrating reward-related information on specific aspects of the environment into conditioned approach-seeking reactions. Once such conditioning has been established in a specific context, however, heightened NAS DA transmission is no longer necessary for its expression, unless organisms experience new opportunities for consummatory responses in those contexts. Thus, in well-trained animals, incentive stimuli can still trigger learned approach responses (e.g., the habit response system) despite the disruption of NAS DA transmission. Fig. 5 highlights key routes involved in such incentive modulation processes. As described above, NAS DA is only involved in learning in the sense that it modulates the initial behavioral responses to potential in-

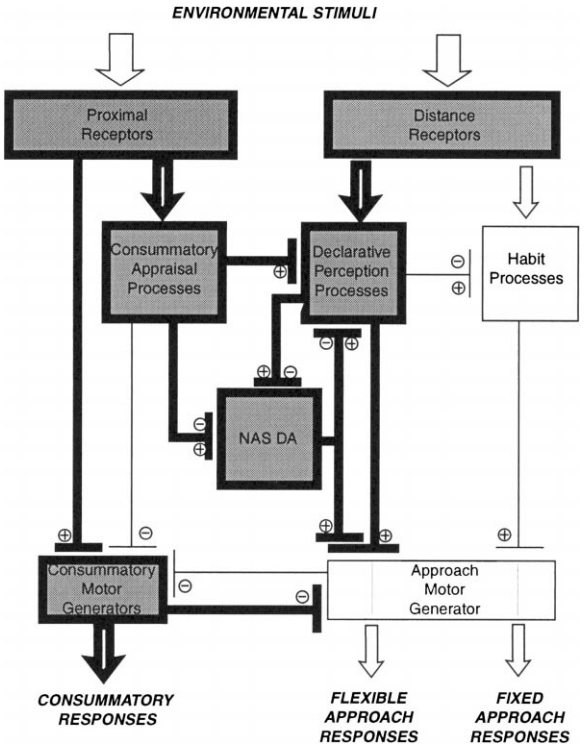

Fig. 5. Conceptual model illustrating the major units involved in consummatory responses and attribution processes related to environmental inputs.

centives, and the development of conditional incentive stimuli (i.e., the automatic valuation of neutral environmental events). It does not appear to be involved in declarative memory formation or retrieval (but see Ref. [234]) nor in procedural learning.

Here, the role of NAS DA is described largely in terms of instrumental performance. It is assumed that the development of stable instrumental performance requires both the flexible approach system and the habit approach system. During initial learning (the acquisition phase), NAS DA plays an important role in invigorating exploratory-seeking behaviors and the formation of new incentive motivational linkages to specific environmental stimuli in contexts in which effective instrumental responses can take place. As instrumental behavior becomes streamlined (a key component of this process is probably DA arousal in the caudate–putamen), NAS DA plays less and less of a role in the instigation of instrumental acts. In other words, unless there are some new environmental factors to be incorporated into the instrumental performance, NAS DA is not essential for maintaining performance. For example, when animals are subjected to extinction contingencies, NAS DA may play an important role in facilitating learning of such new environmental contexts. In this case, the lowering of extracellular NAS DA may facilitate extinction learning. Parenthetically, the commonly observed initial energization of responding at the very beginning of extinction may reflect an acute NAS DA novelty response.

The model described above can be applied to both positive and negative incentive motivational contexts (a similar view is expressed by Dickinson [56]). For positive contexts, incentive processes are formed such that organisms direct approach responses toward unconditioned stimuli. For negative contexts, incentive processes are formed such that organisms direct approach responses away from unconditioned stimuli (i.e., toward ‘‘safety’’). Further discussion of this issue is found below in the Section 4.3, following a discussion of the potential role of NAS DA in mediating reinforcement.

4.2. Reinforcing effects

How can intra-NAS injections of DA agonists contingent on operant responses be reinforcing? According to our hypothesis, intra-NAS delivery of DA agonists promotes the addition of incentive properties to associated environmental stimuli. Thus, when animals move about the test cage and recognize the incentive stimuli previously associated with the delivery of unconditioned stimuli, the incentive stimuli, in turn, trigger flexible approach responses toward them, which are typically likely to increase the probability of further delivery of the reinforcer (This is most strongly supported by findings from conditioned reinforcement studies discussed in Section 6.3.). Particularly those environmental contexts presented just prior to or at the time of marked changes of NAS DA transmission may be ‘stamped in’ as objects worthy of approach-investigatory behaviors. Moreover, the stimulation of NAS DA receptors directly invigorates flexible approach responses that are not necessarily directed toward specific stimuli (the invigoration effect described above). Thus, the dual action of *incentive learning* and *invigoration* allows animals to engage in a variety of flexible approach-seeking responses particularly toward the environmental stimuli that are most clearly associated with the delivery of reinforcers. In sum, this hypothesis aspires to explain the role of NAS DA in operant reinforcement by the combination of the *incentive learning*, which gives direction, and *invigoration*, which ‘energizes’ reward seeking.

4.3. How are aversive stimuli involved in NAS DA?

To achieve a unified viewpoint, recent findings concerning NAS DA activation during aversive paradigms also need to be explicated. How can animals learn to approach some stimuli and to avoid others when both appetitive and aversive unconditioned stimuli can evoke similar types of arousal in the meso-accumbens DA system? Although the underlying neural mechanisms have not been as well-studied, available data suggest that common brain mechanisms may be shared between appetitive and avoidance abilities, with NAS DA being one of the shared

components. In other words, avoidance can be conceptualized as approach toward 'safety'. Indeed, a closer look at conditioned responses regulated by aversive stimuli suggests the activation of many approach elements, even though there are obviously other elements such as freezing that could impair approach to safety in various situations, especially during early learning trials. Indeed, it is worth noting in this context the data reported by Wilkinson et al. [289]. The study reports that brief aversive foot shock delivered for the first time does not increase NAS DA, but NAS DA levels increase more and more as animals experience the stimulus for the second and third times. This finding may be interpreted that with succeeding trials, animals develop more effective approach to safety strategies.

At present, there appears to be general agreement among investigators that no unitary concept adequately explains aversive conditioning [204]. Fear conditioning and avoidance learning can be readily dissociated (see Ref. [159]). Indeed, in their defense motivation system account of avoidance learning, Masterson and Crawford [150] postulated the existence of analogous principles between positive and negative reinforcement when they stated that: ''Essentially, we are proposing that aversions behave like appetites. Obviously, the activation of aversions and appetites follows different rules. However, once activated, aversions, like appetites, potentiate appropriate responses and establish the appropriate consummatory stimuli as positive reinforcers'' (p. 668). Similarly, Gray [85] raised the possibility that active avoidance learning may be based on a positive reward mechanism. Most importantly, it is behaviorally evident that some of the anticipatory avoidance reactions to aversive stimuli are quite similar to appetitive approach responses. In other words, in aversive situations, one major goal toward which behavior is directed is 'safety'. Thus, both avoidance and appetitive behaviors may share the arousal of an approach-seeking system in order to promote life-sustaining states of affairs.

Findings from Beer and Lenard [12] support the idea that anticipatory reactions produced by aversive stimuli consist of two or more neuro-behavioral systems. Intraventricular injections of 6-OHDA resulted in severe disruption of shock avoidance responses that had been acquired prior to the lesions [12]. Since the manipulation did not impair the capacity to escape from the shock, consummatory responses were intact. However, the lesions markedly disrupted avoidance performance; if anything, with repeated trials, avoidance performance got worse. Thus, the study suggests that there are two behavioral tendencies (i.e., active seeking for 'safety' and passive freezing) generated as anticipatory reactions to shock, and that after central catecholamine lesions, the anticipatory tendency to approach to 'safety' is disrupted while the anticipatory tendency to freeze is spared.

The present hypothesis suggests the following account of these behavioral effects. Brain evolution may have taken advantage of a DA-based behavioral energization and guidance system to regulate responses in both positive and negative situations, because the fundamental survival concerns were similar. Aversive stimuli arouse NAS DA release because it can *invigorate* the production of new approach responses that may lead to avenues to safety while also facilitating conditioned preparatory processes for the establishment of new approach responses in specific environmental contexts (incentive learning). In other words, incentive learning consists of selective invigoration of seeking responses in specific contexts. Indeed, we would note that many approach behaviors in natural environments are hindered by intervening obstacles, and it has been repeatedly seen that NAS DA release is especially vigorous in thwarting contexts, most especially when a male rat is physically prevented from gaining access to a nearby receptive female [186].

Our finding, that intra-NAS injections of DA agonists can increase plasma corticosterone [108], also fits into the present hypothesis. Plasma glucocorticoids play an important role in providing metabolic energy needed for vigorous physical movements [167]. Although stress is typically discussed in negatively valenced contexts, in a more general sense, stress responses are adaptive reactions that are necessary to cope with all changing environments. Thus, it may not be surprising that the activation of the brain substrates of approach processes would also promote increased glucocorticoid level in order to prepare the body for increased energy expenditures. Indeed, it has been documented that disruption of normal glucocorticoid responses can diminish the rewarding effects of various appetitive stimuli (for reviews on the relationship between glucocorticoid and reward, see Refs. [81,194]). In summary, the elevation of plasma glucocorticoids by intra-NAS injections of DA agonists can be interpreted to be in accord with the present hypothesis.

How about the role of NAS DA in pain perception? It has been reported that DA systems are involved in analgesic processes for certain types of pain [138,166]; i.e., the activation of DA systems appears to attenuate responses to some types of pain. Franklin et al. have provided further evidence that such analgesic effects may be mediated by the meso-limbic DA system [73,165] or more specifically, the meso-accumbens DA system [44]. The evolutionary perspective that we have discussed above in this section can be applied here as well. Amit and Galina [4] argue that analgesia induced by a variety of stimuli including stressful ones is an adaptive response of organisms, and they suggest that ''the effect of the analgesia seems to be highly adaptive in that it allowed the animals to deal efficiently with a dangerous situation and respond more appropriately to any changes in the environment both when danger became imminent as well as when the danger was terminated'' (p. 957). In our terms, it is reasonable to think that when animals are in the midst of pursuing important goals (whether different types of prey, other necessities of life,

or safety), it would be adaptive for them to be *not* interrupted by pains. Any interruption may promptly compromise the opportunity to obtain such goals. As discussed above, NAS DA is an important component of such flexible approach behavioral processes, and it would be most reasonable if the system would help counteract influences that might detract from the adaptive pursuit of goals. Of course, such speculative hypotheses need to be fully examined empirically before earning any credibility. One prediction that we might make here is that animals exhibiting flexible approach responses (i.e., approaching goals in rather unpredictable environments) would tend to exhibit higher pain thresholds than those that were not.

4.4. Pavlovian conditioned responses

Although Skinner [237] and others postulated that different learning processes underlie appetitive Pavlovian and operant conditioning, we agree with the view advocated by Bindra [20] that essentially the same learning processes may underlie the two conditioning procedures. Of course, both Pavlovian and operant procedures probably recruit multiple learning systems, but the differences between the two may lie in the relative strengths of the underlying components. It is postulated that all forms of appetitive Pavlovian conditioning involving forward locomotion are heavily dependent on the sensorimotor facilitation afforded by the flexible NAS DA approach response system, whereas operant procedures depend only initially on that response system but with training, there is increasing reliance on the 'fixed' habit system (see Figs. 3–5). In this context, it is important to highlight that NAS DA is not involved in all forms of Pavlovian conditioning, especially conditioned taste aversions.

Typically, conditioned taste aversion tests are performed by pairing the ingestion of novel-flavored food or fluid and the administration of lithium chloride, which induces gastric malaise; i.e., animals are given the opportunity to consume novel-flavored food or fluid, followed by the administration of lithium chloride. In a subsequent session, animals are given the opportunity to consume the unconditioned stimulus; however, because of the association of gastric malaise, animals exhibit little or no intake of the illness-associated unconditioned stimuli.

Several studies reviewed below support the idea that the meso-accumbens DA system is not involved in conditioned taste aversions. (1) Mark et al. [146] report that presentation of the conditioned aversive stimulus, i.e., associated with lithium-chloride-induced sickness, if anything, decreased NAS DA levels. Thus, this result is not consistent with the findings that, as discussed in Section 2.2, conditioned stimuli associated with certain other aversive unconditioned stimuli can readily increase DA levels [222,309,311]. (2) Ellenbroek et al. [59] reported that intra-NAS injections of D-amphetamine do not disrupt latent inhibition involving lithium-chloride-induced taste-aversion conditioning, while intra-striatal injections of D-amphetamine do disrupt it. (3) Intra-NAS injections of D-amphetamine produce place preference conditioning but not taste preference or taste aversion, while microinjections of D-amphetamine in the area postrema region in the hindbrain produce conditioned taste aversion but not conditioned place preference [37]. (4) 6-OHDA lesions of NAS enhance place-preference conditioning induced by systemic apomorphine injections (apparently due to enhanced receptor sensitivity of NAS DA), while the NAS DA depletion had no apparent effect on conditioned taste aversions induced by apomorphine [272]. (5) 6-OHDA lesions of the forebrain do not impair associative learning between palatable food and lithium-chloride-induced sickness, which enhances aversive reactions and attenuates hedonic reactions to saccharin/polycose taste [16]. (6) Finally, Mirenowicz and Schultz [161] report that a drop of hypertonic saline placed in the mouth of primates does not readily stimulate phasic responses of DA neurons.

In summary, these results indicate that the acquisition of conditioned taste aversions is not controlled by NAS DA. Although it is possible to interpret these results as evidence to support lack of involvement of NAS DA in Pavlovian associative learning (e.g., Ref. [16]), the present hypothesis interprets these data to affirm the traditional view that Pavlovian conditioning is simply not a unitary phenomenon. The present conception predicts that all forms of Pavlovian conditioning that do not involve conditioning of approach-seeking responses (e.g., autonomic conditioning, eyelid conditioning [263]) do not require the meso-accumbens DA system. Let us highlight this issue in a specific context: when dogs are subjected to a Pavlovian conditioning with an environmental stimulus followed by food reward, the animals not only exhibit conditioned salivary responses but also increased skeletal motor approach responses as well as various other bodily responses (see Ref. [6]). We predict that approach-related responses such as skeletal motor responses and perhaps even visceral motor responses (i.e., respiratory and cardiac changes), that are thought to be important for vigorous approach, will not be as readily conditioned as consummatory-related responses (i.e., salivary secretions) in the absence of normal NAS DA transmission.

Now that our theoretical framework has been summarized, we will detail relevant empirical findings concerning NAS DA functions. We will, first, review correlational studies of behavioral and NAS DA interrelations and then behavioral consequences of directly manipulating NAS DA activities. The results of such studies will be concurrently discussed with reference to the present theoretical viewpoint.

5. Behavior/environment correlates of NAS DA

Three major techniques have been used to explore correlational relationship between the meso-accumbens DA

system and behavior. Unit recordings have identified DA neuron activity changes in behaving animals. Measurement of action potentials in millisecond time frames provides an opportunity to explore detailed temporal relationships between DA neuron activities and behavior. Some caution needs to be exercised in interpreting such results because it is not certain how well activities of the DA cell body translate to DA release at nerve endings in the NAS (but see Refs. [42,252]). In addition, all DA neurons do not necessarily respond to precisely the same conditions, which raises obvious difficulties for making interpretations about general functions.

Current voltammetry techniques enable DA detection at terminal region with time resolutions of about a second. However, it is not always certain how precisely the electrochemical species detected by this method reflects DA; thus, the data obtained by this method must always be interpreted with some reservations.

The advantage of yet another widely used technique, in vivo microdialysis, is that it can detect DA without such ambiguities. The disadvantage of microdialysis is that the technique lacks fine time resolution, requiring detection periods on the order of minutes.

In subsequent sections, we will critically discuss the information obtained by these techniques. One also needs to keep in mind that DA levels at the terminals are detected in the extracellular space, not necessarily in the synaptic spaces. Indeed, DA levels in the synaptic and extracellular space may be regulated differently, and DA may play differential functional roles at these loci [82].

5.1. Unit activity

DA neurons in the ventral tegmentum typically exhibit a stable rate of tonic firing in animals kept in a quiet state. A variety of environmental challenges can elicit phasic changes in the firing of these neurons. An emerging picture is that the activity of DA neurons does not correlate with any fixed movements or fixed sensory stimuli [169,226]. Rather, firing patterns of DA neurons change as a function of repeated experiences. Such dynamic characteristics of DA neuronal activity have been well-characterized in the ventral tegmentum of fully awake monkeys (for a recent review, see Ref. [225]). When monkeys unexpectedly receive a reward such as highly palatable food, the reward markedly stimulates phasic firing of the majority of DA neurons [160]. What is remarkable is that as the contingent presentation of environmental stimuli followed by a reward is repeated, phasic firings of DA neurons produced by the delivery of reward decrease and eventually return to tonic baseline levels [101]. However, now, the mere presentation of the predictive environmental cues (i.e., conditioned stimuli) triggers phasic firing of DA neurons [143,144,160,227]. Furthermore, if the reward is not presented at the time it normally occurs, a brief reduction of DA activity occurs [143,227]. In addition to rewards, physically salient novel stimuli can also stimulate phasic activity of DA neurons [104,144,216,229], but these responses rapidly habituate with repeated presentations [144].

In summary, DA neurons respond to salient novel stimuli, food rewards, and gradually to predictive cues. The ability of these stimuli to trigger phasic firing is apparent very dependent on specific contexts. However, phasic responses of DA neurons do not discriminate between stimuli; whether a response is elicited by a reward, conditioned stimulus, or novel stimulus, changes in the pattern of firing appear to be remarkably uniform [225].

What has not been characterized adequately is how DA neurons respond to a large variety of aversive stimuli in such paradigms. Although Mirenowicz and Schultz [161] reported that aversive air puffs to the hand or drops of hypertonic saline in the mouth do not readily stimulate DA neuron responses, suggesting that rewards preferentially activate phasic firing of DA neurons while aversive stimuli do not. Unfortunately, the extent to which air puffs to the hand or drops to hypertonic saline is aversive was never clearly characterized. According to the present hypothesis, aversive unconditioned stimuli, which provoke directed escape or avoidance behaviors, should trigger phasic firing of DA neurons projecting to the NAS, and such activity of DA should facilitate integrative processes for seeking avenues for avoidance. Indeed, Trulson and Preussler [267] reported in freely moving cats that conditioned stimuli associated with an aversive event increased firing of VTA DA neurons. Moreover, the data obtained by the voltammetry and microdialysis methods (see below, Section 5.2) are not in accord with the conclusion made by Mirenowicz and Schultz [161]. Thus, further research is needed to examine whether or not stimuli that provoke explicit avoidance responses have similar phasic firing in exactly the same neurons that respond to reward-related stimuli. If they were a slightly different population, we would not feel it would compromise our position, but that would require some fine-tuning of the present theoretical view.

5.2. Microdialysis / voltammetry

In vivo microdialysis and voltammetry techniques have revealed a variety of stimuli that can provoke NAS DA release, most extensively in the context of feeding. Reliable increases of extracellular DA in the NAS are usually observed when extracellular NAS DA levels are monitored during combined anticipatory and consummatory phases of feeding; i.e., marked increases of NAS DA have been observed in animals exhibiting instrumental responding for food and eating it [94,130,151,218,238]. Increased DA levels in the NAS were also observed in animals receiving scheduled deliveries of small pieces of food at fixed time

intervals (i.e., a Pavlovian procedure), while NAS DA levels were not elevated when animals received the same amount of food all at once [153,200].

Some have sought to tease out which phase (consummatory vs. preparatory) is more influential in arousing NAS DA release. Blackburn et al. [22] argued that telencephalic DA, especially NAS DA, is more important for the anticipatory phase of feeding than the consummatory phase. Postmortem data indicated that DOPAC/DA ratios were elevated more in the NAS during anticipatory, than consummatory, periods. Indeed, environmental cues predicting food delivery rather consistently stimulate DA release in the NAS [130,147,187,205,291], while no comparable increase in extracellular NAS DA is routinely observed during feeding (i.e., the consummatory phase) [41,153,218]. However, quite a few studies do report that food consumption can stimulate extracellular DA release [43,93,148, 255,281,282,291,307]. Of course, it is possible that animals that are eating fluctuate repeatedly between brief appetitive and consummatory phases of feeding. Thus, as far as these microdialysis studies are concerned, the anticipatory–consummatory controversy remains unresolved.

Electrophysiological studies discussed above indicate that phasic firing of the DA neurons triggered by signaled food presentation habituates as a function of repeated experience. This finding may suggest that NAS DA release is triggered primarily when animals are fed unexpectedly in novel contexts provoking brain mechanisms which can learn the relationship between food rewards and contextual cues. As animals are habituated to the particular feeding context, food delivery loses its ability to trigger NAS DA release. However, Wilson et al. [291] reported that after 10 days of a timed feeding procedure consisting of a 10-min anticipatory phase followed by a 20-min feeding phase in a test chamber, a robust increase of extracellular DA in the NAS was still evident during the consummatory period. Unfortunately, Wilson et al. slightly changed the procedure for the testing from the conditioning phase: The anticipatory phase was increased from 10 min (during conditioning) to 20 min (for testing). Electrophysiological data indicate that a slight temporal delay in the occurrence of food reward stimulates phasic DA neuron activity that is otherwise not seen because of habituation [100]. Thus, it is not clear whether or not the increase of extracellular DA during consumption in the Wilson et al. study might attenuate after repeated consummatory experience as in many of the other microdialysis studies.

On the other hand, Bassareo and Di Chiara [10] reported that novel, highly palatable food (i.e., snack with high fat contents) increases extracellular NAS DA in non-food deprived rats, while previous experience with the novel food significantly attenuates the NAS DA increase. This finding is consistent with electrophysiology data that repeated presentation of food reward decreases phasic activity of tegmental DA neurons [101]. However, in their paradigm, Bassareo and Di Chiara [10] did not find increased DA release in the NAS during the anticipatory phase, but since their animals were not food-deprived, they may not have entered a strong state of anticipatory eagerness.

Recent voltammetry studies have revealed additional dynamic relationship between NAS DA release and instrumental responses [130,205]. As found with the microdialysis method, similar elevations of extracellular DA are found during operant feeding sessions using voltammetry: Within a few minutes, NAS DA levels plateau and remain elevated for the entire operant session. The DA levels gradually decrease to baseline values after the termination of each session. Response-by-response analyses have revealed the following fine dynamics within a session [130,205] — when a stimulus that indicates the start of an operant session comes on, an electrochemical signal of NAS DA promptly starts to increase. As animals continue to lever-press and eat, the voltammetric signal continues to increase. But this increasing pattern only last for the next couple of bouts of lever-pressing and food consumption. The voltammetric signals then begin to exhibit biphasic responses. A minute or so before a lever response, the signal starts to increase, peaking at the time of lever response. As animals eat earned food, the signal decreases until the onset of the next bout of responding. These results suggest that NAS DA is initially released into extracellular space during both anticipatory and consummatory phases, but as animals are habituated to response–reward patterns, gradually the NAS DA release largely occurs during the anticipatory phase.

Table 1 summarizes various factors that influence extracellular NAS DA release in animals that are given the opportunity to feed. Both electrophysiological and voltammetry approach indicate the importance of previous experience on NAS DA increases that accompany the consumption of food. Apparently, food consumption stimulates the meso-accumbens DA system only if feeding in a particular context has not been well-established. Thus, the meso-accumbens DA system may play an important role in learning the cues of environmental contexts in which feeding occurs. As an animal becomes habituated to certain feeding regimens, the meso-accumbens DA system gradually no longer responds to the reward per se. This idea may largely explain the discrepancy found with the microdialysis methods that food consumption does or does not increase extracellular NAS DA levels. The problem is that most microdialysis studies did not take into account the importance of the environmental context in which food was delivered. The importance of conditioned stimuli in stimulating the meso-accumbens DA system is consistent among the three methods except in the study by Bassareo and Di Chiara [10], where, as mentioned already, the animals may not have been eagerly anticipating the food since they were not food-deprived.

In addition to food and its related stimuli and responses, increases in NAS DA are also found using the microdialy-

Table 1
Factors highly associated with extracellular NAS DA increase in the context of feeding

Factor	Microdialysis (order of minutes)	Voltammetry (order of seconds)	Electrophysiology[a] (order of milliseconds to seconds)
Consummatory			
Consumption of food	⇑ [10,43,93,148,255, 281,282,291,307] ⇔ [41,153,218]	⇑ 1st piece [130,205] ⇓ Several pieces later [130,205]	⇑ prior to establishing conditioning [143,144,160,227] ⇔ in the context fully established [143,160,169,227]
Quality of food (taste?, nutritional value?, novelty?)	⇑ [148]		
Food deprivation	⇑ [291]		
Anticipatory + consummatory			
Amount of food presented in relation to expecting amount		⇑ No food [205] ⇓ More [205]	⇓ No food [143,227]
Consumption during scheduled delivery (every 45 s)	⇑ [153,200]		
Instrumental response and consumption	⇑ [94,130,151,218,238]		
Anticipatory			
Presentation of cues associated with feeding	⇑ [147,291]	⇑ [130,187,205]	⇑ [143,144,169,216, 226,227,229]
Instrumental response and/or voluntary approach to food		⇑ [130,205]	⇑ [169,216,226,227,229]
Increased response requirement for food		⇑ [205]	

[a] Based on an assumption that firing of DA neurons in the ventral tegmentum is well-correlated with extracellular DA release in the NAS; ⇑ increase; ⇔ no change; ⇓ decreased.

sis and voltammetry methods with a variety of other reward stimuli. These include water consumption in thirsty rats [307,310], salt intake in salt-deprived animals [97], copulation [53,149,158,185,280], brain-stimulation reward [23,188,189,199,254], administration of drugs of abuse [55], and novel environments [202].

Moreover, the microdialysis and voltammetry methods have revealed that many aversive stimuli can readily increase extracellular NAS DA. They include forced whole-body immobility [117,118], tail or foot shock [1,123, 222,309,311], social defeat [264], and administration of anxiogenic drugs including beta-CCE and FG 7142 [17, 152]. Similar to conditioned stimuli associated with feeding, increased extracellular DA in the NAS can be triggered by conditioned stimuli associated with sexual behavior [53,185] as well as aversive stimuli [222,309,311]. Interestingly, releasing animals from restraint stress also results in a robust increase of extracellular DA in the NAS [114,117].

In summary, extracellular NAS DA increase may not be attributed to either fixed environmental factors or movements, or either fixed rewarding or aversive stimuli. However, more detailed information, particularly in relation to aversive stimuli, needs to be collected for definite conclusions. At present, it may be provisionally concluded that increased extracellular NAS DA takes place during the occurrence of significant environmental stimuli (i.e., novel stimuli, unconditioned stimuli and conditioned stimuli, positive or negative) that are not clearly anticipated by organisms but which evoke appetitive engagement — in other words, during conditions that have not yet been incorporated into an animal's habitual behavioral repertoire.

It should be noted that compared to the core, the shell region of the NAS is typically more responsive to the stimuli discussed above; i.e., more rapid and more pronounced increases in DA level are routinely found in the shell, when direct comparisons are made between the shell and core in animals eating palatable food [258], lever-responding for food [238], exploring novel environment [202], administering substances of abuse [55], and receiving foot shock [123].

6. Behavioral effects of direct NAS DA manipulations

Two major interventions have been used to elucidate functions of NAS DA: the brain microinjection technique and the 6-OHDA lesion approach. The microinjection

technique allows experimenters to manipulate discrete regions of the brain pharmacologically without significantly affecting other parts of the brain directly. An advantage of this technique is that behavior can be assessed immediately, giving a minimal time for the nervous system to compensate for manipulations. A disadvantage of the technique is that the specific effects at intended sites are often short-lasting because of drug diffusion adjacent sites. Thus, it is essential to have anatomical controls, which allow investigators to determine whether the effects produced by the manipulation of target sites can actually be attributed to these sites.

The 6-OHDA lesion approach has made significant contributions for understanding the functions of NAS DA. However, it is not always easy to interpret the data obtained by this method because of many issues. First, 6-OHDA lesions typically have poor anatomical selectivity. Particularly, 6-OHDA injected into the NAS will deplete not only DA in the NAS but DA in the prefrontal cortex, since many DA projections to the prefrontal cortex go through the NAS. Moreover, a high DA depletion level in the NAS inevitably depletes, in part, DA in other nearby regions including the olfactory tubercles and ventrolateral and dorsomedial striata. Second, 6-OHDA damage is usually assessed by dissecting tissues (using rough landmarks) and measuring tissue contents of amines. This method is not optimal for specifying the precise sites of lesions. Particularly, the NAS shell is localized in the ventromedial region (i.e., inner layer) of the NAS; and, many older studies may have overlooked it. Third, 6-OHDA lesions have poor pharmacological selectivity. Even if animals are treated with specific reuptake inhibitors to protect ascending norepinephrine systems, the 6-OHDA treatment does not leave norepinephrine systems completely intact. Fourth, qualitatively different effects of 6-OHDA lesions may be produced depending on the degree of DA depletion. For example, moderate depletion of DA ($\approx 60\%$) can facilitate locomotor activity in open field test, while more severe DA depletion ($> 80\%$) decreases it [122]. Fifth, effects of 6-OHDA change as a function of time. The 6-OHDA lesions typically have larger effects just after the treatment, and the effects dissipate over time (i.e., over days to weeks) (e.g., Ref. [154]). Transient effects of 6-OHDA on some behavioral measures suggest reorganization of the lesioned site as well as the rest of the nervous system to compensate for loss of the mechanisms disturbed by the manipulation (see Discussion Section of Ref. [109]). In summary, these issues make the interpretation of 6-OHDA data challenging and all too often controversial.

Ambiguous results can also be generated when behavioral paradigms employed do not fully capture functions of NAS DA. For example, if prior experiences of food consumption in particular environments (i.e., expectancies) play a critical role in extracellular release of NAS DA, mixed results are expected when relevant variables are not clearly evaluated.

6.1. Locomotor activity, exploration and novelty-seeking behaviors

One consistent hallmark effect of microinjections of DA and DA receptor agonists into the NAS is heightened locomotor activity [120,121,196–198,245]. According to the present hypothesis, animals exhibit heightened locomotor activity after intra-NAS injections of DA agonists because the manipulations facilitate approach-investigation processes as described in Fig. 4. Thus, depending on environmental conditions, the stimulation of NAS DA may arouse different responses. In typical locomotor activity chambers, without any specific objects with which animals can interact, such manipulations might simply stimulate rearing and digging (if there is some bedding) and forward locomotion (e.g., Refs. [40,253]). Accordingly, the effects of DA agonists may be better characterized as elevations in general exploration rather than general motor activity. In other situations, the same manipulations may facilitate other types of approach tendencies such as conditioned responses in operant tasks [32,126,261,306] and invigorated preparatory responses in the presence of sexual cues [62,63].

In contrast to agonist treatments, intra-NAS injections of DA receptor antagonists [3,112] or NAS DA depletion by 6-OHDA [61,69,134,208] can reduce locomotor activity. However, the magnitude of this hypoactivity effect is dependent on testing conditions [61,257]. The present hypothesis provides the following explanation. When animals are tested in an environment with salient stimuli (e.g., novel stimuli and incentive stimuli), the control animals would exhibit heightened locomotor activity while experimental animals would not readily respond to such stimuli, yielding reductions in their activity levels. However, the hypoactivity effects would not reflect general locomotor deficits (see also Section 6.2), but rather, failures to facilitate approach responses in the presence of salient environmental stimuli.

The present theoretical perspective is consistent with the view advocated by Bardo et al. [9] that the meso-accumbens DA system is involved in novelty-seeking behavior. Moreover, intra-NAS injections of DA antagonists may abolish novelty-induced hyperactivity, while having no effect on general activity [103]. However, the issue of whether NAS DA-depleted rats exhibit exploratory deficits needs additional evaluation. Some have found exploratory deficits [69,195,208,257], while others have not [279,292]. The discrepancy may be attributed to differences in the areas lesioned [292]. Indeed, those studies that failed to find such effects appear to have lesioned the dorsomedial NAS (i.e., the core) based on the stereotaxic coordinates provided. Recent studies support differential DA dynamics in different sub-regions of the NAS. An increased transmission of NAS DA, particularly in the shell, was observed during initial exploration of novel areas while a slower response was evident within the core region [202].

6.2. Food consumption

Modulations of NAS DA transmission may influence food consumption, but such effects may be mediated indirectly by modulation of approach processes. Phillips et al. [190] examined effects of intra-NAS injections of the D1 agonist, SKF 38393, the D2 agonist, quinpirole, and combinations of these drugs on both locomotor activity and food intake at the same time. They reported that these treatments, particularly the combination of these drugs, produced increases in locomotor activity while not influencing food consumption. As shown in Fig. 2, Ikemoto and Panksepp [112] reported that blockade of NAS DA receptors impaired instrumental approach responses maintained by sucrose reward but not the consumption of sucrose reward. On the other hand, some studies have reported that intra-NAS injections of high doses of D-amphetamine reduce food consumption [8,39,60], while administration of the DA antagonist, haloperidol, into the NAS can increase food intake in food-deprived rats [7]. Again, the discrepancies in the above studies could be potentially explained by the competitive tendencies between anticipatory and consummatory behaviors in the various experiments, and only detailed neuroethological studies can resolve such issues.

NAS DA depletion produced by 6-OHDA does not result in feeding deficits as indicated by 24-h food intake or body weight [90,109,128,134,208]. Thus, long-term regulation of food intake is not controlled by NAS DA. Although severe aphasia and adipsia are produced by much more extensive brain depletion of DA [251,269,313], such effects are probably due to global sensorimotor deficits from massive brain DA depletion and/or selective damage of the ventrolateral striatum [220].

It appears that modulation of NAS DA transmission changes the ways animals interact with their environment. The study by Koob et al. [134] documented an apparent competitive tendency between consummatory and locomotor response in intact and DA-depleted animals. When the rats were food-deprived and placed for 30 min in a novel environment, NAS DA-depleted rats consumed more food than controls. These DA-depleted rats also exhibited a lower level of locomotor activity than controls. On the other hand, when a 2-h period, instead of a 30-min period, was given for food consumption in the same environment, there was no difference in the amount of food consumed between the two groups of rats. Moreover, after a few days of exposure to daily 30 min food in a test cage, the control animals consumed as much food as lesioned rats. These results suggest that it is not that 6-OHDA rats eat more but that control rats eat less in an unfamiliar environment, and they need to get accustomed to the novelty before feeding returns to normal in those environments. Furthermore, it should be noted that locomotion per se may not be the behavior that is competing with feeding in an unfamiliar environment [61]. The most straightforward idea appears to be that an unfamiliar environment triggers a set of investigatory responses and perhaps mild fear which competes with consummatory tendencies. It makes good sense from a functional point of view that animals need to evaluate unknown environments by first exhibiting investigatory behavior before settling down to eat. In summary, it appears that low DA transmission in the NAS diminishes such exploratory responses.

6.3. Conditioned reinforcement

The conditioned (or secondary) reinforcement paradigm appears to capture the essence of NAS DA functions. When neutral stimuli are paired with unconditioned stimuli, the neutral stimuli become conditioned stimuli. Secondary reinforcement is typically evaluated by operant behavior reinforced by presentation of conditioned stimuli. Mere presentation of secondary reinforcers without any primary reward can facilitate instrumental conditioning. Systemic administration of DA agonists can enhance such responding for conditioned stimuli [96,206]. The typical protocol described by Robbins and Everitt [208] is as follows: Initially, thirsty rats are trained to lick water from a dipper hidden behind a panel. A brief light stimulus and a mechanical noise (conditioned stimuli) always signify the availability of the water dipper. Thus, panel presses following these stimuli always produce access to water. When the rat learns the relationship between the conditioned stimuli and the water availability, the second phase begins. In this phase, two levers are provided in the test chamber. Pressing one of the two levers results in the presentation of the conditioned stimuli, and pressing the other lever has no programmed consequence. Access to the unconditioned stimulus (i.e., water) is no longer available in this phase. Normal rats readily acquire operant responses that produce the presentation of conditioned stimulus. In contrast, NAS DA depletion abolishes the efficacy of such conditioned reinforcers [208]. Conversely, intra-NAS injections of DA agonists amplify the effects of such secondary rewards [32,126,261,306], while injections of DA agonists into other DA terminal regions are not effective [32,126]. This enhanced responding for conditioned stimuli cannot be attributed to a general hyperactivity produced by increased transmission of NAS DA. Responding on the control lever is relatively unaffected by the DA-agonist treatments, and non-contingent pairing of conditioned stimuli does not support such operant behavior [32,126,261]. Furthermore, intra-NAS injections of DA receptor antagonists or 6-OHDA treatments attenuate the enhanced responding for conditioned stimuli induced by systemic amphetamine [260,306].

Another key finding from conditioned reinforcement studies is that NAS DA-depleted rats that do not readily respond for the conditioned stimuli still exhibit vigorous

panel-press responses for the primary reward [208]. These findings are consistent with the proposed interpretation of NAS DA functions that NAS DA transmission plays a critical role in invigorating flexible approach responses that remain to be integrated into habit processes. In other words, the behavioral invigoration effect of secondary reinforcers may operate through conditioned facilitation of incentive stimuli on DA transmission. This suggests that NAS DA may not be necessary for expression of well-established conditioned responses that are generated by established habits. This aspect of the hypothesis is further supported by findings from hoarding research.

6.4. Hoarding

Rats exhibit hoarding behavior, defined as taking food to another location (often a home area) for later consumption. It has been shown that disruption of DA transmission produced by intra-NAS injections of 6-OHDA [128] or haloperidol [163] disrupts hoarding behavior. Since disruption of NAS DA transmission does not affect consummatory motivation for food (see Section 6.2), thus, the disruption in hoarding cannot be explained by consummatory motivational deficits.

Whishaw and Kornelsen [283] employed ibotenic acid lesions of the NAS, which results in more extensive, non-specific neural destruction. Such lesions also disrupted hoarding, but spared food-carrying behavior, taking food to a safe place for immediate consumption [283]. Thus, deficits in hoarding cannot be explained by general motor deficits either. Whishaw and Kornelsen [283] suggested that NAS neural processes are involved in inducing responses that do not immediately precede consummatory feeding. This suggestion is consistent with the present hypothesis that NAS DA transmission plays a critical role in invigorating flexible approach responses, while destruction of NAS DA transmission should not disrupt habitual responses in familiar environments.

6.5. Response allocation paradigm

Another informative paradigm is called the response allocation procedure developed by Cousins et al. [47,48] and Salamone et al. [221]. The results obtained with this measure appear to indicate that disruption of NAS DA transmission cannot be easily explained by a simple deficit in motoric abilities, consummatory motivation or simple incentive salience. In this paradigm, hungry rats are given two types of food access opportunities in a test chamber. Rats can eat regular chow on the floor, and they can also earn a more palatable food pellets by pressing on a lever. Under such conditions, food-deprived rats typically respond vigorously to earn food pellets and hardly eat any of the food on the floor. However, disruption of NAS DA transmission produced by intra-NAS injections of haloperidol or 6-OHDA markedly decreases operant responses for food but increases the consumption of the freely available food [221]. This effect is site-specific: DA depletion of the dorsal striatum has no reliable effect on the pattern of feeding, while DA depletion of the ventrolateral striatum reduces both lever-press responses and free food consumption [47]. Furthermore, this effect may also be due to disrupted DA transmission in the core rather than the shell [239].

It is difficult to account for this pattern of results on the basis of traditional views of NAS DA function (i.e., motor, pleasure, and simple incentive motivation deficits). The present hypothesis may provide a straightforward explanation for the effects. Food delivery requiring several responses on a lever depends more on the flexible approach response system than does simply consuming food from the floor.

6.6. Learning motivated by food reward

Findings from several runway foraging paradigms also suggest a role of NAS DA in the formation of incentive properties to environments but not in the expression of already acquired incentives. In an eight-arm maze foraging paradigm, Floresco et al. [70] found that intra-NAS injections of haloperidol disrupt free foraging performance but not delayed win-shift foraging. The delayed win-shift test consists of two phases. First, rats are given a chance to collect food pellets from four arms, while entry to the other four arms is blocked. In the second phase, all arms are open, but only those arms that had been blocked in the first phase are baited. Efficient performance on the task requires rats to remember what has happened in the first phase and to choose the four arms that they have not visited earlier in order to collect food pellets most efficiently. Intra-NAS haloperidol injections just prior to the second phase do not affect the performance of this task, suggesting that NAS DA transmission is not involved in memory-retrieval processes, incentive salience-retrieval, consummatory motivation or motor performance. On the other hand, the same manipulations disrupt free foraging performance, in which rats need to collect food pellets most efficiently from eight arms, of which only four arms are baited.

The lack of effects of intra-NAS injections of haloperidol on this delayed win-shift foraging strategy is not easy to interpret from most other perspectives. The present hypothesis interprets the finding, that once the integrative processes for incentive stimuli are formed in a specific context, normal NAS DA transmission is no longer required to mediate incentive-mediated behavioral actions, particularly if tasks have been overlearned and are performed in familiar, fixed environments. On the other hand,

if NAS DA transmission is disrupted at the time such integrative processes are occurring, foraging tendencies should be markedly disrupted, and they are.

Indeed, NAS DA depletion can impair much simpler foraging tasks. Rats with NAS DA depletion take significantly more trials to consistently choose one of two arms for food reward in a simple 'T'-maze [256]. Furthermore, when the baited arm is reversed, lesioned rats again take significantly longer to consistently reverse their behavior. Similar effects were reported in rats with ibotenic acid lesions of the NAS [5]. Again, these results cannot be explained by consummatory motivational deficits (Section 6.2). The results are explicable if NAS DA helps mediate learning the relationship between unconditioned stimuli and the environments in which consummatory responses take place. Thus, even though animals are physically capable of performing tasks, animals do not efficiently perform tasks that require integration of incentive information from prior trials.

6.7. Sexual behavior

As previously discussed, decreased NAS DA transmission appears to disrupt flexible approach responses that are triggered by dynamic environmental stimuli that usually instigate and guide behavior but not those behaviors that are triggered by proximal consummatory objects per se. Although sexual behavior has not been studied as extensively as ingestion-related behaviors, a complementary picture has emerged. Disruption of NAS DA neurotransmission produced by intra-NAS injections of 6-OHDA or DA antagonists compromises the anticipatory phase of male sexual behavior as well as sexual arousal as indicated in latencies for mounting and intromission, sex-cue-induced penile erections, anticipatory locomotor activities, and lever-pressing for sexual opportunities. The same manipulations have comparatively little effect on consummatory aspects of sexual behavior (i.e., the acts of mounting, intromission, and ejaculation) [62,142,186]. Conversely, enhanced NAS DA neurotransmission induced by intra-NAS injection of low doses of D-amphetamine facilitates such anticipatory aspects of sexual behavior [62,63].

This pattern of effects of NAS DA manipulations is evident in female rats as well. Selective DA depletion in the NAS produced by 6-OHDA disrupts the appetitive phase of sexual behavior including hopping, darting and ear-wiggling in female rats, while preserving normal expressions of the consummatory lordotic behavior [207]. These results nicely complement findings from ingestion research, further affirming that NAS DA transmission plays an important role in facilitating species-specific preparatory approach-seeking responses triggered by salient distal stimuli. These studies were conducted in sexually naive rats, and it would be expected that as rats become experienced in sexual interactions, particularly with the same partners in a single environment, depletion of NAS DA may produce less and less disruptive effects on sexual behavior.

6.8. Active avoidance

The limited information that is available for active avoidance also suggests involvement of NAS DA in that behavior. Wadenberg et al. [273] reported that microinjections of sulpiride, a D2 antagonist, into the NAS severely disrupted the performance of shuttle box avoidance responses to foot shock, while injections into the caudate–putamen, prefrontal cortex, or amygdala had little or no effect. Similarly, McCullough et al. [154] reported that NAS DA depletion produced by 6-OHDA disrupted lever-press avoidance responses to foot shock, although animals displayed significant improvement in avoidance over several days. On the other hand, Koob et al. [135] reported that DA depletion of neither the NAS nor the caudate–putamen had much effect on shuttle avoidance acquisition. However, DA depletion of both the NAS and caudate–putamen completely abolished acquisition of avoidance.

These results suggest that NAS DA plays some role in avoidance processes. The lack of consistent effects of either NAS or caudate–putamen DA depletion alone suggests that the rest of the nervous system can compensate for the unitary loss of the respective mechanisms controlled by these regions. However, the loss of both mechanisms does not appear to be compensated. The discrepancy between the McCullough et al. [154] study and the Koob et al. [135] study may be due to differential lengths of recovery following DA depletion. The McCullough et al. [154] study allowed only 2 days of recovery before testing, while the Koob et al. [135] study permitted 10–24 days before testing. The Wadenberg et al. [273] study started testing immediately after the active interruption of NAS DA transmission, which allowed no time for the brain to compensate for lost functions.

Moreover, there are substantial differences in avoidance tasks among the studies. The animals in the Wadenberg et al. study had to rely on unpredictable environmental cues, whereas the animals in the McCullough et al. study and the Koob et al. study were provided with internal temporal cues; i.e., animals were shocked on a fixed interval schedule. Perhaps responses controlled by internal cues are not as dependent on normal NAS DA transmission [122] as responses controlled by environmental cues. Also, the McCullough et al. study employed lever pressing as the avoidance response, which requires an extensive period of training to become a stable habit. On the other hand, the Wadenberg et al. study and the Koob et al. study employed simple locomotion, which requires little training for orientation and forward movement in the right direction. Although the role of these discrepancies cannot be resolved without additional studies, the patterns suggest that com-

pensatory mechanisms, as well as the specific tasks that animals need to perform, need further investigation.

The studies performed by Jackson et al. provide additional information on the role of NAS DA in avoidance performance. Systemic treatments of the catecholamine biosynthesis inhibitor, alpha-methyl-*p*-tyrosine, diminished active avoidance task; however, intra-NAS injections of DA restored active avoidance responses in a dose-dependent manner [28,29,119]. An important implication of these studies is that NAS DA is not only involved in approach responses acquired and maintained by rewards but also avoidance (i.e., approach to safely) maintained by aversive stimuli.

6.9. Latent inhibition

Findings from latent inhibition paradigms also support the role of NAS DA in incentive learning functions within aversive contexts. When a novel conditional stimulus such as a light is paired with an unconditioned stimulus such as foot shock, an association between the environmental stimulus and the unconditioned stimulus is formed very rapidly. For example, if an animal receives an aversive foot shock that is preceded by an unfamiliar light cue, subsequent presentation of the light will rapidly result in an avoidance response or disruption of some ongoing behavior. On the other hand, when a very familiar stimulus is paired with the same unconditioned stimulus, animals do not readily make an association between the conditional (to-be-conditioned) stimulus and the unconditioned stimulus. In other words, stimuli to which animals have been habituated do not become conditioned stimuli as readily as do novel stimuli. This attenuated capacity of familiar stimuli to produce conditioning effects with unconditioned stimuli called *latent inhibition* (for reviews, see Refs. [86,87, 240,275,276]).

We do not think that NAS DA is involved directly in processes for detecting novel environment cues. But when non-NAS DA systems detect 'novelty', they may in turn arouse NAS DA transmission, while familiar stimuli are not able to do this. Consistent with this is the finding that the mere presentation of novel stimuli can arouse VTA neuronal activity and selectively increase extracellular NAS DA release in the NAS, while familiar stimuli cannot [144,311]. Our hypothesis aspires to explain why novel stimuli are more effective than familiar ones in producing conditional relations between unconditioned incentive stimuli and environmental cues: We propose that it is because of the heightened facilitation in NAS DA transmission produced by novel stimuli. Indeed, systemic manipulations of DA systems are consistent with this idea. Systemic administration of haloperidol enhances latent inhibition [182], while systemic administration of D-amphetamine disrupts latent inhibition [129].

However, some controversial findings are also evident among the available studies. For instance, in agreement with our hypothesis, it has been reported that disruption of DA transmission by intra-NAS injections of haloperidol or 6-OHDA enhanced latent inhibition (Peters et al. cited in Ref. [86]). Likewise, Solomon and Staton [241] reported that increased NAS DA transmission by intra-NAS injections of D-amphetamine facilitates the associative learning between a familiar cue and an unconditioned stimulus. On the other hand, Killcross and Robbins [129] reported a failure to replicate the disruption of latent inhibition by intra-NAS injections of D-amphetamine, while they did find that systemic injections of D-amphetamine did produce disruptions.

Gray et al. [87] argue that multiple injections of D-amphetamine are needed to induce the disruption of latent inhibition by intra-NAS injections of D-amphetamine. If systemic injections of D-amphetamine, which have not been associated with any stimuli, thereby not having affected latent inhibition, precede intra-NAS injections of D-amphetamine that is administered during the conditioning phase, the intra-NAS injections of D-amphetamine do disrupt latent inhibition. Thus, it may be that the DA system needs to be 'sensitized' by D-amphetamine prior to intra-NAS injections of D-amphetamine. Weiner and Feldon [276] and Weiner et al. [277], on the other hand, attributed the inconsistent results reported by Killcross and Robins [129] to the anatomical differences: the NAS shell vs. core. Weiner et al. [277] found differential effects of electrolytic lesions of the shell and core; particularly, electrolytic lesions of the shell, but not of the core, abolished latent inhibition. It appears that additional studies are needed to resolve this ongoing controversy.

7. Issues and implications

Considering the well-accepted role of DA imbalances in the genesis of schizophrenia and obsessive–compulsive disorders, the present views should have implications for those types of psychiatric disorders (e.g., Ref. [83]). Indeed, the development and solidification of human belief system (as well as core delusions) may be promoted by the functional dynamics of these NAS DA meaning-construction mechanisms [174]. Because the clinical issues are not directly relevant to the present coverage, those dimensions of the present theoretical views will not be discussed further. However, because of their more direct relevance, we would briefly focus on certain subjective issues related to NAS DA manipulations as well as the potential implications of these ideas for substance abuse problems.

7.1. Subjective effects

How do subjective experiences play a role in mediating the rewarding effect of NAS DA? Does the stimulation of NAS DA release have anything to do with pleasure or

euphoria? It would be important to have an extensive discussion on this, since NAS DA has been touted as a pleasure molecule for the public [168]. As individuals, each of us knows how important subjective experiences are in pursuing our lives. Yet, behavioral science has yet to experimentally identify the role of subjective experience in the control of behavior. Although it is tempting, scientists cannot simply assume causal linkages between subjective experiences and what organisms do. There are many obvious examples of situations where conscious experience has no role in the instigation of behavioral processes. For instance, we are typically not aware of the essential individual muscle movements involved in throwing or reaching out and catching a ball.

On the other hand, it is undeniable that subjective terms often seem to have a utility for describing the behavior of other human as well as, at times, our own behavior. For example, people commonly repeat certain responses to obtain objects without any obvious external instigation, and claim that they pursue such courses of action because they bring pleasure or satisfaction. At present, despite the massive evidence for reward mediation summarized earlier, there is no solid evidence to support the idea that the activation of the meso-accumbens DA system results in obligatory affective experiences of pleasure or euphoria which control behavioral output [16,219,294]. Indeed, the issue remains so troublesome that most neuroscientists take pains to avoid the topic altogether. Whether such central events actually control human and animal behaviors remains a controversial issue that will have to be resolved with better neural conceptions of how conscious experience might be constituted within the brain and what role it has in behavioral control, as well as new ways of triangulating between brain mechanisms, animal behaviors and human subjective responses [174]).

Recent technological innovations in visualizing brain activity are beginning to provide important data for understanding the relationship between subjective experiences and the activity of the brain. Breiter et al. [30] studied the relationship between subjective effects of cocaine and discrete brain activities using functional MRI. Cocaine is known to produce its reinforcing effect by blocking the DA transporter and thereby increasing DA at synapses in the brain, particularly in the ventral striatum, including the NAS. They found that the activation of the ventral striatum is correlated with both subjective experiences of euphoria and craving that occurs during the phase-out of cocaine administration. Interestingly, craving was better correlated with ventral striatal activity than euphoria. An important point to keep in mind in this kind of research is that the causal relationship between such subjective experiences and actually working for drugs presently still remains uncertain. Indeed, a recent study by Berns et al. does not support such a causal linkage.

Berns et al. [14] reported a dissociation between the activity of the ventral striatum and subjective awareness. In their study, the blood flow in the ventral striatum was found to correlate well with the detection of novelty. While being monitored by PET scan, human subjects were asked to touch a numbered key that appeared on a computer screen and to perform on a series of numbers consecutively. There was a pattern in which the numbers appeared, but the task was sufficiently implicit that subjects were not aware of the contingencies. After subjects were trained on this task, a novel sequence was introduced. When subjects had to touch numbered keys with the novel sequences, an increased blood flow was detected in several limbic–cortical regions, with ventral striatal arousal being most marked; i.e., the increased blood flow in the ventral striatum was correlated only with the introduction of a novel sequence of numbers; however, when asked, subjects were not aware of the novelty. An important aspect of this report is that some regions of the brain including the NAS may respond to environmental changes even if the activity of these regions is not reflected in awareness. Thus, it remains quite a challenge to define any causal relationship between subjective experiences and the objective behaviors that both animals and humans exhibit.

Furthermore, Berridge and Robinson [16] reported that 6-OHDA lesions of the striatal complex including the NAS do not affect the way in which animals respond to highly palatable ‘hedonic’ food. Thus, their paradigm also suggests that ascending DA systems are not necessary for simple hedonic (consummatory pleasure) processes. The data of Ikemoto and Panksepp [112], as discussed in Section 2.2 (Fig. 2), are also not consistent with the idea that NAS DA plays a critical role in generating such experiences. The disruption of NAS DA transmission by DA antagonists did not affect the consumption of sucrose solutions, while having strong effects on instrumental responses maintained by the sweet reward. This pattern of results is not consistent with a simple notion that subjective pleasure experience is mediated by NAS DA. Had there been such a linkage, it would have been expected that the consumption of the reward as well as the vigor of the instrumental responses might decline in a similar manner. Most difficult of all for any type of hedonic interpretation of NAS DA arousal, it is simply not conceivable how increased extracellular NAS DA during the presentation of aversive stimuli is to be explained in that context, unless it is strictly related to shock offset.

The above lines of evidence simply do not support the idea that the activation of the meso-accumbens DA system produces simple pleasure or satisfaction experiences that are widely assumed to accompany consummatory behaviors and by some are assumed to be essential for animals to exhibit instrumental responses. This is not to say, however, that there are no relationships at all between NAS DA and subjective experiences. It is certainly reasonable to hypothesize that the activity of the NAS may participate in conscious experience, particularly when NAS activity is rapidly and markedly heightened.

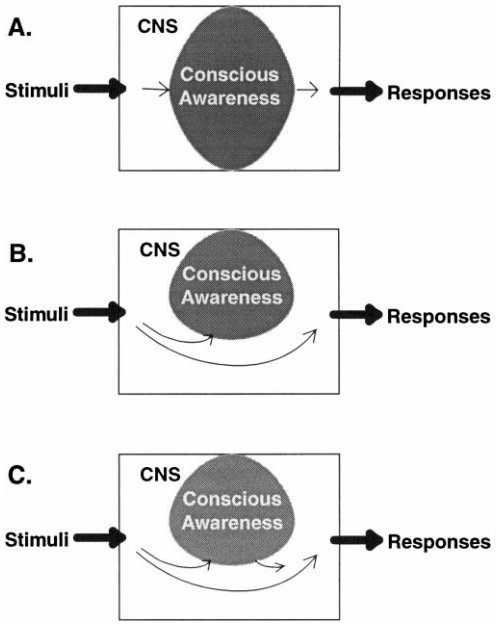

Fig. 6. Conscious experience in relation to stimulus–response processes of the CNS. All of the models accept the assumption that consciousness is based on the CNS activity. Model A depicts a linear relationship among sensory, motor and conscious processes: sensory processes activate conscious processes, which in turn generate motor processes. This unlikely model assumes that subjective experience has total control over behavioral outputs. Model B depicts conscious experience as an epiphenomenal reflection of higher CNS processes with no causal effects on behavior. From a psychological point of view, since we do have subjective experiences, conscious experience must exist, and from an evolutionary perspective, it is likely to have some survival advantages. Therefore, it is reasonable to suppose that subjective experience should interact with ongoing subconscious processes to modify behavioral outputs, but no empirical demonstration of how this occurs in the CNS has yet been provided. Model C illustrates the type of flow of control that should exist if conscious experience within the brain does modulate behavioral output.

To highlight some possibilities, Fig. 6 depicts the possibilities we must consider when we discuss such issues: The most problematic remains the role of conscious phenomena in the control of behavior. Namely, do conscious experiences have any absolute control over complex behaviors (Fig. 6A) or are they mere epiphenomenal reflections of the CNS activity (Fig. 6B)? Alternatively, might conscious experience not only arise from brain activities but also participate in changing those activities, so as to partially mold certain behavioral outputs (see Fig. 6C)? In our estimation, and in agreement with other concerned investigators [52,232], whatever conscious experience is, it is ultimately reflective of CNS activity, and we believe that the third option is most likely to be the most accurate one. Therefore, we might at least entertain some predictions as to what types of conscious experiences might arise when the extracellular DA levels in the NAS are increased. As indicated before, we believe that such subjective effects can only arise from complex and subtle neural interactions among many brain areas [51,178].

As should be evident from our literature review, the role of NAS DA is context-dependent. Let us provide some predictions, taking this context dependency into consideration: Considering the role of NAS DA in behavioral *invigoration*, mild, moderate and high increases in extracellular release of NAS DA may be, respectively, *associated* with subjective feelings of 'curiosity,' mounting 'interest' and 'urge' (as suggested by Panksepp [174]). Presumably, such subjective states would be present just prior to consummatory responses in various positively and negatively valenced contexts. Considering the role of NAS DA in incentive learning, bursts of extracellular NAS DA release followed by effective consummatory responses are likely to be accompanied by a sense of accomplishment and 'relief' in both positive and negative contexts, and perhaps some variant of ecstatic well-being in positive contexts. In any event, the simplistic notion, that environmental events or stimuli that can produce heightened NAS DA release are always experienced as pleasurable, remains dubious and certainly has not been empirically verified to the satisfaction of critical observers. Again, let us re-emphasize that our discussion here is based on an assumption that subjective experience can only arise from interactions among many CNS regions, with some being more critical than others [178].

7.2. Substance abuse

7.2.1. Drug reinforcement issues

Drugs of abuse comprise a heterogeneous assortment of substances, each of which has distinct pharmacological properties, the most relevant of which is their ability to interact with distinct neuroanatomical systems and specific receptor types within brain. Despite a large variety of such *initial* action sites, recent evidence indicates that most drugs of abuse eventually do recruit activities in certain common brain mechanism. As discussed above, extracellular levels of DA in the NAS markedly increase when organisms are treated with substances such as amphetamines, cocaine, opioids, ethanol, nicotine and cannabinoids [34,115,116,184,259,278,301,308]. Indeed, Wise and Bozarth [300] suggested that rewarding effects of drugs of abuse are mediated through the neural mechanisms that also mediate approach responses, and that the meso-accumbens DA system is a component of the common underlying mechanism. The current hypothesis on NAS DA function, which is in general agreement with that thesis, adds additional perspectives and predictions relative to substance abuse issues, especially since so many drugs of abuse stimulate NAS DA.

As highlighted in Fig. 3, the role of NAS DA is to amplify integrative processes for adaptive approach-seeking processes that are triggered and guided by environmental stimuli. During the initial learning phase of instrumental behavior (the acquisition phase), NAS DA plays an important role by forming new incentive relationships to

environment cues and contexts in which instrumental responses take place. To review the critical theoretical points: as animals perfect instrumental performance (a key component of this process being a shift of control from accumbens systems to those in the caudate–putamen), NAS DA may play less and less of a role in instrumental behavior. In other words, unless there are some new environmental factors to be incorporated into instrumental performance, NAS DA may neither be acutely aroused nor essential in the chain of behavioral control. Although drugs of abuse continue to elevate NAS DA levels, this may no longer be as important in controlling the ongoing instrumental behaviors of the organism. Rather, the repeated elevation of NAS DA activity may actually result, through ongoing psychomotor facilitation effects, in various maladaptive aspects of drug abuse behavior [55] such as excessive responses to drug-related cues and paranoid schizophrenic-like symptoms.

Thus, the present view of NAS DA function generates the following hypothesis: When drug-seeking behavior is repeated and comes to be an established habit in a fixed environment, NAS DA transmission is no longer essential to express instrumental responses for the drug since the habit approach system can guide organisms to drugs. Indeed, our preliminary data indicate that although 6-OHDA lesions of the ventral striatum attenuate the acquisition of ethanol self-administration, the same manipulation has little effect on animals that have already developed the habit of ethanol self-administration prior to the imposition of lesions [109]. Likewise, it has been reported that the acquisition of a conditioned place preference with morphine or heroin administration to naive rats is disrupted severely by 6-OHDA lesions of the NAS and intra-NAS injections of DA antagonists [236,242], but such effects have yet to be contrasted with stable maintenance effects. As discussed above, in animals that have already acquired self-administration of opioids and ethanol, 6-OHDA lesions of the ventral striatum have very little effect on self-administration [58,64,78,109,183,201]. These effects now need to be contrasted to the acquisition of self-administration behaviors and the present hypothesis suggests that the acquisition of all forms of drug self-administration behavior will be reduced with NAS DA damage. This hypothesis may even be extended to human drug abuse. Once a drug intake habit is established (i.e., as one has becomes addicted), NAS DA is no longer needed to sustain such habits.

To support the hypothesis mentioned above, we should be able to account why DA depletion of the ventral striatum with 6-OHDA severely disrupts the self-administration of psychostimulants that have been acquired *prior* to lesion placement [33,78,145,183,212,213]? Let us provide an alternative hypothesis. The straightforward, established explanation is that the psychologically rewarding effects of psychostimulants are largely *mediated* by DAergic mechanisms within the ventral striatum. To do this, we need to introduce an important conceptual distinction between effects that are *mediated* vs. those that are *initiated*. We propose that the ventral striatum does not mediate but only initiates the rewarding effects of psychostimulants. At a trivial level, it should be obvious that the ventral striatum alone is not sufficient to mediate such effects, which must be dependent on a variety of other CNS mechanisms. However, at a more substantive level, we would argue that DA in the NAS may be little more than the initial link in a cascade of brain effects that constitute 'DA reward'. Because 6-OHDA destroys the very cytoarchitectural mechanisms that *initiate* the critical cascade of effects of psychostimulants, administration of psychostimulants no longer initiates rewarding effects.

According to this view, any of a variety of substances that can locally arouse the NAS DA system or the flexible approach system should be self-administered readily into the brain, even though global effects of such agents via systemic or intraventricular routes might not support self-administration behaviors. Such an idea is supported by recent findings using intracranial self-administration techniques utilizing substances without apparent abuse potential. The modulations of several neurotransmitters (e.g., acetylcholine and GABA) which converge on the meso-accumbens axis can, in fact, serve as powerful reinforcers [54,80,106,110,111]. Such a role of other neurotransmitters in mediating the behavioral consequences of apparent drug reward effects is often underemphasized, perhaps because systemic manipulations of those neurotransmitters do not typically have any apparent reinforcing effect in either humans or animals, while the more direct DA stimulants readily do. The detailed mechanisms of neural circuitries that mediate such effects and how they operate in natural situations remain to be worked out, but may have important implications for the control of drug abuse.

7.2.2. Drug reinstatement issues

Currently, only a handful of studies have actually examined the role of NAS DA evaluating direct manipulations on reinstatement behaviors. Despite the paucity of data, however, the meso-accumbens DA system is commonly thought to play an important role in reinstatement of drug self-administration (see Ref. [233]), especially since the meso-accumbens DA system now appears to be widely believed to be involved in the direct *mediation* of incentive motivation [214,249]. Indeed, systemic treatments of DA agonists can reinstate self-administration of cocaine and heroin in animals that have been subjected to extinction [302]. More importantly, intra-NAS injections of D-amphetamine also reinstate heroin self-administration after extinction [250]. Since we have proposed that NAS DA is not involved in retrieval of incentive properties of specific environments, such findings may be deemed contradictory to the present hypothesis. However, they are not. According to our hypothesis, animals reinstate such self-administration behavior because the activation of NAS DA recep-

tors facilitates flexible approach responses; i.e., reinstated behavior is not due to the retrieval of incentive stimuli but due to a generalized arousal of goal-directed responses in an animal's behavioral repertoire which have been previously directed toward uncertain outcomes (i.e., flexible responses).

Our hypothesis appears to be supported by a recent antagonist study. McFarland and Ettenberg [156] initially trained animals to produce an instrumental response for heroin reward given conditioned stimuli but no unconditioned stimuli. After establishing reliable responding, animals were subjected to an extinction procedure without providing the conditioned stimuli (This treatment is important to retain incentive properties of the conditioned stimuli.). When animals were presented with the conditioned stimuli, the animals reinstated responses equally well whether or not pretreated systemically with haloperidol. This result is consistent with our hypothesis that NAS DA is not necessary for retrieving incentive properties out of environmental stimuli, while a simple incentive motivational hypothesis of reinstatement does not appear to be able to provide a viable explanation for this finding. However, it has yet to be determined whether direct manipulation of NAS DA with antagonists can also provide similar results as the systemic manipulations.

7.3. More predictions

To be useful, theoretical views should help us to interrelate diverse observations and to provide conceptual frameworks from which new predictions can be derived. The present conceptual framework does lead to a variety of new hypotheses and empirical perspectives: In addition to ones already discussed in the course of this review (see Sections 4.4, 6.7, 7.1 and 7.2), we would share several additional ones which, to our knowledge, remain to be evaluated.

(1) Since rats normally forage for food, we would predict that animals freely exploring an open field (with lots of interesting objects) or a holeboard, where treats are randomly placed in different holes each day vs. predictable holes, there would be characteristic investigation-related changes in the activity of VTA-DA projecting the NAS. Our hypothesis is that in a holeboard, each investigation of a hole would be accompanied by more VTA bursting and NAS DA release, more so when the placements of rewards are unpredictable than when they are predictable. Likewise, in the open field, bursting would occur whenever animals encountered new objects. Finally, when animals are consuming small treats, the DA arousal should be linked most tightly to the brief foraging segments that are interspersed between successive consummatory acts. In other words, active foraging–searching would be systematically related to neuronal activity in the meso-accumbens DA system.

As a corollary to this, we would predict that facilitation of NAS DA activity will promote foraging in such situations, as well as more structured operant situations where animals are working on various schedules of reinforcement. For instance, we would especially predict that facilitation of DA in the NAS would increase fixed ratio (FR) 'strain' for all rewards. In other words, as one gradually increases the FR requirements, animals with heightened NAS DA activity should go to higher ratio levels while those with lower than normal activities would terminate responding at lower levels. (Note: We can happily report that since the submission of this paper, this prediction has been confirmed in a recent report by Aberman and Salamone [2].)

(2) Disruption of NAS DA arousal should retard the acquisition of place-preference conditioning with any reward that would normally produce place conditioning. However, if place preferences have had already been well-established, these same NAS DA manipulations should have more modest effects on the expression of the behavior. Moreover, the present hypothesis makes novel predictions in *place-aversion conditioning* as well: disruption of NAS DA transmission should retard acquisition conditioning with most stimuli that would normally produce place aversions. On the other hand, once place aversions have been established, they should again be influenced more modestly by those manipulations.

(3) Since arousal of brain DA in aversive environmental circumstances is seen to be an essential component for adaptive avoidance (approach to safety), it would be predicted that in learned-helplessness paradigms, experimental animals (i.e., the helpless ones) would exhibit less NAS DA release than controls (i.e., the animals that had control over the negative events). Of course, all animals may exhibit initially high DA release while they are searching for avenues of safety. The low DA levels should only gradually emerge in the helpless animals as they stop seeking solutions to their dilemma.

A variety of other predictions could be made, and have been made throughout this paper. To the extent that such predictions hold, the present view can be empirically confirmed. To the extent that they do not, the present views can be disconfirmed.

8. Coda: the function of NAS DA and beyond

As should be evident from this review, a massive amount of perplexing evidence is now encouraging investigators to utilize more subtle concepts than those that have been used before — in the present case to envision the meso-accumbens DA system, along with closely related brain systems, as a generalized approach-seeking system that was designed by evolution to allow organisms to generate efficient goal-directed activities in response to a large number of positive and negative incentives. Through experience, this system can become increasingly oriented

toward the pursuit of positive incentives or toward the alleviation of negative ones. In short, NAS DA is a brain component that allows organisms to rapidly orient attentional resources to novel events, to extract 'meaning' from these sensory experiences and to energize a unique class of investigatory and appetitive approach responses to a great variety of biologically important environmental events.

The view advocated here is based on the simple recognition that animals subsist in unpredictable worlds and that their brains have to create predictable meanings from the relationships among those events. In sum, it would seem that the meso-accumbens DA system is (i) designed to respond to novelty, (ii) able to focus the animals' sensorimotor apparatus into approach, seeking and investigatory activities directed toward those novel events, especially if they are related to rewards, and (iii) if some of those events are life-supporting or life-threatening, to sustain the aforementioned response tendencies toward predictive environmental cues on future occasions. In other words, we envision NAS DA to be a central component in the dynamic creation of value-laden relational connections among world events and the generation of invigorated approach and seeking responses to all types of environmental events that help sustain survival.

Obviously, the only way NAS DA can operate is within the context of a great number of other specific brain systems that have not been discussed here in any detail. For instance, there are those bound to many physiological influences on this system which allow it to better cope with environmental exigencies. Some have already been demonstrated: For instance, social isolation and other forms of stress modify the arousability of this system [24,125]. It is easy to imagine that such effects may allow animals to behave more effectively in a variety of situations. However, such issues would fall under the category of how various factors influence the long-term competence of the NAS DA system as opposed to what are the basic behavioral functions of this system. Also, in no way do we intend to imply that other DA systems do not participate in closely related brain functions. Most likely, mesocortical DA systems participate in a harmonious parallel streams of psychobehavioral control, establishing higher types of behavioral priorities that are mediated by the more cognitive sensorimotor integrations of the cortex.

There is also a great deal of work left to be done in characterizing the details of NAS DA functions. How the NAS DA components interact with other critical brain systems remains to be fully characterized. Major questions include: What types of information are actually coming in from structures that send major afferent inputs to the NAS? In particular, what are the functional roles of glutamate inputs arising from hippocampus, amygdala, thalamus and the prefrontal cortices? What is the nature of the interactions among these inputs and NAS DA to how they influence GABAergic projection neurons of the NAS? What do the various NAS efferents contribute to the many structures in which they terminate (Fig. 1)? Indeed, some are already expending substantial efforts on such questions (e.g., Refs. [124,209]), and these types of research are bound to remain as major focuses of behavioral neuroscience during the next decade.

Our conceptual approach here has been to elucidate the local functions of a well-identified discrete neurochemical system of the brain in relation to the more global functions in which they participate. We believe that this psychobiological strategy is a fruitful one, and there are many other discrete brain systems, both aminergic and peptidergic, for which this strategy could be deployed.

Acknowledgements

We would like to thank Drs. David Highfield, Roy Wise and Jeff Witkin for their helpful comments on earlier versions of the manuscript. The first author would like to express appreciation to Roy Wise for his discussions on conceptual issues and support on this review and related projects.

References

[1] E.D. Abercrombie, K.A. Keefe, D.S. DiFrischia, M.J. Zigmond, Differential effect of stress on in vivo dopamine release in striatum, nucleus accumbens, and medial frontal cortex, J. Neurochem. 52 (1989) 1655–1658.

[2] J.E. Aberman, J.D. Salamone, Nucleus accumbens dopamine depletions make rats more sensitive to high ratio requirements but do not impair primary food reinforcement, Neuroscience 92 (1999) 545–552.

[3] S. Ahlenius, V. Hillegaart, G. Thorell, O. Magnusson, C.J. Fowler, Suppression of exploratory locomotor activity and increase in dopamine turnover following the local application of cis-flupenthixol into limbic projection areas of the rat striatum, Brain Res. 402 (1987) 131–138.

[4] Z. Amit, Z.H. Galina, Stress-induced analgesia plays an adaptive role in the organization of behavioral responding, Brain Res. Bull. 21 (1988) 955–958.

[5] L.E. Annett, A. McGregor, T.W. Robbins, The effects of ibotenic acid lesions of the nucleus accumbens on spatial learning and extinction in the rat, Behav. Brain Res. 31 (1989) 231–242.

[6] P.K. Anokhin, A new conception of the physiological architecture of conditioned reflex, in: A. Fessard, R.W. Gerard, J. Konorski (Eds.), Brain Mechanisms and Learning: A Symposium, Blackwell, Oxford, 1961.

[7] V.P. Bakshi, A.E. Kelley, Dopaminergic regulation of feeding behavior: I. Differential effects of haloperidol microinfusion into three striatal subregions, Psychobiology 19 (1991) 223–232.

[8] V.P. Bakshi, A.E. Kelley, Dopaminergic regulation of feeding behavior: II. Differential effects of amphetamine microinfusion into three striatal subregions, Psychobiology 19 (1991) 233–242.

[9] M.T. Bardo, R.L. Donohew, N.G. Harrington, Psychobiology of novelty-seeking and drug-seeking behavior, Behav. Brain Res. 77 (1996) 23–43.

[10] V. Bassareo, G. Di Chiara, Differential influence of associative and non-associative 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.

[11] V. Bassareo, G. Tanda, P. Petromilli, C. Giua, G. Di Chiara, Non-psychostimulant drugs of abuse and anxiogenic drugs activate with differential selectively dopamine transmission in the nucleus accumbens and in the medial prefrontal cortex of the rat, Psychopharmacology (Berlin) 124 (1996) 293–299.
[12] B. Beer, L.G. Lenard, Differential effects of intraventricular administration of 6-hydroxydopamine on behavior of rats in approach and avoidance procedures: reversal of avoidance decrements by diazepam, Pharmacol. Biochem. Behav. 3 (1975) 879–886.
[13] R.J. Beninger, The role of dopamine in locomotor activity and learning, Brain Res. Rev. 6 (1983) 173–196.
[14] G.S. Berns, J.D. Cohen, M.A. Mintun, Brain regions responsive to novelty in the absence of awareness, Science 276 (1997) 1272–1275.
[15] G.G. Berntson, D.J. Micco, Organization of brainstem behavioral systems, Brain Res. Bull. 1 (1976) 471–483.
[16] K.C. Berridge, T.E. Robinson, What is the role of dopamine in reward: hedonic impact, reward learning or incentive salience?, Brian Res. Rev. 28 (1998) 309–369.
[17] M. Bertolucci-D'Angio, A. Serrano, B. Scatton, Mesocorticolimbic dopaminergic systems and emotional states, J. Neurosci. Methods 34 (1990) 135–142.
[18] D. Bindra, How adaptive behavior is produced: a perceptual–motivational alternative to response-reinforcement, Behav. Brain Sci. 1 (1978) 41–91.
[19] D. Bindra, Neuropsychological interpretation of the effects of drive and incentive-motivation on general activity and instrumental behavior, Psychol. Rev. 75 (1968) 1–22.
[20] D. Bindra, A unified account of classical conditioning and operant training, in: A.H. Black, W.F. Prokasy (Eds.), Classical Conditioning: II. Current Research and Theory, Appleton-Century-Crofts, New York, 1972, pp. 453–481.
[21] J.R. Blackburn, J.G. Pfaus, A.G. Phillips, Dopamine functions in appetitive and defensive behaviors, Prog. Neurobiol. 39 (1992) 247–279.
[22] 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.
[23] C.D. Blaha, A.G. Phillips, Application of in vivo electrochemistry to the measurement of changes in dopamine release during intracranial self-stimulation, J. Neurosci. Methods 34 (1990) 125–133.
[24] G. Blanc, D. Herve, H. Simon, A. Lisoprawski, J. Glowinski, J.P. Tassin, Response to stress of mesocorticofrontal dopaminergic neurones in rats after long-term isolation, Nature 284 (1980) 265–267.
[25] R.C. Bolles, Reinforcement, expectancy, and learning, Psychol. Rev. 79 (1972) 394–409.
[26] R.V.D. Bos, G.A. Charria Ortiz, A.C. Bergmans, A.R. Cools, Evidence that dopamine in the nucleus accumbens is involved in the ability of rats to switch to cue-directed behaviors, Behav. Brain Res. 42 (1991) 107–114.
[27] R.V.D. Bos, A.R. Cools, The involvement of the nucleus accumbens in the ability of rats to switch to cue-directed behaviors, Life Sci. 44 (1989) 1697–1704.
[28] P.U. Bracs, D.M. Jackson, P. Gregory, Dopamine applied into the nucleus accumbens and discriminative avoidance in rats, Pharmacol. Biochem. Behav. 20 (1984) 49–54.
[29] P.U. Bracs, D.M. Jackson, P. Gregory, a-Methyl-*p*-tyrosine inhibition of a conditioned avoidance response: reversal by dopamine applied to the nucleus accumbens, Psychopharmacology (Berlin) 77 (1982) 159–163.
[30] 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.
[31] C.L.E. Broekkamp, A.J.J. Pijnenburg, A.R. Cools, J.M. Van Rossum, The effect of microinjections of amphetamine into the neostriatum and the nucleus accumbens on self-stimulation behavior, Psychopharmacologia 42 (1975) 179–183.
[32] M. Cador, J.R. Taylor, T.W. Robbins, Potentiation of the effects of reward-related stimuli by dopaminergic-dependent mechanisms in the nucleus accumbens, Psychopharmacology (Berlin) 104 (1991) 377–385.
[33] S.B. Caine, G.F. Koob, Effects of mesolimbic dopamine depletion on responding maintained by cocaine and food, J. Exp. Anal. Behav. 61 (1994) 213–221.
[34] E. Carboni, A. Imperato, L. Perezzani, G. Di Chiara, Amphetamine, cocaine, phencyclidine and nomifensine increases extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats, Neuroscience 28 (1989) 653–661.
[35] W.A. Carlezon Jr., D.P. Devine, R.A. Wise, Habit-forming actions of nomifensine in nucleus accumbens, Psychopharmacology (Berlin) 122 (1995) 194–197.
[36] G.D. Carr, H.C. Fibiger, A.G. Phillips, Conditioned place preference as a measure of drug reward, in: J.M. Liebman, S.J. Cooper (Eds.), The Neuropharmacological Basis of Reward, Clarendon Press, Oxford, 1989, pp. 264–319.
[37] G.D. Carr, N.M. White, Anatomical disassociation of amphetamines rewarding and aversive effects: an intracranial microinjection study, Psychopharmacology (Berlin) 89 (1986) 340–346.
[38] G.D. Carr, N.M. White, Conditioned place preference from intra-accumbens but not intra-caudate amphetamine injections, Life Sci. 33 (1983) 2551–2557.
[39] G.D. Carr, N.M. White, Contributions of dopamine terminal areas to amphetamine-induced anorexia and adipsia, Pharmacol. Biochem. Behav. 25 (1986) 17–22.
[40] G.D. Carr, N.M. White, Effects of systemic and intracranial amphetamine injections on behavior in the open field: a detailed analysis, Pharmacol. Biochem. Behav. 27 (1987) 113–122.
[41] M.A. Cenci, P. Kalen, R.J. Mandel, A. Bjorklund, Regional differences in the regulation of dopamine and noradrenaline release in medial frontal cortex, nucleus accumbens and caudate–putamen: a microdialysis study in the rat, Brain Res. 581 (1992) 217–228.
[42] K. Chergui, M.F. Suaud-Chagny, F. Gonon, Non-linear relationship between impulse flow, dopamine release and dopamine elimination in the rat brain in vivo, Neuroscience 62 (1994) 641–645.
[43] W.H. Church, J.B. Justice, D.B. Neill, Detecting behaviorally relevant changes in extracellular dopamine with microdialysis, Brain Res. 412 (1987) 397–399.
[44] P.B.S. Clarke, K.B.J. Franklin, Infusions of 6-hydroxydopamine into the nucleus accumbens abolish the analgesic effect of amphetamine but not of morphine in the formalin test, Brain Res. 580 (1992) 106–110.
[45] L.M. Colle, R.A. Wise, Effects of nucleus accumbens amphetamine on lateral hypothalamic brain stimulation reward, Brain Res. 459 (1988) 361–368.
[46] D. Corbett, Differences in sensitivity to neuroleptic blockade: medial forebrain bundle versus frontal cortex self-stimulation, Behav. Brain Res. 36 (1990) 91–96.
[47] M.S. Cousins, J.D. Sokolowski, J.D. Salamone, Differential effects of nucleus accumbens and ventrolateral striatal dopamine depletions on instrumental response selection in the rat, Pharmacol. Biochem. Behav. 46 (1993) 943–951.
[48] 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 (Berlin) 116 (1994) 529–537.
[49] T.J. Crow, The relation between electrical self-stimulation sites and catecholamine-containing neurones in the rat mesencephalon, Experientia 27 (1971) 662.
[50] A. Dahlstrom, K. Fuxe, Evidence for the existence of monoamine-containing neurons in the central nervous system: I. Demonstration

of monoamine in the cell bodies of brain stem neurons, Acta Physiol. Scand. 62 (232) (1964) 1–55, Suppl.
[51] A.R. Damasio, The Feeling of What Happens: Emotion, Reason, and the Human Brain, G.P. Putnam, New York, 1999.
[52] A.R. Damasio, Emotion in the perspective of an integrated nervous system, Brain Res. Rev. 26 (1998) 83–86.
[53] G. Damasma, 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.
[54] V. David, T.P. Durkin, P. Cazala, Self-administration of the $GABA_A$ antagonist bicuculline into the ventral tegmental area in mice: dependence on D2 dopaminergic mechanisms, Psychopharmacology (Berlin) 130 (1997) 85–90.
[55] G. Di Chiara, A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use, J. Psychopharmacol. 12 (1998) 54–67.
[56] A. Dickinson, Expectancy theory in animal conditioning, in: S.B. Klein, R.R. Mowrer (Eds.), Contemporary Learning Theories: Pavlovian Conditioning and the Status of Traditional Learning Theory, Lawrence Erlbaum Associates, Hillsdale, NJ, 1989, pp. 279–308.
[57] A. Dickinson, Instrumental conditioning, in: N.J. Mackintosh (Ed.), Animal Learning and Cognition, Academic Press, San Diego, 1994, pp. 45–79.
[58] S.I. Dworkin, G.F. Guerin, C. Co, N.E. Goeders, J.E. Smith, Lack of an effect of 6-hydroxydopamine lesions of the nucleus accumbens on intravenous morphine self-administration, Pharmacol. Biochem. Behav. 30 (1988) 1051–1057.
[59] B.A. Ellenbroek, D.A. Knobbout, A.R. Cools, The role for mesolimbic and nigro-striatal dopamine in latent inhibition as measured with the conditioned taste aversion paradigm, Psychopharmacology (Berlin) 129 (1997) 112–120.
[60] K.R. Evans, F.J. Vaccarino, Intra-nucleus accumbens amphetamine: dose-dependent effects on food intake, Pharmacol. Biochem. Behav. 25 (1986) 1149–1151.
[61] J.L. Evenden, M. Carli, The effects of 6-hydroxydopamine lesions of the nucleus accumbens and caudate nucleus of rats on feeding in a novel environment, Behav. Brain Res. 15 (1985) 63–70.
[62] B.J. Everitt, Sexual motivation: a neural and behavioral analysis of the mechanisms underlying appetitive and copulatory responses of male rats, Neurosci. Biobehav. Rev. 14 (1990) 217–232.
[63] 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.
[64] C. Fahlke, S. Hansen, J.A. Engel, E. Hard, Effects of ventral striatal 6-OHDA lesions or amphetamine sensitization on ethanol consumption in the rat, Pharmacol. Biochem. Behav. 47 (1994) 345–349.
[65] J.H. Fallon, R.Y. Moore, Catecholamine innervation of the basal forebrain: IV. Topography of the dopamine projection to the basal forebrain and neostriatum, J. Comp. Neurol. 180 (1978) 545–580.
[66] H.C. Fibiger, Drugs and reinforcement mechanisms: a critical review of the catecholamine theory, Annu. Rev. Pharmacol. Toxicol. 18 (1978) 37–56.
[67] H.C. Fibiger, D.A. Carter, A.G. Phillips, Decreased intracranial self-stimulation after neuroleptics or 6-hydroxydopamine: evidence for mediation by motor deficits rather than by reduced reward, Psychopharmacology (Berlin) 47 (1976) 21–27.
[68] H.C. Fibiger, A.G. Phillips, Reward, motivation, cognition: psychobiology of mesotelencephalic dopamine systems, in: V.B. Mountcastle, F.E. Bloom, S.R. Geiger (Eds.), Handbook of Physiology: 4. The Nervous System, American Physiological Society, Bethesda, MD, 1986, pp. 647–675.
[69] J.S. Fink, G.P. Smith, Mesolimbicocortical dopamine terminal fields are necessary for normal locomotor and investigatory exploration in rats, Brain Res. 199 (1980) 359–384.
[70] S.B. Floresco, J.K. Seamans, A.G. Phillips, A selective role for dopamine in the nucleus accumbens of the rat in random foraging but not delayed spatial win-shift-based foraging, Behav. Brain Res. 80 (1996) 161–168.
[71] G. Fouriezos, P. Hansson, R.A. Wise, Neuroleptic-induced attenuation of brain stimulation reward in rats, J. Comp. Physiol. Psychol. 92 (1978) 661–671.
[72] G. Fouriezos, R. Wise, Pimozide-induced extinction of intracranial self-stimulation: response patterns rule out motor or performance deficits, Brain Res. 103 (1976) 377–380.
[73] K.B.J. Franklin, Analgesia and the neural substrate of reward, Neurosci. Biobehav. Rev. 13 (1989) 149–154.
[74] K.B.J. Franklin, Catecholamines and self-stimulation: reward and performance effects dissociated, Pharmacol. Biochem. Behav. 9 (1978) 813–820.
[75] C.R. Gallistel, G. Freyd, Quantitative determination of the effects of catecholaminergic agonists and antagonists on the rewarding efficacy of brain stimulation, Pharmacol. Biochem. Behav. 26 (1987) 731–741.
[76] C.R. Gallistel, D. Karras, Pimozide and amphetamine have opposing effects on the reward summation function, Pharmacol. Biochem. Behav. 20 (1984) 73–77.
[77] D.C. German, K.F. Manaye, Midbrain dopaminergic neurons (nuclei A8, A9, A10): three-dimensional reconstruction in the rat, J. Comp. Neurol. 331 (1993) 297–309.
[78] M.A. Gerrits, J.M. Van Ree, Effects of nucleus accumbens dopamine depletion on motivational aspects involved in initiation of cocaine and heroin self-administration in rats, Brain Res. 713 (1996) 114–124.
[79] S.E. Glickman, B.B. Schiff, A biological theory of reinforcement, Psychol. Rev. 74 (1967) 81–109.
[80] P.W. Glimcher, A.A. Giovino, B.G. Hoebel, Neurotensin self-injection in the ventral tegmental area, Brain Res. 403 (1987) 147–150.
[81] N.E. Goeders, A neuroendocrine role in cocaine reinforcement, Psychoneuroendocrinology 22 (1997) 237–259.
[82] A.A. Grace, The tonic/phasic model of dopamine system regulation: its relevance for understanding how stimulant abuse can alter basal ganglia function, Drug Alcohol Depend. 37 (1995) 111–129.
[83] A.A. Grace, H. Moore, Regulation of information flow in the nucleus accumbens: a model for the pathophysiology of schizophrenia, in: M.F. Lenzenweger, H. Dworkin (Eds.), Origins and Development of Schizophrenia: Advances in Experimental Psychopathology, American Psychological Association Press, Washington, DC, 1998, pp. 123–157.
[84] A. Gratton, B.J. Hoffer, G.A. Gerhardt, Effects of electrical stimulation of brain reward sites on release of dopamine in rat: an in vivo electrochemical study, Brain Res. Bull. 21 (1988) 319–324.
[85] J.A. Gray, The Psychology of Fear and Stress, 2nd edn., Cambridge Univ. Press, Cambridge, 1987, 422 pp.
[86] J.A. Gray, M.H. Joseph, D.R. Hemsley, A.M.J. Young, E.C. Warburton, P. Bouleguez, G. Grigoryan, S.L. Peters, J.N.P. Rawlings, C.-T. Taib, B.K. Yee, H. Cassaday, I. Weiner, G. Gal, O. Gusak, D. Joel, E. Shadach, U. Shalev, R. Tarrasch, J. Feldon, The role of mesolimbic dopaminergic and retrohippocampal afferents to the nucleus accumbens in latent inhibition: implications for schizophrenia, Behav. Brain Res. 71 (1995) 19–31.
[87] J.A. Gray, P.M. Moran, G. Grigoryan, S.L. Peters, A.M.J. Young, M.H. Joseph, Latent inhibition: the nucleus accumbens connection revisited, Behav. Brain Res. 88 (1997) 27–34.
[88] J.A. Gray, A.M.J. Young, M.H. Joseph, Dopamine's role, Science 278 (1997) 1548–1549.
[89] A.M. Graybiel, The basal ganglia and chunking of action repertories, Neurobiol. Learn. Mem. 70 (1998) 119–136.
[90] J.J. Hagan, J.E. Alpert, R.G. Morris, S.D. Iversen, The effects of

central catecholamine depletions on spatial learning in rats, Behav. Brain Res. 9 (1983) 83–104.
[91] L. Heimer, D.S. Zahm, G.F. Alheid, Basal Ganglia, in: G. Paxinos (Ed.), The Rat Nervous System, Academic Press, San Diego, 1995, pp. 579–628.
[92] 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.
[93] L. Hernandez, B.G. Hoebel, Feeding and hypothalamic stimulation increase dopamine turnover in the accumbens, Physiol. Behav. 44 (1988) 599–606.
[94] 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.
[95] O. Hikosaka, Neural systems for control of voluntary action — a hypothesis, Adv. Biophys. 35 (1998) 81–102.
[96] R.T. Hill, Facilitation of conditioned reinforcement as a mechanism of psychomotor stimulation, in: E. Costa, S. Garattini (Eds.), Amphetamine and Related Compounds, Raven Press, New York, 1970, pp. 781–795.
[97] B.G. Hoebel, L. Hernandez, D.H. Schwartz, G.P. Mark, G.A. Hunter, Microdialysis studies of brain norepinephrine, serotonin, and dopamine release during ingestive behavior, Ann. N.Y. Acad. Sci. 575 (1988) 171–193.
[98] B.G. Hoebel, A.P. Monaco, L. Hernandez, E.F. Aulisi, B.G. Stanley, L. Lenard, Self-infusion of amphetamine directly into the brain, Psychopharmacology (Berlin) 81 (1983) 158–163.
[99] D.C. Hoffman, The use of place conditioning in studying the neuropharmacology of drug reinforcement, Brain Res. Bull. 23 (1989) 373–387.
[100] J.R. Hollerman, W. Schultz, Activity of dopamine neurons during learning in a familiar task context, Soc. Neurosci. Abstr. 22 (1996) 1388.
[101] J.R. Hollerman, W. Schultz, Dopamine neurons report an error in the temporal prediction of reward during learning, Nat. Neurosci. 1 (1998) 304–309.
[102] K.L. Hollis, Contemporary research on Pavlovian conditioning: a 'new' functional analysis, Am. Psychol. 52 (1997) 956–965.
[103] M.S. Hooks, P.W. Kalivas, The role of meso-accumbens–pallidal circuitry in novelty-induced behavioral activation, Neuroscience 64 (1995) 587–597.
[104] J.C. Horvitz, T. Stewart, B.L. Jacobs, Burst activity of ventral tegmental dopamine neurons is elicited by sensory stimuli in the awake cat, Brain Res. 759 (1997) 251–258.
[105] T. Humby, L.S. Wilkinson, T.W. Robbins, M.A. Geyer, Prepulses inhibit startle-induced reductions of extracellular dopamine in the nucleus accumbens of rat, J. Neurosci. 16 (1996) 2149–2156.
[106] S. Ikemoto, B.S. Glazier, J.M. Murphy, W.J. McBride, Rats self-administer carbachol directly into the nucleus accumbens, Physiol. Behav. 63 (1998) 811–814.
[107] S. Ikemoto, B.S. Glazier, J.M. Murphy, W.J. McBride, Role of D1 and D2 receptors in the nucleus accumbens in mediating reward, J. Neurosci. 17 (1997) 8580–8587.
[108] S. Ikemoto, N.E. Goeders, Microinjections of dopamine agonists and cocaine elevate plasma corticosterone: dissociation effects among the ventral and dorsal striatum and medial prefrontal cortex, Brain Res. 814 (1998) 171–178.
[109] S. Ikemoto, W.J. McBride, J.M. Murphy, L. Lumeng, T.-K. Li, 6-OHDA-lesions of the nucleus accumbens disrupt the acquisition but not the maintenance of ethanol consumption in the alcohol-preferring P line of rats, Alcohol. Clin. Exp. Res. 21 (1997) 1042–1046.
[110] S. Ikemoto, J.M. Murphy, W.J. McBride, Regional differences within the rat ventral tegmental area for muscimol self-infusions, Pharmacol. Biochem. Behav. 61 (1998) 87–92.
[111] S. Ikemoto, J.M. Murphy, W.J. McBride, Self-infusion of $GABA_A$ antagonists directly into the ventral tegmental area and adjacent regions, Behav. Neurosci. 111 (1997) 369–380.
[112] S. Ikemoto, J. Panksepp, Dissociations between appetitive and consummatory responses by pharmacological manipulations of reward-relevant brain regions, Behav. Neurosci. 110 (1996) 331–345.
[113] S. Ikemoto, J. Panksepp, The relationship between self-stimulation and sniffing in rats: does a common brain system mediate these behaviors?, Behav. Brain Res. 61 (1994) 143–162.
[114] A. Imperato, L. Angelucci, P. Casolini, A. Zocchi, S. Puglisi-Allegra, Repeated stressful experiences differently affect limbic dopamine release during and following stress, Brain Res. 577 (1992) 194–199.
[115] A. Imperato, G. Di Chiara, Preferential stimulation of dopamine release in the nucleus accumbens of freely moving rats by ethanol, J. Pharmacol. Exp. Ther. 239 (1986) 219–228.
[116] A. Imperato, A. Mulas, G. Di Chiara, Nicotine preferentially stimulates dopamine release in the limbic system of freely moving rats, Eur. J. Pharmacol. 132 (1986) 337–338.
[117] A. Imperato, S. Puglisi-Allegra, P. Casolini, L. Angelucci, Changes in brain dopamine and acetylcholine release during and following stress are independent of the pituitary–adrenocortical axis, Brain Res. 538 (1991) 111–117.
[118] A. Imperato, S. Puglisi-Allegra, P. Casolini, A. Zocchi, L. Angelucci, Stress-induced enhancement of dopamine and acetylcholine release in limbic structures: role of corticosterone, Eur. J. Pharmacol. 165 (1989) 337–338.
[119] D.M. Jackson, S. Ahlenius, N.-E. Anden, J. Engel, Antagonism by locally applied dopamine into the nucleus accumbens or the corpus striatum of *a*-methyltyrosine-induced disruption of conditioned avoidance behaviour, J. Neural Transm. 41 (1977) 231–239.
[120] D.M. Jackson, N. Anden, A. Dahlstrom, A functional effect of dopamine in the nucleus accumbens and in some other dopamine-rich parts of the rat brain, Psychopharmacologia 45 (1975) 139–149.
[121] B. Johnels, Locomotor hypokinesia in the reserpine-treated rat: drug effects from the corpus striatum and nucleus accumbens, Pharmacol. Biochem. Behav. 17 (1982) 283–289.
[122] G.H. Jones, T.W. Robbins, Differential effects of mesocortical, mesolimbic, and mesostriatal dopamine depletion on spontaneous, conditioned, and drug-induced locomotor activity, Pharmacol. Biochem. Behav. 43 (1992) 887–895.
[123] 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.
[124] P.W. Kalivas, M. Nakamura, Neural systems for behavioral activation and reward, Curr. Opin. Neurobiol. 9 (1999) 223–227.
[125] P. Kehoe, W.J. Shoemaker, C. Arons, L. Triano, G. Suresh, Repeated isolation stress in the neonatal rat: relation to brain dopamine systems in the 10-day-old rat, Behav. Neurosci. 112 (1998) 1466–1474.
[126] A.E. Kelley, J.M. Delfs, Dopamine and conditioned reinforcement: I. Differential effects of amphetamine microinjections into striatal subregions, Psychopharmacology (Berlin) 103 (1991) 187–196.
[127] A.E. Kelley, A.M. Gauthier, C.G. Lang, Amphetamine microinjections into distinct striatal subregions cause dissociable effects on motor and ingestive behavior, Behav. Brain Res. 35 (1989) 27–39.
[128] A.E. Kelley, L. Stinus, Disappearance of hoarding behavior after 6-hydroxydopamine lesions of the mesolimbic dopamine neurons and its reinstatement with L-DOPA, Behav. Neurosci. 99 (1985) 531–545.
[129] A.S. Killcross, T.W. Robbins, Differential effects of intra-accumbens and systemic amphetamine on latent inhibition using an on-baseline, within-subject conditioned suppression paradigm, Psychopharmacology (Berlin) 110 (1993) 479–489.
[130] 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.

[131] B.J. Knowlton, J.A. Mangels, L.R. Squire, A neostriatal habit learning system in humans, Science 273 (1996) 1399–1402.
[132] J. Konorski, Integrative Activity of the Brain: An Interdisciplinary Approach, The University of Chicago, Chicago, 1967, 530 pp.
[133] G.F. Koob, E.J. Nestler, The neurobiology of drug addiction, J. Neuropsychiatry Clin. Neurosci. 9 (1997) 482–497.
[134] G.F. Koob, S.J. Riley, S.C. Smith, T.W. Robbins, Effects of 6-hydroxydopamine lesions of the nucleus accumbens septi and olfactory tubercle on feeding, locomotor activity, and amphetamine anorexia in the rat, J. Comp. Physiol. Psychol. 92 (1978) 917–927.
[135] G.F. Koob, H. Simon, J.P. Herman, M. Le Moal, Neuroleptic-like disruption of the conditioned avoidance response requires destruction of both the mesolimbic and nigro-striatal dopamine systems, Brain Res. 303 (1984) 319–329.
[136] M. Le Moal, H. Simon, Mesocorticolimbic dopaminergic network: functional and regulatory roles, Physiol. Rev. 71 (1991) 155–234.
[137] J.M. Liebman, L.L. Butcher, Effects on self-stimulation behavior of drugs influencing dopaminergic neurotransmission mechanisms, Naunyn-Schmiedeberg's Arch. Pharmacol. 277 (1973) 305–318.
[138] Y. Lin, T.J. Morrow, J.A. Kiritsy-Roy, L.C. Terry, K.L. Casey, Cocaine: evidence for supraspinal, dopamine-mediated, non-opiate analgesia, Brain Res. 479 (1989) 306–312.
[139] O. Lindvall, A. Bjorklund, The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method, Acta Physiol. Scand. Suppl. 412 (1974) 1–48.
[140] A.S. Lippa, S.M. Antelman, A.E. Fisher, D.R. Canfield, Neurochemical mediation of reward: a significant role for dopamine?, Pharmacol. Biochem. Behav. 1 (1973) 23–28.
[141] X. Liu, R.E. Strecker, J. Brener, Dopamine depletion in nucleus accumbens influences locomotion but not force and timing of operant responding, Pharmacol. Biochem. Behav. 59 (1998) 737–745.
[142] Y.-C. Liu, B.D. Sachs, J.D. Salamone, Sexual behavior in male rats after radiofrequency or dopamine-depleting lesions in nucleus accumbens, Pharmacol. Biochem. Behav. 60 (1998) 585–592.
[143] T. Ljungberg, P. Aplicella, W. Schultz, Responses of monkey dopamine neurons during delayed alternation performance, Brain Res. 567 (1991) 337–341.
[144] T. Ljungberg, P. Aplicella, W. Schultz, Responses of monkey dopamine neurons during learning of behavioral reactions, J. Neurophysiol. 67 (1992) 145–163.
[145] W.H. Lyness, N.M. Friedle, K.E. Moore, Destruction of dopaminergic nerve terminals in nucleus accumbens: effect on D-amphetamine self-administration, Pharmacol. Biochem. Behav. 11 (1979) 553–556.
[146] 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.
[147] 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.
[148] P. Martel, M. Fantino, Mesolimbic dopaminergic system activity as a function of food reward: a microdialysis study, Pharmacol. Biochem. Behav. 53 (1996) 221–226.
[149] M. Mas, B. Fumero, J.L. Gonzalez-Mora, Voltammetric and microdialysis monitoring of brain monoamine neurotransmitter release during sociosexual interactions, Behav. Brain Res. 71 (1995) 69–79.
[150] F.A. Masterson, M. Crawford, The defense motivation system: a theory of avoidance behavior, Behav. Brain Sci. 5 (1982) 661–696.
[151] L.D. McCullough, M.S. Cousins, J.D. Salamone, The role of nucleus accumbens dopamine in responding on a continuous reinforcement operant schedule: a neurochemical and behavioral study, Pharmacol. Biochem. Behav. 46 (1993) 581–586.
[152] L.D. McCullough, J.D. Salamone, Anxiogenic drugs beta-CCE and FG 7142 increase extracellular dopamine levels in nucleus accumbens, Psychopharmacology (Berlin) 109 (1992) 379–382.
[153] L.D. McCullough, J.D. Salamone, Involvement of nucleus accumbens dopamine in the motor activity induced by periodic food presentation: a microdialysis and behavioral study, Brain Res. 592 (1992) 29–36.
[154] L.D. McCullough, J.D. Sokolowski, J.D. Salamone, A neurochemical and behavioral investigation of the involvement of nucleus accumbens dopamine in instrumental avoidance, Neuroscience 52 (1993) 919–925.
[155] K. McFarland, A. Ettenberg, Haloperidol does not affect motivational processes in an operant runway model of food-seeking behavior, Behav. Neurosci. 112 (1998) 630–635.
[156] K. McFarland, A. Ettenberg, Reinstatement of drug-seeking behavior produced by heroin-predictive environmental stimuli, Psychopharmacology (Berlin) 131 (1997) 86–92.
[157] G.E. Meredith, C.M.A. Pennartz, H.J. Groenewegen, The cellular framework for chemical signalling in the nucleus accumbens, in: G.W. Arbuthnott, P.C. Emson (Eds.), Progress in Brain Research, Vol. 99, Elsevier, Amsterdam, 1993, pp. 3–24.
[158] 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.
[159] S. Mineka, The role of fear in theories of avoidance learning, flooding, and extinction, Psychol. Bull. 86 (1979) 985–1010.
[160] J. Mirenowicz, W. Schultz, Importance of unpredictability for reward responses in primate dopamine neurons, J. Neurophysiol. 72 (1994) 1024–1027.
[161] J. Mirenowicz, W. Schultz, Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli, Nature 379 (1996) 449–451.
[162] G. Mogenson, D. Jones, C.Y. Yim, From motivation to action: functional interface between the limbic system and the motor system, Prog. Neurobiol. 14 (1980) 69–97.
[163] G.J. Mogenson, M. Wu, Disruption of food hoarding by injections of procaine into mediodorsal thalamus, GABA into subpallidal region and haloperidol into accumbens, Brain Res. Bull. 20 (1988) 247–251.
[164] R.Y. Moore, F.E. Bloom, Central catecholamine neuron systems: anatomy and physiology of the dopamine system, Annu. Rev. Neurosci. 1 (1978) 129–169.
[165] M.J. Morgan, K.B. Franklin, 6-Hydroxydopamine lesions of the ventral tegmentum abolish D-amphetamine and morphine analgesia in the formalin test but not in the tail-flick test, Brain Res. 519 (1990) 144–149.
[166] M.J. Morgan, K.B. Franklin, Dopamine receptor subtypes and formalin test analgesia, Pharmacol. Biochem. Behav. 40 (1991) 317–322.
[167] A. Munck, Glucocorticoid inhibition of glucose uptake by peripheral tissues: old and new evidence, molecular mechanisms, and physiological significance, Perspect. Biol. Med. 14 (1971) 265–289.
[168] J.M. Nash, Addicted: why do people get hooked? Mounting evidence points to a powerful brain chemical called dopamine, Time 149 (1997) 68–76.
[169] H. Nishino, T. Ono, K. Muramoto, M. Fukuda, K. Sasaki, Neuronal activity in the ventral tegmental area (VTA) during motivated bar press feeding in the monkey, Brain Res. 413 (1987) 302–313.
[170] R.D. Oades, The role of noradrenaline in tuning and dopamine in switching between signals in the CNS, Neurosci. Biobehav. Rev. 9 (1985) 261–282.
[171] R.D. Oades, G.M. Halliday, Ventral tegmental (A10) system: neurobiology: 1. Anatomy and connectivity, Brain Res. Rev. 12 (1987) 117–165.
[172] J. Olds, Self-stimulation of the brain, Science 127 (1958) 315–324.
[173] J. Olds, P. Milner, Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain, J. Comp. Physiol. Psychol. 47 (1954) 419–427.
[174] J. Panksepp, Affective Neuroscience: The Foundations of Human and Animal Emotions, Oxford Univ. Press, New York, 1998, 466 pp.

[175] J. Panksepp, The anatomy of emotions, in: R. Plutchik, H. Kellerman (Eds.), Emotion: Theory, Research and Experience: III. Biological Foundations of Emotions, Academic Press, Orlando, FL, 1986, pp. 91–124.
[176] J. Panksepp, A critical role for 'affective neuroscience' in resolving what is basic about basic emotions, Psychol. Rev. 99 (1992) 554–560.
[177] J. Panksepp, Hypothalamic integration of behavior: rewards, punishments, and related psychological processes, in: P.J. Morgane, J. Panksepp (Eds.), Handbook of Hypothalamus: 2. Behavioral Studies of the Hypothalamus, Marcel-Dekker, New York, 1981, pp. 289–431.
[178] J. Panksepp, The periconscious substrates of consciousness: affective states and the evolutionary origins of the SELF, J. Consci. Stud. 5 (1998) 566–582.
[179] J. Panksepp, Toward a general psychobiological theory of emotions, Behav. Brain Sci. 5 (1982) 407–467.
[180] I.P. Pavlov, Conditioned Reflexes: An Investigation of the Physiological Activity of the Cerebral Cortex, Oxford Univ. Press, Oxford, England, 1927.
[181] C.M.A. Pennartz, H.J. Groenewegen, F.H. Lopes Da Silva, The nucleus accumbens as a complex of functionally distinct neuronal ensembles: an integration of behavioral, electrophysiological and anatomical data, Prog. Neurobiol. 42 (1994) 719–761.
[182] S.L. Peters, M.H. Joseph, Haloperidol potentiation of latent inhibition in rats: evidence for a critical role at conditioning rather than pre-exposure, Behav. Pharmacol. 4 (1993) 183–186.
[183] H.O. Pettit, A. Ettenberg, F.E. Bloom, G.F. Koob, Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats, Psychopharmacology (Berlin) 84 (1984) 167–173.
[184] H.O. Pettit, J.B. Justice Jr., Dopamine in the nucleus accumbens during cocaine self-administration as studied by in vivo microdialysis, Phamacol. Biochem. Behav. 34 (1989) 899–904.
[185] J.G. Pfaus, G. Damsma, G.G. Nomikos, D.G. Wenkstern, C.D. Blaha, A.G. Phillips, H.C. Fibiger, Sexual behavior enhances central dopamine transmission in the male rat, Brain Res. 530 (1990) 345–348.
[186] J.G. Pfaus, A.G. Phillips, Role of dopamine in anticipatory and consummatory aspects of sexual behavior in the male rat, Behav. Neurosci. 105 (1991) 727–743.
[187] 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.
[188] A.G. Phillips, C.D. Blaha, H.C. Fibiger, Neurochemical correlates of brain-stimulation reward measured by ex vivo and in vivo analyses, Neurosci. Biobehav. Rev. 13 (1989) 99–104.
[189] A.G. Phillips, A. Coury, D. Fiorino, F.G. LePiane, E. Brown, H.C. Fibiger, Self-stimulation of the ventral tegmental area enhances dopamine release in the nucleus accumbens: a microdialysis study, Ann. N.Y. Acad. Sci. 654 (1992) .
[190] G.D. Phillips, S.R. Howes, R.B. Whitelaw, T.W. Robbins, B.J. Everitt, Analysis of the effects of intra-accumbens SKF-38393 and LY-171555 upon the behavioural satiety sequence, Psychopharmacology (Berlin) 117 (1995) 82–90.
[191] G.D. Phillips, T.W. Robbins, B.J. Everitt, Bilateral intra-accumbens self-administration of D-amphetamine: antagonism with intra-accumbens SCH-23390 and sulpiride, Psychopharmacology (Berlin) 114 (1994) 477–485.
[192] O.T. Phillipson, Afferent projections to the ventral tegmental area of Tsai and interfascicular nucleus: a horseradish peroxidase study in the rat, J. Comp. Neurol. 187 (1979) 117–144.
[193] O.T. Phillipson, The cytoarchitecture of the interfascicular nucleus and ventral tegmental area of Tsai in the rat, J. Comp. Neurol. 187 (1979) 85–98.
[194] P.V. Piazza, M. Le Moal, Glucocorticoids as a biological substrate of reward: physiological and pathological implications, Brain Res. Rev. 25 (1997) 359–372.
[195] R.C. Pierce, C.A. Crawford, A.J. Nonneman, B.A. Mattingly, M.T. Bardo, Effect of forebrain dopamine depletion on novelty-induced place preference behavior in rats, Pharmacol. Biochem. Behav. 36 (1990) 321–325.
[196] A.J.J. Pijnenburg, W.M.M. Honig, J.M. Van Rossum, Effects of chemical stimulation of the mesolimbic dopamine system upon locomotor activity, Eur. J. Pharmacol. 35 (1976) 45–58.
[197] A.J.J. Pijnenburg, W.M.M. Honig, J.M. Van Rossum, Inhibition of D-amphetamine-induced locomotor activity by injection of haloperidol into the nucleus accumbens of the rat, Psychopharmacology (Berlin) 41 (1975) 87–95.
[198] A.J.J. Pijnenburg, J.M. Van Rossum, Stimulation of locomotor activity following injection of dopamine into the nucleus accumbens, J. Pharm. Pharmacol. 25 (1973) 1003–1005.
[199] P.V. Rada, G.P. Mark, B.G. Hoebel, Dopamine release in the nucleus accumbens by hypothalamic stimulation–escape behavior, Brain Res. 782 (1998) 228–234.
[200] F.S. Radhakishun, J.M. van Ree, B.H.C. Westerink, Scheduled eating increases dopamine release in the nucleus accumbens of food-deprived rats as assessed with on-line brain dialysis, Neurosci. Lett. 85 (1988) 351–356.
[201] S. Rassnick, L. Stinus, G.F. Koob, The effects of 6-hydroxydopamine lesions of the nucleus accumbens and the mesolimbic dopamine system on oral self-administration of ethanol in the rat, Brain Res. 623 (1993) 16–24.
[202] G.V. Rebec, J.R. Christensen, C. Guerra, M.T. Bardo, Regional and temporal differences in real-time dopamine efflux in the nucleus accumbens during free-choice novelty, Brain Res. 776 (1997) 61–67.
[203] P. Redgrave, T.J. Prescott, K. Gurney, Is the short-latency dopamine response too short to signal reward error?, TINS 22 (1999) 146–151.
[204] R.A. Rescorla, R.L. Solomon, Two-process learning theory: relationships between Pavlovian conditioning and instrumental learning, Psychol. Rev. 74 (1967) 151–182.
[205] 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.
[206] T.W. Robbins, Relationship between reward-enhancing and stereotypical effects of psychomotor stimulant drugs, Nature 264 (1976) 57–59.
[207] 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.
[208] T.W. Robbins, B.J. Everitt, Functional studies of the central catecholamines, Int. Rev. Neurobiol. 23 (1982) 303–365.
[209] T.W. Robbins, B.J. Everitt, Neurobehavioral mechanisms of reward and motivation, Curr. Opin. Neurobiol. 6 (1996) 228–236.
[210] T.W. Robbins, V. Giardini, G.H. Jones, P. Reading, B.J. Sahakian, Effects of dopamine depletion from the caudate–putamen and nucleus accumbens septi on the acquisition and performance of a conditioned discrimination task, Behav. Brain Res. 38 (1990) 243–261.
[211] T.W. Robbins, G.F. Koob, Selective disruption of displacement behavior by lesions of the mesolimbic dopamine system, Nature 285 (1980) 409–412.
[212] D.C.S. Roberts, M.E. Corcoran, H.C. Fibiger, On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine, Pharmacol. Biochem. Behav. 6 (1977) 615–620.
[213] D.C.S. Roberts, G.F. Koob, P. Klonoff, H.C. Fibiger, Extinction and recovery of cocaine self-administration following 6-hydroxydopamine lesions of the nucleus accumbens, Pharmacol. Biochem. Behav. 12 (1979) 781–787.
[214] 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.

[215] E.T. Rolls, B.J. Rolls, P.H. Kelly, S.G. Shaw, R.J. Wood, R. Dale, The relative attenuation of self-stimulation, eating and drinking produced by dopamine-receptor blockade, Psychopharmacologia (Berlin) 38 (1974) 219–230.
[216] 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.
[217] J.D. Salamone, The involvement of nucleus accumbens dopamine in appetitive and aversive motivation, Behav. Brain Res. 61 (1994) 117–133.
[218] J.D. Salamone, M.S. Cousins, L.D. McCullough, D.L. Carriero, R.J. Berkowitz, Nucleus accumbens dopamine release increases during instrumental lever pressing for food but not free food consumption, Pharmacol. Biochem. Behav. 49 (1994) 25–31.
[219] 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.
[220] 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.
[221] 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 (Berlin) 104 (1991) 515–521.
[222] N. Saulskaya, C.A. Marsden, Conditioned dopamine release: dependence upon *N*-methyl-D-aspartate receptors, Neuroscience 67 (1995) 57–63.
[223] M.D. Schechter, D.J. Calcagnetti, Trends in place preference conditioning with a cross-indexed bibliography; 1957–1991, Neurosci. Biobehav. Rev. 17 (1993) 21–41.
[224] T.C. Schneirla, An evolutionary and developmental theory of biphasic process underlying approach and withdrawal, in: M.R. Jones (Ed.), Nebraska Symposium on Motivation, Vol. VII, University of Nebraska, Lincoln, 1959, pp. 1–42.
[225] W. Schultz, Predictive reward signal of dopamine neurons, J. Neurophysiol. 80 (1998) 1–27.
[226] W. Schultz, Responses of midbrain dopamine neurons to behavioral trigger stimuli in the monkey, J. Neurophysiol. 56 (1986) 1439–1461.
[227] 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.
[228] W. Schultz, P. Dayan, P.R. Montague, A neural substrate of prediction and reward, Science 275 (1997) 1593–1599.
[229] W. Schultz, R. Romo, Dopamine neurons of the monkey midbrain: contingencies of responses to stimuli eliciting immediate behavioral reactions, J. Neurophysiol. 63 (1990) 607–624.
[230] W. Schultz, R. Romo, T. Ljungberg, J. Mirenowicz, J.R. Hollerman, A. Dickinson, Reward-related signals carried by dopamine neurons, in: J.R. Houk, J.L. Davis, D. Beiser (Eds.), Models of Information Processing in the Basal Ganglia, MIT Press, Cambridge, MA, 1995, pp. 233–248.
[231] C.R. Schuster, T. Thompson, Self-administration of and behavioral dependence on drugs, Annu. Rev. Pharmacol. 9 (1969) 483–502.
[232] J.R. Searle, How to study consciousness scientifically, Brain Res. Rev. 26 (1998) 379–387.
[233] D.W. Self, E.J. Nestler, Relapse to drug-seeking: neural and molecular mechanisms, Drug Alcohol Depend. 51 (1998) 49–60.
[234] B. Setlow, The nucleus accumbens and learning and memory, J. Neurosci. Res. 49 (1997) 515–521.
[235] C.S. Sherrington, The Integrative Action of the Nervous System, Charles Scribner's Sons, New York, 1906, 433 pp.
[236] T.S. Shippenberg, R. Bals-Kubik, A. Herz, Examination of the neurochemical substrates mediating the motivational effects of opioids: role of the mesolimbic dopamine system and D1 vs. D2 dopamine receptors, J. Pharmacol. Exp. Ther. 265 (1993) 53–59.
[237] B.F. Skinner, The Behavior of Organisms, Appleton-Century-Crofts, New York, 1938.
[238] J.D. Sokolowski, A.N. Conlan, J.D. Salamone, A microdialysis study of nucleus accumbens core and shell dopamine during operant responding in the rat, Neuroscience 86 (1998) 1001–1009.
[239] 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.
[240] P.R. Solomon, Neural and behavioral mechanisms involved in learning to ignore irrelevant stimuli, in: I. Gormezano, W.F. Prokasy, R.F. Thompson (Eds.), Classical Conditioning, Lawrence Erlbaum Associates, Hillsdale, NJ, 1987, pp. 117–159.
[241] P.R. Solomon, D.M. Staton, Differential effects of microinjections of D-amphetamine into the nucleus accumbens or the caudate–putamen on the rat's ability to ignore an irrelevant stimulus, Biol. Psychiatry 17 (1982) 743–756.
[242] C. Spyraki, H.C. Fibiger, A.G. Phillips, Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system, Psychopharmacology (Berlin) 79 (1983) 278–283.
[243] L.R. Squire, Memory and the hippocampus: a synthesis from findings with rats, monkeys, and humans, Psychol. Rev. 99 (1992) 195–231.
[244] L.R. Squire, S.M. Zola, Structure and function of declarative and non-declarative memory systems, Proc. Natl. Acad. Sci. U.S.A. 93 (1996) 13515–13522.
[245] D.M. Staton, P.R. Solomon, Microinjections of D-amphetamine into the nucleus accumbens and caudate–putamen differentially affect stereotypy and locomotion in the rat, Physiol. Psychol. 12 (1984) 159–162.
[246] L. Stein, Effects of interaction of imipramine, chlorpromazine, reserpine and amphetamine on self-stimulation: possible neurophysiological basis of depression, in: J. Wortis (Ed.), Recent Advances in Biological Psychiatry, Vol. IV, Plenum, New York, 1962, pp. 288–309.
[247] 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.
[248] J.R. Stellar, A.E. Kelley, D. Corbett, Effects of peripheral and central dopamine blockade on lateral hypothalamic self-stimulation: evidence for both reward and motor deficits, Pharmacol. Biochem. Behav. 18 (1983) 433–442.
[249] J. Stewart, H. de Wit, R. Eikelboom, Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants, Psychol. Rev. 91 (1984) 251–268.
[250] J. Stewart, P. Vezina, A comparison of the effects of intra-accumbens injections of amphetamine and morphine on reinstatement of heroin intravenous self-administration behavior, Brain Res. 457 (1988) 287–294.
[251] E.M. Stricker, M.J. Zigmond, Effects on homeostasis of intraventricular injections of 6-hydroxydopamine in rats, J. Comp. Physiol. Psychol. 86 (1974) 973–994.
[252] M.F. Suaud-Chagny, K. Chergui, G. Chouvet, F. Gonon, Relationship between dopamine release in the rat nucleus accumbens and the discharge activity of dopaminergic neurons during local in vivo application of amino acids in the ventral tegmental area, Neuroscience 49 (1992) 63–72.
[253] C.J. Swanson, S. Heath, T.R. Stratford, A.E. Kelley, Differential behavioral responses to dopaminergic stimulation of nucleus accumbens subregions in the rat, Pharmacol. Biochem. Behav. 58 (1997) 933–945.
[254] M.T. Taber, H.C. Fibiger, Electrical stimulation of the prefrontal cortex increases dopamine release in the nucleus accumbens of the rat: modulation by metabotropic glutamate receptors, J. Neurosci. 15 (1995) 3896–3904.

[255] M.T. Taber, H.C. Fibiger, Feeding-evoked dopamine release in the nucleus accumbens: regulation by glutamatergic mechanisms, Neuroscience 76 (1996) 1105–1112.
[256] K. Taghzouti, A. Louilot, J.P. Herman, M. Le Moal, H. Simon, Alternation behavior, spatial discrimination, and reversal disturbances following 6-hydroxydopamine lesions in the nucleus accumbens of the rat, Behav. Neural Biol. 44 (1985) 354–363.
[257] K. Taghzouti, H. Simon, A. Louilot, J.P. Herman, M. Le Moal, Behavioral study after local injection of 6-hydroxydopamine into the nucleus accumbens in the rat, Brain Res. 344 (1985) 9–20.
[258] G. Tanda, G. Di Chiara, A dopamine-m_1 opioid link in the rat ventral tegmentum shared by palatable food (Fonzies) and non-psychostimulant drugs of abuse, Eur. J. Neurosci. 10 (1998) 1179–1187.
[259] G. Tanda, F.E. Pontieri, G. Di Chiara, Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common m1 opioid receptor mechanism, Science 276 (1997) 2048–2050.
[260] J.R. Taylor, T.W. Robbins, 6-Hydroxydopamine lesions of the nucleus accumbens, but not of the caudate nucleus, attenuate enhanced responding with reward-related stimuli produced by intra-accumbens D-amphetamine, Psychopharmacology (Berlin) 90 (1986) 390–397.
[261] J.R. Taylor, T.W. Robbins, Enhanced behavioral control by conditioned reinforcers following microinjections of D-amphetamine into the nucleus accumbens, Psychopharmacology (Berlin) 84 (1984) 405–412.
[262] A.M. Thierry, J.P. Tassin, G. Blanc, J. Glowinski, Selective activation of the mesocortical DA system by stress, Nature 263 (1976) 242–244.
[263] R.F. Thompson, S. Bao, L. Chen, B.D. Cipriano, J.S. Grethe, J.J. Kim, J.K. Thompson, J.A. Tracy, M.S. Weninger, D.J. Krupa, Associative learning, Int. Rev. Neurobiol. 41 (1997) 151–189.
[264] J.W. Tidey, K.A. Miczek, Social defeat stress selectively alters mesocorticolimbic dopamine release: an in vivo microdialysis study, Brain Res. 721 (1996) 140–149.
[265] F. Toates, Motivational Systems, Cambridge Univ. Press, Cambridge, 1986, 188 pp.
[266] J.A. Trowill, J. Panksepp, R. Gandelman, An incentive model of rewarding brain stimulation, Psychol. Rev. 76 (1969) 264–281.
[267] 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.
[268] T.M. Tzschentke, Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues, Prog. Neurobiol. 56 (1998) 613–672.
[269] U. Ungerstedt, Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system, Acta Physiol. Scand. Suppl. 367 (1971) 95–122.
[270] U. Ungerstedt, Stereotaxic mapping of the monoamine pathways in the rat brain, Acta Physiol. Scand. Suppl. 367 (1971) 1–48.
[271] E.S. Valenstein, V.C. Cox, J.W. Kakolewski, Reexamination of the role of the hypothalamus in motivation, Psychol. Rev. 77 (1970) 16–31.
[272] D. van der Kooy, N.R. Swerdlow, G.F. Koob, Paradoxical reinforcing properties of apomorphine: effects of nucleus accumbens and area postrema lesions, Brain Res. 259 (1983) 111–118.
[273] M.-L. Wadenberg, E. Ericson, O. Magnusson, S. Ahlenius, Suppression of conditioned avoidance behavior by the local application of (−)sulpiride into the ventral, but not the dorsal, striatum of the rat, Biol. Psychiatry 28 (1990) 297–307.
[274] M. Wallace, G. Singer, J. Finlay, S. Gibson, The effect of 6-OHDA lesions of the nucleus accumbens septum on schedule-induced drinking, wheelrunning and corticosterone levels in the rat, Pharmacol. Biochem. Behav. 18 (1983) 129–136.
[275] I. Weiner, Neural substrates of latent inhibition: the switching model, Psychol. Bull. 108 (1990) 442–461.
[276] I. Weiner, J. Feldon, The switching model of latent inhibition: an update of neural substrates, Behav. Brain Res. 88 (1997) 11–25.
[277] I. Weiner, G. Gal, J.N.P. Rawlings, J. Feldon, Differential involvement of the shell and core subterritories of the nucleus accumbens in latent inhibition and amphetamine-induced activity, Behav. Brain Res. 81 (1996) 123–133.
[278] F. Weiss, M.T. Lorang, F.E. Bloom, G.F. Koob, Oral alcohol self-administration stimulates dopamine release in the rat nucleus accumbens: genetic and motivational determinants, J. Pharmacol. Exp. Ther. 267 (1993) 250–258.
[279] R. Weissenborn, P. Winn, Regulatory behavior, exploration and locomotion following NMDA or 6-OHDA lesions in the rat nucleus accumbens, Behav. Brain Res. 51 (1992) 127–137.
[280] D. Wenksten, J.G. Pfaus, H.C. Fibiger, Dopamine transmission increases in the nucleus accumbens of male rats during their first exposure to sexually receptive female rats, Brain Res. 618 (1993) 41–46.
[281] B.H.C. Westerink, H.-F. Kwint, J.B. de Vries, Eating-induced dopamine release from mesolimbic neurons is mediated by NMDA receptors in the ventral tegmental area: a dual-probe microdialysis study, J. Neurochem. 69 (1997) 662–668.
[282] B.H.C. Westerink, A. Teisman, J.B. de Vries, Increase in dopamine release from the nucleus accumbens in response to feeding: a model to study interaction between drugs and naturally activated dopaminergic neurons in the rat brain, Naunyn-Schmiedeberg's Arch Pharmacol. 349 (1994) 230–235.
[283] I.Q. Whishaw, R.A. Kornelsen, Two types of motivation revealed by ibotenic acid nucleus accumbens lesions: dissociation of food carrying and hoarding and the role of primary and incentive motivation, Behav. Brain Res. 55 (1993) 283–295.
[284] I.Q. Whishaw, G. Mittleman, J.L. Evenden, Training-dependent decay in performance produced by the neuroleptic *cis*(*Z*)-flupentixol on spatial navigation by rats in a swimming pool, Pharmacol. Biochem. Behav. 32 (1989) 211–220.
[285] N.M. White, Addictive drugs as reinforcers: multiple partial actions on memory system, Addiction 91 (1996) 921–949.
[286] N.M. White, Reward or reinforcement: what's the difference?, Neurosci. Biobehav. Rev. 13 (1989) 181–186.
[287] N.M. White, M.G. Packard, N. Hiroi, Place conditioning with dopamine D1 and D2 agonists injected peripherally or into nucleus accumbens, Psychopharmacology (Berlin) 103 (1991) 271–276.
[288] N.M. White, Mnemonic functions of the basal ganglia, Curr. Opin. Neurobiol. 7 (1997) 164–169.
[289] L.S. Wilkinson, T. Humby, A.S. Killcross, E.M. Torres, B.J. Everitt, T.W. Robbins, Dissociation in dopamine release in medial prefrontal cortex and ventral striatum during the acquisition and extinction of classical aversive conditioning in the rat, Eur. J. Neurosci. 10 (1998) 1019–1026.
[290] P. Willner, J. Scheel-Kruger, (Eds.), The Mesolimbic Dopamine System: From Motivation to Action, Wiley, Chichester, 1991.
[291] C. Wilson, G.G. Nomikos, M. Collu, H.C. Fibiger, Dopaminergic correlates of motivated behavior: importance of drive, J. Neurosci. 15 (1995) 5169–5178.
[292] P. Winn, T.W. Robbins, Comparative effects of infusions of 6-hydroxydopamine into nucleus accumbens and anterolateral hypothalamus induced by 6-hydroxydopamine on the response to dopamine agonists, body weight, locomotor activity and measures of exploration in the rat, Neuropharmacology 24 (1985) 25–31.
[293] R.A. Wise, The brain and reward, in: J.M. Liebman, S.J. Cooper (Eds.), The Neuropharmacological Basis or Reward, Clarendon Press, Oxford, UK, 1989, pp. 377–424.
[294] 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.

[295] R.A. Wise, Catecholamine theories of reward: a critical review, Brain Res. 152 (1978) 215–247.
[296] R.A. Wise, Lateral hypothalamic electrical stimulation: does it make animals 'hungry'?, Brain Res. 67 (1974) 187–209.
[297] R.A. Wise, Neurobiology of addiction, Curr. Opin. Neurobiol. 6 (1996) 243–251.
[298] R.A. Wise, Neuroleptic attenuation of intracranial self-stimulation: reward or performance deficits?, Life Sci. 22 (1978) 535–542.
[299] R.A. Wise, Neuroleptics and operant behavior: the anhedonia hypothesis, Behav. Brain Sci. 5 (1982) 39–87.
[300] R.A. Wise, M.A. Bozarth, A psychomotor stimulant theory of addiction, Psychol. Rev. 94 (1987) 469–492.
[301] 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.
[302] R.A. Wise, A. Murray, M.A. Bozarth, Bromocriptine self-administration and bromocriptine-reinstatement of cocaine-trained and heroin-trained lever pressing in rats, Psychopharmacology (Berlin) 100 (1990) 355–360.
[303] R.A. Wise, P.-P. Rompre, Brain dopamine and reward, Annu. Rev. Psychol. 40 (1989) 191–225.
[304] R.A. Wise, J. Spindler, H. de Wit, G.J. Gerber, Neuroleptic-induced 'anhedonia' in rats: pimozide blocks reward quality of food, Science 201 (1978) 262–264.
[305] R.A. Wise, J. Spindler, L. Legault, Major attenuation of food reward with performance-sparing doses of pimozide in the rat, Can. J. Psychol. 32 (1978) 77–85.
[306] G. Wolterink, G. Phillips, M. Cador, I. Donselaar-Wolterink, T.W. Robbins, B.J. Everitt, Relative roles of ventral striatal D1 and D2 dopamine receptors in responding with conditioned reinforcement, Psychopharmacology (Berlin) 110 (1993) 355–364.
[307] M. Yoshida, H. Yokoo, K. Mizoguchi, H. Kawahara, A. Tsuda, T. Nishikawa, M. Tanaka, Eating and drinking cause increased dopamine release in the nucleus accumbens and ventral tegmental area in the rat: measurement by in vivo microdialysis, Neurosci. Lett. 139 (1992) 73–76.
[308] K. Yoshimoto, W.J. McBride, L. Lumeng, T.-K. Li, Alcohol stimulates the release of dopamine and serotonin in the nucleus accumbens, Alcohol 9 (1991) 17–22.
[309] A.M.J. 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.
[310] A.M.J. Young, M.H. Joseph, J.A. Gray, Increased dopamine release in vivo in nucleus accumbens and caudate nucleus of the rat during drinking: a microdialysis study, Neuroscience 48 (1992) 871–876.
[311] A.M.J. Young, M.H. Joseph, J.A. Gray, Latent inhibition of conditioned dopamine release in rat nucleus accumbens, Neuroscience 54 (1993) 5–9.
[312] D.S. Zahm, L. Heimer, Specificity in the efferent projections of the nucleus accumbens in the rat: comparison of the rostral pole projection patterns with those of the core and shell, J. Comp. Neurol. 327 (1993) 220–232.
[313] M.J. Zigmond, E.M. Stricker, Recovery of feeding and drinking by rats after intraventricular 6-hydroxydopamine or lateral-hypothalamic lesions, Science 182 (1973) 717–720.