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Review

# A top-down perspective on dopamine, motivation and memory

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**Abstract**

Dopamine (DA) activity, in the form of increased neural firing or enhanced release of transmitter from nerve terminals and varicosities, is linked to a number of important psychological processes including: movement; hedonic reactions to positive reward; provision of an error detection signal during the acquisition of new learning; response to novel stimuli; provision of reinforcement signals essential for acquisition of new action patterns; and incentive motivation. This review focuses primarily on our research linking dynamic changes in DA efflux on the timescale of minutes, with incentive motivation, as revealed by brain dialysis experiments in behaving animals. Recent experiments on sensory-specific satiety and successive positive and negative contrast are discussed along with the distinction between preparatory behaviors that precede contact with biologically significant stimuli and subsequent consummatory behaviors. The relationship between DA efflux in the medial prefrontal cortex (mPFC) and foraging for food based on working memory is also discussed in support of the conjecture that DA may serve as a link between motivation and memory functions. Evidence in support of 'top-down' regulation of dopaminergic activity in the mesocorticolimbic DA pathways is reviewed briefly to introduce a mechanism by which activation of ascending DA projections in this manner might optimize dopaminergic modulation of executive function within regions such as the mPFC. Collectively, these processes could ensure coordination between cognitive processes that assess current opportunities and the motivational systems that select and engage patterns of approach behavior that bring organisms into contact with the essentials for survival.


*Keywords:* Dopamine; $D_1$ receptors; Incentive motivation; Memory; Sensory-specific satiety; Successive contrast effects; Amygdala; Prefrontal cortex; Nucleus accumbens; Hippocampus; Rodents; Brain dialysis

**Contents**



*Abbreviations:* BLA, basolateral nucleus of the amygdala; CeN, central nucleus of the amygdala; LH, lateral hypothalamus; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; RRF, retrorubral field; vHip, ventral CA1/subicular region of the hippocampus; VTA, ventral tegmental area.

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## 1. Introduction

The ability to move with purpose in complex environments is key to optimizing access to limited resources. It is also a defining feature of motivated behavior and, accordingly, constitutes one of the major areas of inquiry in the fields of behavioral and cognitive neuroscience. The modern era of research into the synaptic mechanisms of motivation can be traced to the classical studies of Ungerstedt (1971) in which severe aphagia and adipsia were induced by stereotaxic injections of the neurotoxin 6-hydroxydopamine into afferent projections of the mesocorticolimbic dopamine (DA) system. These findings were amongst the first to link DA to putative drive systems for hunger, thirst and sex thought to control different aspects of basic motivation (Hull, 1943; Stellar, 1954). Drive theory proposed that the sole purpose of motivated behaviors such as feeding, drinking and sexual activity was to restore homeostasis by removing an underlying physiological disturbance. Drive reduction produced by successful procurement of food, fluids or a receptive mate (primary reward stimuli) was said to reinforce those behaviors that immediately preceded ingestion or copulation. Wise has argued strongly that the pleasurable aspects of positive reinforcement arise when sensory inputs activate brain DA neurons (Wise, 1980, 1982). Not only did this influential hypothesis about DA function lead to an emphasis on the transduction of sensory information into subjective hedonic experiences, by extension it supported the assumption that DA neurons in the mesencephalon are activated by secondary sensory afferent pathways in a manner that could be construed as a 'bottom-up' sequence of events.

By the mid-sixties to early 1970s, drive theory was surpassed by the concept of incentive motivation which emphasized the critical role of external incentive stimuli that acquired salience through association with primary reward stimuli (Bindra, 1969; Bolles, 1972; Toates, 1986). As reliable predictors of objects of desire, incentive stimuli become powerful attractors of orientation and approach behaviors which are the hallmarks of motivation. The subjective psychological state triggered by salient incentive stimuli has been characterized as 'wanting' (Berridge and Robinson, 1998). Forceful arguments against the hedonia hypothesis have been marshaled by Berridge (see 2007) and it not our intention to reiterate them here. Rather our primary objective is to review previous evidence and to describe two new findings that support the incentive motivation hypothesis of DA function (see Fibiger and Phillips, 1986; Ikemoto and Panksepp, 1999; Mogenson and Phillips, 1978). Most of the data discussed in this article come from recent studies using brain dialysis to sample DA efflux under conditions in which motivational states change dramatically within a single test session. We also address two additional issues: 1) Do phasic increases in DA efflux in major terminal areas of the mesocorticolimbic DA system modulate cognitive functions that optimize search behavior? 2) Is there a role for 'top-down', as distinct from 'bottom-up', modulation of activity within the mesocorticolimbic DA system by corticolimbic afferents that could coordinate the effects of DA on processes such as attention, memory and executive function?

With respect to a 'bottom-up' perspective on mechanisms by which sensory systems, in particular those conveying visual information, evoke activity within midbrain DA neurons, we acknowledge the fundamental contributions by Redgrave and Gurney (2006). Focusing mainly on DA neurons in the substantiate nigra, which in turn project to the dorsal striatum, this group has shown convincingly that efferent projections from the superior colliculus in the dorsal tegmentum are the most likely candidate for conveying early visual input to DA neurons (Dommett et al., 2005). Furthermore they provide a persuasive argument that the ensuing phasic activity in these DA neurons can serve to reinforce new instrumental responses in accordance with the principles of instrumental learning. It is not our intention here to reconcile the present emphasis on mechanisms by which activity in telencephalic structures may influence DA neurons in the midbrain, with the collicular–nigral circuit, other than to note that they may represent fundamental differences between the mesocorticolimbic and nigrostriatal DA systems.

## 2. Dopamine and incentive motivation in the context of preparatory and consummatory behavior

Ecological theories of animal behavior provide a functional behavioral perspective on motivation by emphasizing the distinction between preparatory and consummatory behaviors (Konorski, 1967). Preparatory behaviors, also referred to as appetitive or approach behaviors (Ikemoto and Panksepp, 1999), such as foraging and hoarding represent flexible patterns of activity designed to located and bring the organism into contact with goal objects such as food or water. As such, these aspects of motivated behavior can be sustained over extended periods — a fact that must be considered when seeking a biological basis for incentive motivation. Following contact with a reward stimulus, this pattern of behavior is terminated and is usually replaced by a separate class of consummatory behaviors such as chewing, swallowing and licking in the case of feeding, all of which have precise response topographies that facilitate ingestion of food. It is noteworthy that different patterns of preparatory behavior may lead to identical consummatory responses. With respect to the concept of incentive motivation, preparatory behaviors can be readily triggered by presentation of a conditioned incentive stimulus paired with the delivery of food (Weingarten, 1984).

Studies in our laboratory have paired a cue light as a conditional stimulus (CS+) with the subsequent delivery of food into a niche after an extended delay and rats readily developed a preparatory response of approaching and investigating the 'food-niche' whenever the CS+ was illuminated (Blackburn et al., 1987, 1989). Several related experiments led us to the conclusion that the mesocorticolimbic DA system plays an essential role in incentive motivation and preparatory behavior. First we demonstrated that pretreatment with the DA antagonist pimozide significantly increased the latency to enter the 'food-niche' following presentation of the CS+ and decreased the number of niche entries prior to delivery of food, without affecting food consumption (Blackburn et al., 1987). Post-mortem analyses of DOPAC:DA ratios of rats

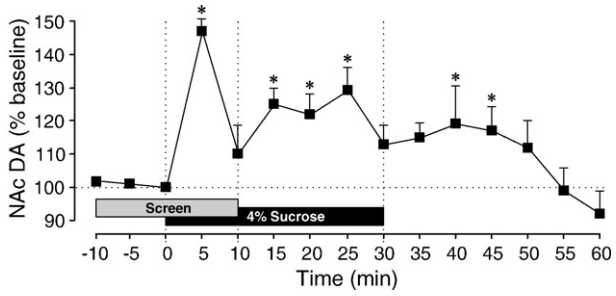


Fig. 1. Changes in DA efflux in the NAc prior to and during access to a 4% sucrose solution. Dashed lines highlight the initial preparatory phase in which sucrose was presented behind a perforated screen, and the consummatory phase, when rats were given access to the sucrose following removal of the screen. Data are shown per 5 min bin and represented as mean±SEM. The last baseline sample collected at Time 0 was used as the control mean in Dunnett's method of multiple comparisons (*$p<0.05$). Modified from Vacca et al. (2007).

given presentations on a CS+ alone revealed a significant increase in dopaminergic activity in the NAc. In contrast, no significant increases in DOPAC:DA ratios were observed in rats permitted to consume an unsignaled meal for 7 min (Blackburn et al., 1989). In a subsequent *in vivo* experiment we observed a significant increase in an electrochemical signal of DA oxidation in the NAc immediately following presentation of the CS+, an effect that was maintained during ingestion of a meal (Phillips et al., 1993).

Numerous experiments have observed significant increases in DA efflux during food or fluid consumption (Bassareo and Di Chiara, 1997; Cenci et al., 1992; Phillips et al., 1993; Taber and Fibiger, 1997; Wilson et al., 1995), but there is still debate as to whether DA efflux is increased reliably during preparatory phases of motivated behavior. This may reflect the deprivation state of the animal during preparatory and consummatory behavior, as Wilson et al. (1995) failed to observe a significant increase in DA efflux in the NAc in nondeprived rats during a preparatory phase prior to consumption of a palatable food or fluid, although increases were readily observed in deprived animals.

As the occurrence of phasic increases in DA efflux during preparatory behaviors is critical to DA hypothesis of incentive motivation, we recently undertook a formal test in rats that were given repeated training in a test apparatus that was divided into two compartments by a perforated screen (Vacca et al., 2007). After each rat had spent a variable interval in one of the compartments, a drinking tube containing a 4% sucrose solution was attached to the end wall of the second compartment. 10 min later the screen was removed and food deprived rats, maintained at 85–90% of pre-deprivation weight, were given access to the

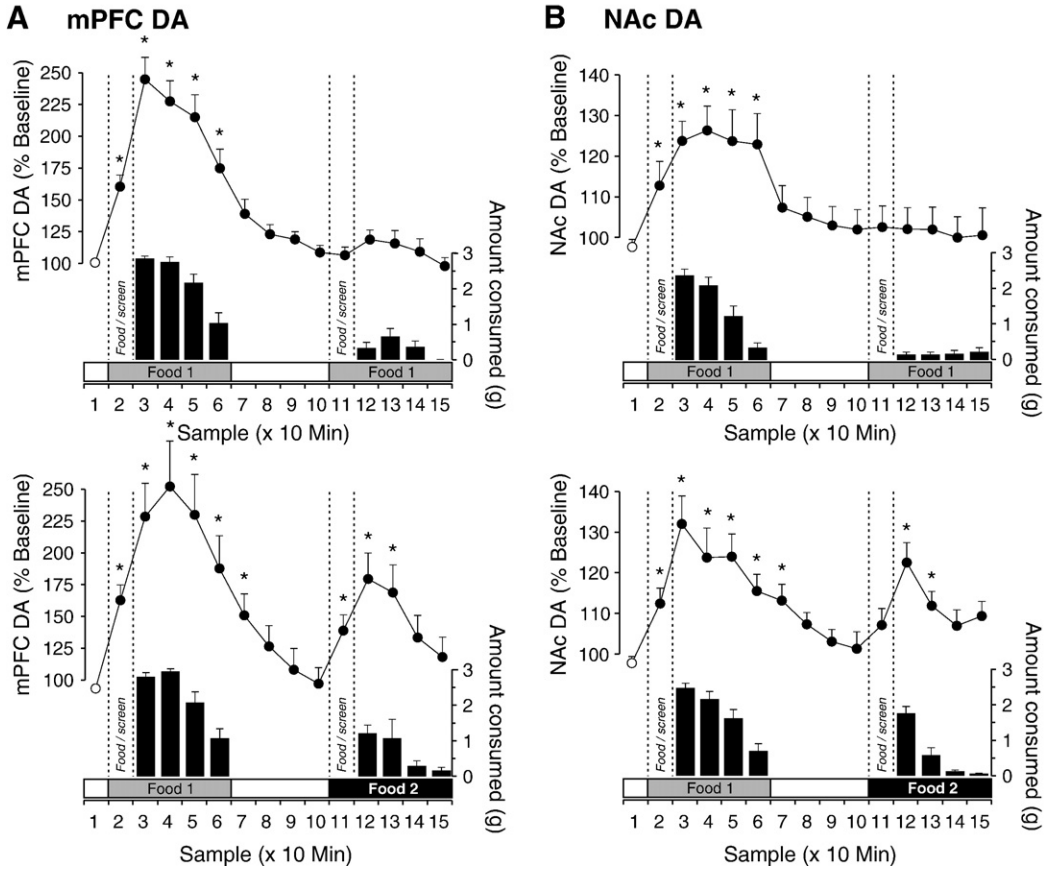


Fig. 2. Changes in DA efflux (line graphs) in the (A) mPFC and (B) NAc plus the amount of food consumed (bar graphs) during sensory-specific satiety experiments. In the upper panels, Food 1 was presented during two consecutive meals. In the lower panels, Food 1 was presented during the first meal and Food 2 during the second meal. Samples 1 and 7–10 represent periods during which no food is present behind the screen (S). Samples 2 and 11 represent the presence of food behind the screen (S′), and changes in DA efflux during these periods are highlighted by dashed lines. Data are shown per 10 min bin and represented as mean±SEM. The last baseline value (Sample 1) was used as the control mean in Dunnett's method of multiple comparisons (**$p<0.01$; *$p<0.05$). Modified from Ahn and Phillips (1999).

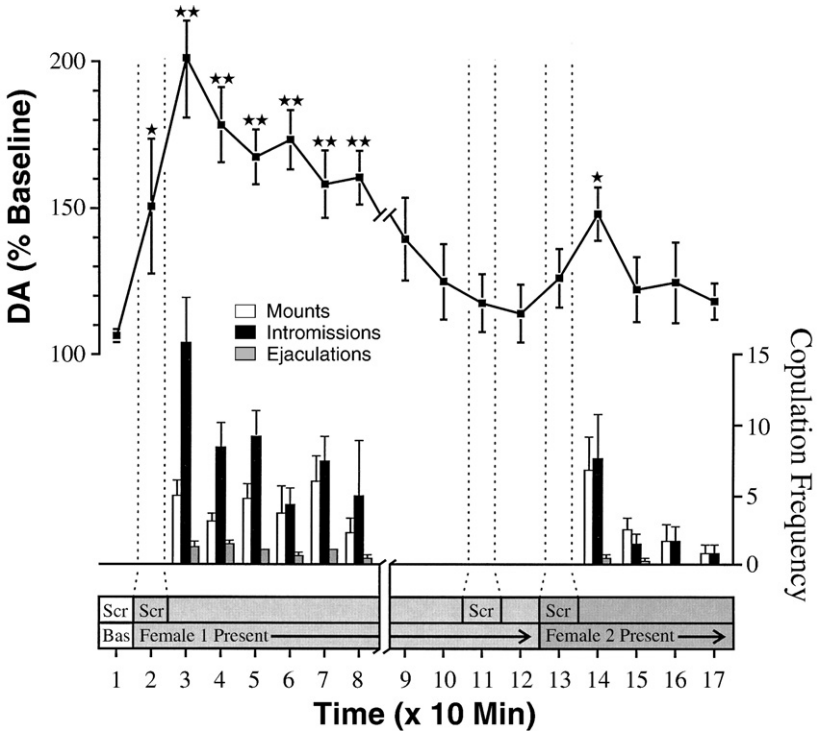


Fig. 3. Dopamine efflux in the NAc during the development of sensory-specific satiety for sexual behavior by male rats. Each male interacted successively with two different female conspecifics. Each female was first placed behind a wire mesh screen (preparatory phase) which was subsequently removed to permit active copulation expressed as Mounts, Intromissions or Ejaculations (histograms). Data are shown per 10 min. bin and represent mean±SEM. From Fiorino et al. (1997).

sucrose solution which they readily consumed. After a further 20 min period, the drinking tube was removed and the rats remained in the test box for a final 30 min period. As the animals became familiar with this procedure, they displayed increased locomotor and rearing activity directed at the perforated screen; behavior that was most intense during the 5 min period immediately following introduction of the drinking tube in the second compartment. Each rat had been prepared with a guide cannulae implanted stereotaxically over the NAc and 18 h prior to the 4th test session a dialysis probe was inserted into the NAc according to published procedures. During the final test, dialysis samples (1 μL/min) were collected every 5 min throughout the baseline, preparatory and consummatory phases of sucrose consumption and the contents assayed immediately by HPLC-ED using a standard protocol (Ahn and Phillips, 1999).

As shown in Fig. 1, the results of this study were unequivocal with a significant 40% increase in DA efflux occurring in the first 5 min sample following attachment of the sucrose drinking tube to the wall of the second compartment. DA efflux returned to near baseline values during minutes 6–10, and then was increased significantly (+25%) during the first sampling period of sucrose consumption. During the post sucrose consumption phase, the DA values returned to baseline. These data collected from food deprived rats showed clearly that the prospect of gaining access to a palatable sucrose solution was accompanied by a rapid rise in DA efflux in the NAc that in this instance was greater in magnitude than that observed during consumption of the 4% sucrose solution. Importantly, this pattern of DA efflux was observed in rats that had been tested on 3 previous occasions, thereby removing any suggestion that this is a transient phenomenon subject to rapid habituation.

## 3. Dopaminergic correlates of sensory-specific satiety during feeding and sexual behavior

Sensory-specific satiety plays an important role in motivation for food and is especially important in the selection of a varied diet by animals (Berridge, 1991; Rolls, 1999) and humans (Rolls and Rolls, 1997). Hungry animals that satiate on one type of palatable food display minimal interest when given the same food again, but do consume a second meal when given a novel food with different sensory properties. Balleine and Dickinson (1998) suggest that when food is consumed to satiety, its incentive value is gradually devalued through consummatory contact. According to the incentive salience hypothesis (Berridge and Robinson, 1998), such changes in the incentive value of stimuli should be accompanied by corresponding changes in mesotelencephalic DA activity.

This conjecture was fully supported by our findings with brain dialysis to monitor changes in DA efflux in the NAc and medial prefrontal cortex (mPFC) of the rat during the development of food-related sensory-specific satiety (Ahn and Phillips, 1999). When rats displayed sensory-specific satiety, by sampling only very small quantities of the original food presented as a second meal, there was no increase in DA efflux in either terminal region. In contrast, when satiated rats were presented with a novel food having different taste and olfactory properties, they ate a second meal that was accompanied by a significant increase in DA efflux in both the NAc and mPFC

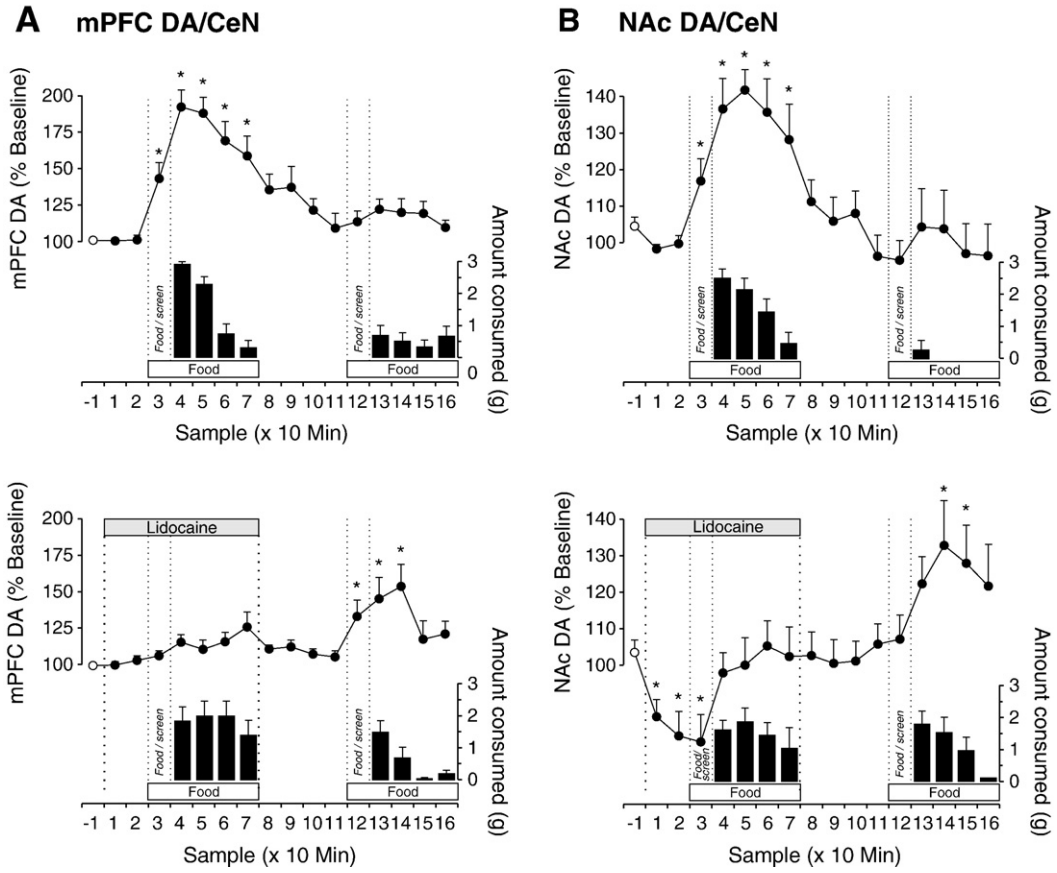


Fig. 4. Effect of reversible inactivation of the CeN on DA efflux (line graphs) in the (A) mPFC and (B) NAc and amount of food consumed (bar graphs) during food-devaluation experiments. The CeN was perfused with either ACSF (upper panels) or 2% lidocaine (lower panels) just prior to and during the first meal. Samples 4 and 13 represent periods during which a palatable food was presented behind a perforated screen, and changes in DA efflux during these periods are highlighted by dashed lines. Samples 5–8 and 14–17 represent periods during which animals had access to the food. Data are shown per 10 min bin and represented as mean+SEM. Sample 1 (white circle) represents the baseline value used as the control mean in Dunnett's method of multiple comparison (*$p<0.05$). Comparisons between ACSF and lidocaine conditions were conducted using Dunn's tests (†$p<0.05$). Modified from Ahn and Phillips (2002).

(Fig. 2). We concluded, in agreement with Balleine and Dickinson (1998) that the reduction in DA efflux observed in both of these terminal regions of the mesocorticolimbic DA system during the development of satiety reflects the devaluation in the incentive value of a food eaten to satiety.

These findings may also be relevant to the previous discussion about the permissive role of food deprivation in evoked increases in DA efflux in the NAc during preparatory behavior (Wilson et al., 1995). As noted, rats satiated on rat chow in their home cages, failed to display increased DA efflux immediately before access to a palatable chocolate flavored drink. This in turn implies that sensory-specific satiety is facilitated by consumption of a large meal at one sitting and not when a highly familiar food such as rat chow is consumed in many small bouts over the course of several hours as is the normal pattern of food intake by these rodents.

The close relationship between phasic changes in DA efflux and sensory-specific satiety is not limited to food-related stimuli. In a related study, we observed that DA efflux in the NAc of a sexually mature male rat was enhanced initially during a 60 min bout of active copulation, and then decreased in magnitude during the development of satiety (Fiorino et al., 1997). In concordance with the earlier discussion about DA and preparatory behavior, DA efflux in the NAc increased significantly in the presence of a receptive female behind a wire screen (Fig. 3). We attributed the significant increase in DA efflux in the presence of a receptive female to the effects of pheromones, vocalizations and perceptive movements displayed by the receptive female. Importantly, DA efflux was again increased during renewed copulation with a second and novel receptive female. Earlier studies have shown that the majority of rats allowed to copulate to satiety did not resume mating when tested with the same female 24 h later (Beach and Jordan, 1956). Again it is likely that renewed motivation to engage in a second bout of active copulation was triggered by the presence of the stimulus properties of the novel female, which may include olfactory, visual and auditory cues.

These findings with sensory-specific satiety for familiar food and sexually receptive mates are consistent with the dopaminergic hypothesis of incentive motivation in several respects. First, a significant increase in DA efflux is observed in anticipation of reward when the rat is separated from the food reward or receptive female by a perforated wire screen. Second, a decline in DA efflux parallels the development of satiety for both the initial food and copulation with the first receptive female. Furthermore, exposure to a novel food or female and

the reinstatement of motivated behavior is accompanied by a rebound increase in DA efflux. It is also important to emphasize the role of memory in sensory-specific satiety, as this may be a particularly important factor in the reactivation of the mesocorticolimbic DA system and the renewed interest in a novel food or receptive female. The ability to distinguish a novel stimulus from a familiar counterpart is highly dependent on stored representations of the stimulus features of the familiar object. Presumably, such memories would be stored in limbic structures such as the amygdala and hippocampus. This again raises the question of whether memory-related activity within these higher brain regions could directly evoke increased DA release within terminal regions of the mesocorticolimbic DA pathways.

## 4. Modulation of neurochemical and behavioral correlates of sensory-specific satiety by the central but not basolateral amygdalar nuclei

The amygdala is a forebrain structure that receives sensory information (e.g., olfactory and gustatory) from the brainstem and the cortex, as well as physiological signals related to hunger and satiety via brainstem nuclei (Mei, 1994; Norgren, 1995; Shipley et al., 1995; Woods et al., 1998; Zeigler, 1994). Food-related behaviors including indiscriminate sampling of nonfood items, altered food preferences, and interference with reward devaluation effects are disrupted in monkeys and rats following amygdala lesions, (Aggleton and Passingham, 1982; Box and Mogenson, 1975; Màlkovà et al., 1997; Murray et al., 1996). These observations, together with known neuroanatomical connections, suggest that the amygdala may serve to interface external and internal sensory information with the motivational systems of the brain, especially the mesocorticolimbic DA system (Rolls, 1999). Two sub-regions, the central nucleus (CeN) and the basolateral amygdala (BLA) delineated by anatomical connectivity and immunohistochemical markers, are of particular interest (McDonald, 1991; Pitkänen et al., 1997; Swanson and Petrovich, 1998). Of relevance to feeding behavior are reports that the CeN and the BLA are involved in the coding of incentive value of food (Kesner et al., 1989; Salinas et al., 1996; Uwano et al., 1995). We hypothesize that an interaction between the CeN and/or the BLA with DA transmission in the NAc and/or the mPFC may be a mechanism by which the incentive value of food could activate the mesocorticolimbic DA system and thereby influence the current focus of incentive motivation.

Accordingly, we compared the effect of reversible inactivation of the CeN versus the BLA on DA efflux in the NAc and mPFC in rats that were tested in a food-devaluation procedure (Ahn and Phillips, 2003). During microdialysis experiments, hungry rats were reverse dialyzed with lidocaine, a sodium channel blocker, into the CeN or the BLA before and during an initial meal of Froot Loops. Forty minutes later, they were presented with a second meal of Froot Loops to investigate the effects of these transient lesions on intake of food devalued by satiety. Loss of CeN function impaired the development of satiety during an initial meal and, consequently, diminished the

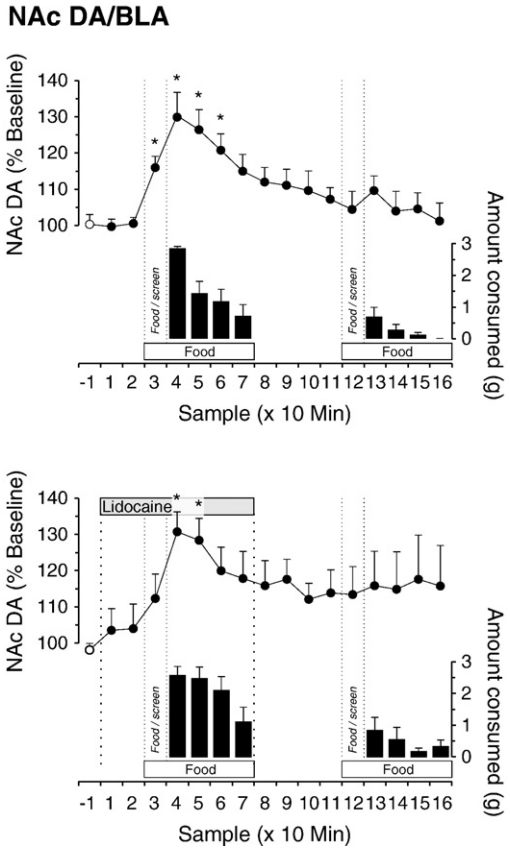


Fig. 5. Effect of reversible inactivation of the BLA on DA efflux (line graphs) in the NAc and amount of food consumed (bar graphs) during food-devaluation experiments. The BLA was perfused with either ACSF (upper panel) or 2% lidocaine (lower panel) just prior to and during the first meal. See Fig. 4 legend for explanation of symbols and statistics. Modified from Ahn and Phillips (2002).

effect of devaluation by satiety on intake of the same food during a second meal. Inactivation of the CeN was also associated with decreased basal levels of DA efflux in the NAc before food intake and attenuated increases in DA efflux related to anticipatory and consummatory aspects of feeding in both the NAc and mPFC (Fig. 4). In contrast, inactivation of the BLA did not affect feeding behavior or DA efflux (Fig. 5). In a previous study, we observed that inactivation of the BLA triggered large fluctuations in DA efflux in the mPFC, which indicates that the BLA may exert a stabilizing influence on basal levels of DA in the mPFC (Ahn and Phillips, 2003). Using electrical stimulation to examine amygdala-DA interactions we have also reported a dissociation effect complementary to the lidocaine data. A brief 10 s stimulation of the BLA, but not the CeN, caused a significant increase in DA efflux in the NAc (Howland et al., 2002). Note, however, that during inactivation of the BLA, a novel food stimulus was still able to evoke a significant increase in DA efflux in the NAc. These findings suggest a dissociation in the modulation of DA neurotransmission by the CeN and BLA. Specifically, basal or tonic levels of DA efflux are determined in part by tonic CeN inputs, but not by the BLA.

The disruption of satiety in rats after inactivation of the CeN may also be related to the concept of “oral metering”, which

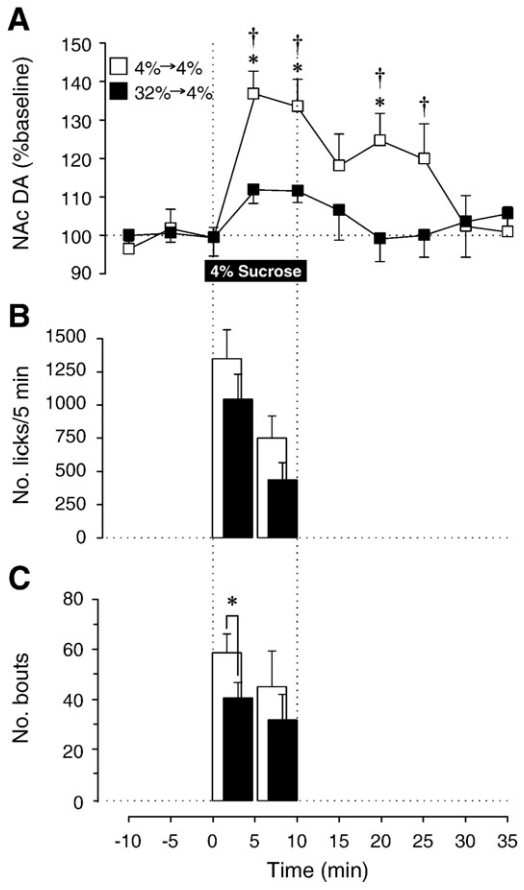


Fig. 6. Changes in DA efflux and lick microstructure parameters during successive negative contrast. All data are shown per 5 min bin and represented as mean ± SEM. (A) Changes in DA efflux in the NAc during a 10 min access period to a 4% sucrose solution in the 32%➔4% (negatively shifted) and 4%➔4% (unshifted) groups. Dashed lines highlight changes in DA efflux during the 10 min period of consumption. The last baseline sample collected at Time 0 was used as the control mean in Dunnett's method of multiple comparisons (*$p<0.05$). Between groups comparison of DA efflux for each 5 min time period was conducted by means of a protected $t$ test (†$p<0.05$). (B) Number of licks and (C) number of bouts per 5 min initiated by 32%➔4% and 4%➔4% groups during a 10 min access period to a 4% sucrose solution (*$p<0.05$). Modified from Genn et al. (2004).

refers to the ability to remember what and how much has been eaten. This construct is exemplified in rare case studies of densely amnesic patients (Hebben et al., 1985; Rozin et al., 1998). All had suffered damage to the mediotemporal lobe, including the hippocampus and amygdala. These individuals would consume a large meal and 10–20 min later were unable to recall having eaten the meal and consequently accepted and consumed a second and sometimes a third identical meal (Rozin et al., 1998). These intriguing data indicate that memory for what has been consumed recently is an important determinant of the initiation and termination of food intake.

## 5. Successive positive and negative contrast effects and DA efflux

The data presented above provide clear evidence of an increase in DA efflux in both the NAc and mPFC *before* contact with food (Ahn and Phillips, 1999) or sexual reward stimuli (Fiorino et al., 1997). Furthermore, the patterns of change in DA efflux in these regions reflect shifts in the motivational salience of rewards as a result of a number of factors, ranging from the development of satiety for a specific type of food (Ahn and Phillips, 1999, 2003) or with an individual sexual partner in an extended test session (Fiorino et al., 1997), to consumption of palatable food several days earlier (Bassareo and Di Chiara, 1997). Together these findings underscore the fact that the incentive value associated with a stimulus is not a static intrinsic property of that stimulus but is determined instead by the internal physiological state at the time the stimulus is encountered and prior experience with the stimulus (Balleine and Dickinson, 1998; Cabanac, 1992; Dickinson and Balleine, 1994; Toates, 1986).

Positive and negative contrast effects, arising from unexpected shifts in incentive properties to values that are greater or lesser than experienced previously, provide another perspective on the role of memory in determining current incentive salience. In the successive negative contrast procedure, rats that have established a strong memory for a sweeter concentration of sucrose exhibit an attenuated pattern of licking when given a less sweet solution on a subsequent test, relative to those maintained on the lower concentration of sucrose (Dunham, 1968; Flaherty, 1996). An important feature of incentive contrast phenomena is their bivalent nature. Animals trained to respond for a reward of a fixed value will often respond more vigorously when they unexpectedly receive one of higher incentive value, as compared to animals that have only experienced the stimulus with greater incentive value (Crespi, 1942; Flaherty, 1996). We have used brain dialysis to monitor changes in NAc DA efflux in rats displaying successive negative contrast when shifted from a 32% to a 4% concentration of sucrose (Genn et al., 2004) and as predicted, observed a significant attenuation in DA efflux when rats unexpectedly experienced a reward of lesser value (Fig. 6).

These findings encouraged us to undertake a similar microdialysis experiment to monitor DA efflux in the NAc during positive contrast and these new data are presented here. In this protocol, two groups of rats ($n=10$/group), were trained to lick a spout to obtain either a 32% or 4% sucrose solution during daily 5 min tests that continued for 7–10 days. Once the lick rates had stabilized for three successive test sessions, all rats had a microdialysis probe inserted into the NAc approximately 5 h prior to the experimental session. Mean lick rate for the 4% sucrose solution over a 5 min interval was 935 ± 33.2 (data are presented as mean ± SEM), which was significantly less than a mean of 1501 ± 55.4 for the 32% solution. During the dialysis test session, all rats in the 32% sucrose condition were maintained on this concentration and allowed to drink for 10 min. Rats in the 4% sucrose group were switched unexpectedly to the 32% sucrose solution. During the 1–5 min period of this session, rats in the 32% group maintained their lick rate at 1508 ± 81.6, but reduced their rate to 596 ± 86.9 during the 6–10 min period. Rats switched from 4% to 32% sucrose displayed an immediate increase in lick rate to 1546 ± 81.6 in the first 5 min bin and maintained their lick rate at a much higher rate of 1117 ± 107.9 in the second 5 min bin, thereby displaying positive contrast (Fig. 7B). This was confirmed by a 2-way ANOVA which

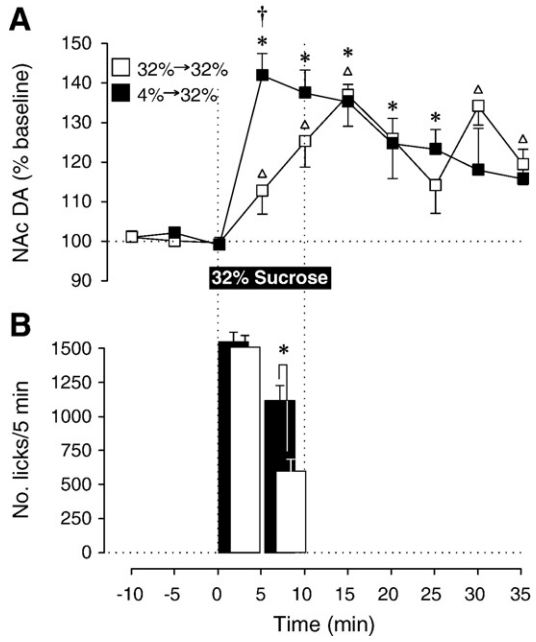


Fig. 7. Changes in DA efflux in the NAc and number of licks during successive positive contrast. All data are shown per 5 min bin and represented as mean±SEM. (A) Changes in DA efflux during a 10 min access period to a 32% sucrose solution in the 4%➔32% (positively shifted) and 32%➔32% (unshifted) rats ($n=10$ per group). Dashed lines highlight changes in DA efflux during the 10 min period of sucrose consumption. The last baseline sample collected at Time 0 was used as the control mean in Dunnett's method of multiple comparisons (*4%➔32% and △ 32%➔32%, $p<0.05$). DA efflux was compared between groups for each 5 min time period by means of a protected $t$ test (†$p<0.05$). (B) Number of licks in the 4% ➔32% and 32%➔32% groups during a 10 min access period to a 32% sucrose solution (*$p<0.05$).

revealed a significant Group×Time interaction [$F(1,18)=17.33$, $p<0.001$].

Significant differences in DA efflux in the NAc during successive positive contrast were observed between the two groups (Fig. 7A). Specifically, DA values were increased significantly in both groups when sampled during two 5 min bins while sucrose was consumed. These values remained elevated significantly for 30–40 min [1 way ANOVA, with time as the within subjects factor: 32%–32% group, $F(7,49)=5.61$, $p<0.001$;4%–32% group, $F(97,63)=5.21$, $p<0.001$]. Importantly, DA efflux during sucrose consumption was significantly greater in the group switched from 4% to 32% sucrose ($t=3.28$; $p<0.005$).

It is important to note that direct comparisons between the magnitude of DA efflux observed in the positive and negative contrast experiments cannot be made as these studies were conducted at different points in time under different experimental conditions (e.g., different investigators, testing apparatus, housing conditions). Despite this caveat, these two studies provide another powerful demonstration that DA efflux in the NAc is not a simple reflection of the hedonic properties inherent in positive rewards. In the context of successive contrast effects, the release of DA appears to represent the motivational state of the organism as determined by the current incentive salience of a stimulus such as a sweet solution, in comparison to a specific value retained in memory. The level of DA efflux appears to reflect a current motivational state that determines whether an organism will respond more vigorously or switch away to better alternatives. The prolonged increase in DA efflux may also reflect an expectation of reward in which behavior is determined by information held in working memory, rather than new learning based on reward.

These data on DA and contrast effects are also relevant to the conjecture by Shultz et al. that DA activity serves as an error detection signal which facilitates temporal difference learning (Schultz et al., 1997). Specifically, DA neurons in the ventral mesencephalon of the rhesus monkey show increased rates of firing when the value of a received reward stimulus exceeds the predicted value (Tobler et al., 2005). To the extent that the cumulative effect of increased action potentials by a large population of DA neurons over a period of many minutes could contribute to a sustained increase in DA efflux in the NAc, this may be an important factor in the enhanced DA function observed in our positive contrast experiment. Importantly, a significant decrease in the firing rate of these DA neurons also reflects situations in which the magnitude of reward is less than predicted, including those when reward is omitted all together (Tobler et al., 2005). This in turn is consistent with an attenuated increase in DA efflux in the NAc during successive negative contrast.

At first blush, the emphasis on changes in DA neuron firing as a prediction error may seem incompatible with our hypothesis that DA activity is a neural correlate of incentive motivation. However, McClure et al. (2003) have recently developed a new computational model that reconciles the two different theoretical perspectives. These computational neuroscientists emphasize that most proponents of the incentive motivation/incentive salience hypothesis agree that the functional correlate of increased dopaminergic activity is to predict the occurrence of future reward and to ensure that appropriate actions are selected and initiated to maximize the opportunity to obtain the reward. The resulting computational model accounts successfully for the detrimental effect of DA receptor antagonists on traversing a maze to obtain a sweet reward, while preserving consumption of a sweet solution when the drug-treated rat is place in front of the spout. It also affords an explanation of the gradual extinction of previously learned approach responses after repeated daily administration of low concentrations of DA antagonists. This computational model of incentive salience is a welcome contribution to the debate on DA function and the next step will be to integrate the role of dynamic changes in DA efflux that occur on a timescale of many minutes rather than the subsecond perspective provided by single unit recording studies.

## 6. The role of dopamine in memory-guided search behaviors

Motivated behavior is rarely seen as a random search strategy for locating the essentials for life. Indeed, preparatory behaviors are optimized by prior experience which enables many organisms to associate specific features of the environment including spatial locations with the objects they are seeking. The neural substrates of efficient foraging behavior have been studied extensively using radial-arm maze procedures pioneered by Olton and Samuelson (1976). The hippocampus has been implicated in search behavior

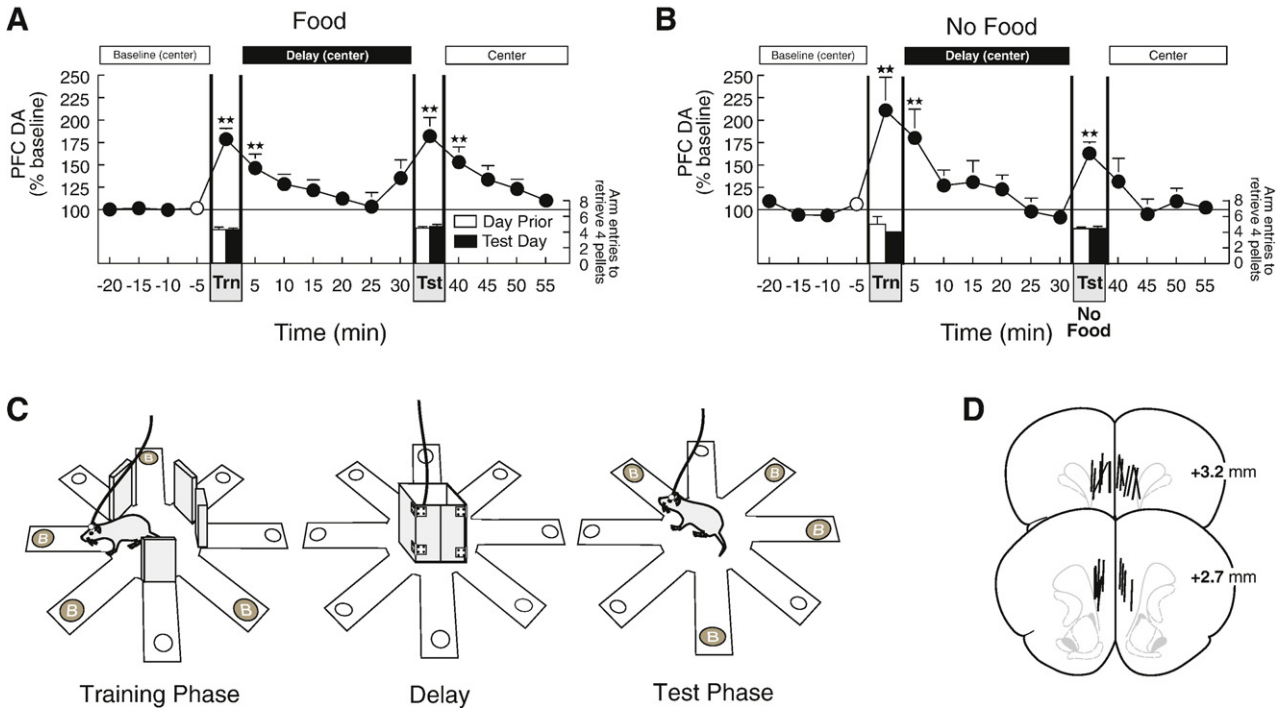


Fig. 8. Dopamine efflux in the mPFC during memory-guided search behavior for food on a delayed spatial win-shift task on an 8-arm radial maze. A. Rats were trained (Trn) with 4 arms open and 4 arms blocked and were then restricted to the center of the maze for a 30 min delay period. During the test (Tst) phase, all arms were open and rats made minimal errors by choosing arms that were blocked during training. DA efflux increased significantly during the training and test periods. B. The increase in DA efflux during the test phase was not due to food consumption as a significant increase again accompanied accurate selection of previously blocked arms. C. Schematic of radial-arm maze and different phases of the experimental procedure. D. Location of dialysis probes in the mPFC. Modified from Phillips et al. (2004).

using spatial cues (Jarrard, 1993; Olton and Papas, 1979). More recently the focus has expanded to include other neural structures such as the prelimbic region of the rat mPFC and the NAc (Seamans et al., 1995; Seamans and Phillips, 1994). The ventral CA1/subiculum region of the hippocampus (vHip) projects to both the mPFC (Conde et al., 1993; Jay and Witter, 1991) and the medial NAc (Groenewegen et al., 1987). In addition, the prelimbic mPFC sends dense projections to the NAc (Groenewegen et al., 1987; Sesack et al., 1989). Spatial information essential for foraging behavior could be relayed via these pathways from the hippocampus to the NAc and/or mPFC to guide search strategies according to the demands of specific tasks.

The hippocampus, the mPFC and the NAc form interconnected neural circuits that may underlie aspects of spatial cognition and memory. In a recent series of experiments, we investigated functional interactions between these limbic and associational cortical systems in rats during the performance of delayed food searching behavior mediated by spatial cues. In the training phase of this spatial win-shift (SpWS) task, rats were provided with information about where food would be located on an 8-arm radial maze, 30 min later, during a test phase. Transient inactivation of the vHip by a bilateral injection of lidocaine disrupted performance this task (Floresco et al., 1997). Asymmetric lidocaine injection into the vHip in one hemisphere and the prelimbic region of the mPFC of the opposite hemisphere was employed to disconnect these two brain regions of the brain. This transient disconnection of the vHip from the mPFC significantly impaired foraging during the delayed memory-based foraging task. These data suggested that serial transmission of information between the vHip and the mPFC is required when trial-unique, short-term memory is used to guide search behavior. Rats clearly learned to predict the location of food on the maze at the start of the test phase of the delayed task, based on the trial-unique pattern of four baited arms and four blocked arms in the training phase of each daily test. Previous studies suggested that following a delay rats employ a 'prospective' search for food on a radial-arm maze because they can use information acquired before the delay to predict the probable location of food on the maze (Cook et al., 1985).

In a related series of experiments we showed that activation of $D_1$ receptors in the mPFC is required for accurate foraging behavior by rats with prior knowledge about the location of food on the maze. Bilateral infusions of the $D_1$ receptor antagonist SCH 23390 into the mPFC prior to the test phase significantly increased the number errors, whereas similar transient lesion prior to the training phase had no effect. Furthermore, asymmetric inactivation of the vHip in combination with contralateral infusion of SCH 23390 into the prelimbic region of the mPFC also disrupted delayed spatial win-shift performance in the test phase (Seamans et al., 1998). Collectively, these data suggest that $D_1$ receptor activity in the mPFC is of critical importance when an animal must use previously acquired information about the probable location of food to forage efficiently.

Other pharmacological studies have shown that blockage of DA $D_1$ receptors in the mPFC disrupts choice behavior guided by working memory, following short delays (Sawaguchi and

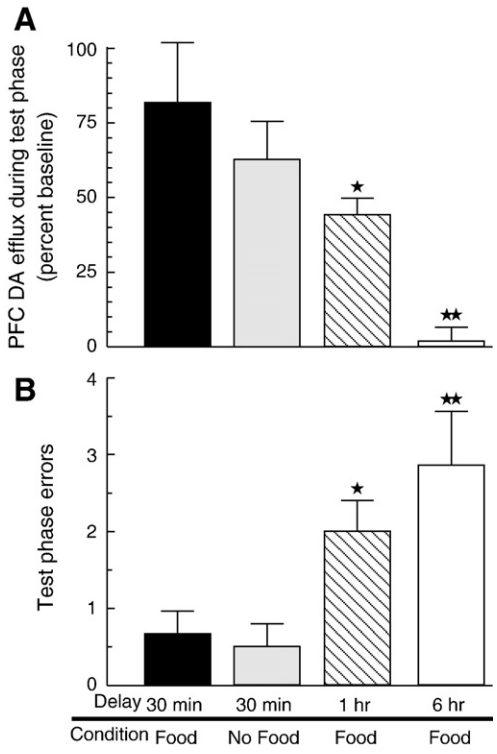


Fig. 9. Extended delays of 1 or 6 h, between training and test phases of the delayed spatial win-shift task, are accompanied by reduced levels of DA efflux in the mPFC during the recall phase and impaired memory for the correct baited arms on the maze. (A) Change in DA efflux in the mPFC during (1) a recall test in which rats received food at the end of the correct arms (30 min delay, black bar), (2) a recall test with no food available (30 min delay, grey bar), (3) a recall test following a 1 h delay (hatched bar) and (4) a 6 h extended delay between training and recall test phases (white bar). Rats in the 1 and 6 h extended delay conditions had significantly lower extracellular levels of DA efflux in the mPFC during the recall test phase compared to rats in the 30 min delay condition. (B) Number of errors committed during the recall test by rats after a standard 30 min delay (black bar), during a recall test with no food available (30 min delay, grey bar) and for rats tested for recall after either the 1 h (hatched bar) or 6 h (white bar) extended delay. Rats in the 1 and 6 h extended delay condition made significantly more errors than rats in the 30 min delay condition. For both A and B, stars and double stars denote significance vs. the 30 min delay (food) at $p<0.05$ and $p<0.01$, respectively. Modified from Phillips et al. (2004).

Goldman-Rakic, 1994; Sawaguchi et al., 1990). As described above, blockage of DA $D_1$ receptors in the mPFC during retrieval, but not acquisition, selectively disrupted memory-based search behavior in rats (Seamans et al., 1998). Furthermore, it has been proposed that working memory function is optimized when DA $D_1$ occupancy is within a critical range of an inverted U-shaped function (Arnsten, 1998; Floresco and Phillips, 2001; Zahrt et al., 1997). Increased DA efflux in the primate PFC has been observed during repeated performance of a brief 10 s delayed alternation task (Watanabe et al., 1997).

These findings indicate a general role for DA in working memory and we have recently demonstrated that phasic changes in mesocortical DA efflux occur during different phases (i.e., acquisition, delay and retrieval) of a delayed response task. Our study employed *in vivo* brain dialysis to monitor changes in DA release in the mPFC of rats performing the delayed response task on a radial-arm maze described above, using the relatively long delay period (30 min). We hypothesized that a significant increase in DA release in the mPFC would occur during accurate recall of the correct location of food sources in a complex spatial environment, independent of the presence or absence of food (Phillips et al., 2004).

Consistent with previous observations of increased DA release during feeding behavior, a significant increase in DA efflux (179%) in the mPFC was observed during the search for and ingestion of food pellets in the 5 min acquisition phase (Fig. 8A). DA levels remained elevated for a further 5 min period and returned to baseline values for the remaining 25 min of the delay period. A second significant increase in DA efflux (182%) was observed when rats displayed accurate recall, making only $0.67\pm0.3$ errors in their choice of arms that contained food (Fig. 8A). Importantly, a similar profile of increased DA efflux was observed in a second experiment, even though food was not available during the recall phase (Fig. 8B). The absence of food reward during this test day had no effect on accuracy of responding in this separate group of rats that were trained previously with food available during both phases ($0.5\pm0.3$ errors).

Given that accurate recall was facilitated by an increase in DA efflux in the mPFC evoked by stimuli that predict the presence and location of reward, it follows that a disruption of working memory should be accompanied by a progressive decline in DA efflux. To test this hypothesis, we conducted separate experiments to determine whether a decrease in the working memory function was associated with a corresponding decrease in DA levels during retrieval. Accordingly, rats were trained with a standard 30 min delay but received subsequent tests for recall, in conjunction with brain dialysis, at delays extended unexpectedly to 1 or 6 h. Previous studies have shown that increasing the delay between acquisition and recall degrades memory retrieval during the test phase of the foraging task employed here (Floresco and Phillips, 2001; Packard and White, 1989).

Rats in both the 1 and 6 h delay condition displayed a significant increase in DA efflux in the mPFC during the training phase comparable to that observed in previous tests. No reliable increase in DA efflux was observed after 30 min, when rats would normally have been allowed to explore the maze. However, when rats were released from the chamber in the center of the maze after a 1 h delay, the magnitude of DA efflux in the mPFC was blunted significantly (144%); relative to the increase observed in control rats (188%) at the 30 min delay (Fig. 9, upper panel). Moreover, these rats made significantly more errors during the recall phase than rats tested at a standard 30 min delay (Fig. 9, lower panel). This effect was even more pronounced following a 6 h delay, as there was no significant increase in DA release when these rats searched for food during the test phase. The memory deficit observed after a 6 h delay was consistent with the hypothesis that a brief but significant increase in DA release in the mPFC is an important factor in memory retrieval.

The question remains as to whether the increase in retrieval errors during the extended delay condition was due to attenuated release of mesocortical DA, or whether the reduction in DA efflux in the mPFC was due to forgetting. Resolution of this question was provided by neuropharmacological data showing

that disruption in working memory caused by an extended delay was alleviated in part by infusion of a DA $D_1$ receptor agonist (SKF 81297) into the mPFC prior to retrieval (Floresco and Phillips, 2001). The fact that pharmacological stimulation of $D_1$ receptors in the PFC restored working memory when mesocortical DA release would have been attenuated by an extended delay provided further support for the contention that the magnitude of DA release and the accuracy of working memory are casually linked. Moreover, these data implied that forgetting this information was due to reduced release of DA in the mPFC, and not vice versa. This finding, in combination with the pattern of results observed across the three delay conditions (Fig. 9), indicated that the magnitude of DA efflux in the mPFC during the retrieval phase of a delayed response task was predictive of the accuracy of recall of baited arms, with lower levels of DA efflux associated with poorer performance.

Although increased DA efflux in the mPFC has been reported to occur prior to and during consumption of palatable food rewards (Fig. 1), two additional observations from this study argued against a role for mesocortical DA in the hedonic sensory properties of food. First, comparable increases in DA efflux were observed during memory-based behavior following a 30 min delay, whether or not food was available. Second, when the same quantity of food was consumed following an extended delay of 6 h, no significant increase in DA efflux was observed in the mPFC. These findings supported the hypothesis that DA efflux in this region of the cortex plays an essential role in integrating memories for the probable location of food with approach behavior.

## 7. Corticolimbic regulation of mesocorticolimbic dopamine function

Recent anatomical studies indicate that pyramidal neurons in the mPFC (including cells that receive hippocampal inputs) send excitatory glutamatergic projections to DA neurons in the VTA, which, in turn, are connected in a reciprocal manner to the PFC (Fig. 10A Right) (Carr and Sesack, 2000; Christie et al., 1985; Jay et al., 1995). As such, both the increase in task-related firing of PFC neurons and the enhanced efflux of mesocortical DA may be interrelated. Specifically, changes in PFC neural activity (either an increase or decrease) essential for efficient search behavior may, in turn, initiate corresponding changes in mPFC DA efflux. Support for this suggestion is provided by data from our laboratory (Taepavarapruk and Phillips, 2001) and others (Gurden et al., 2000), confirming that stimulation of hippocampal afferents can increase DA efflux in the mPFC, an effect that is mediated by reciprocal connections between the PFC and VTA (Taepavarapruk and Phillips, 2001). Similar data confirm that neural activity within the vHip can regulate the release of DA in the NAc in a frequency-dependent manner (Blaha et al., 1997; Taepavarapruk et al., 2000). Two mechanisms have been proposed to account for these effects. The first assumes that glutamatergic activation from the vHip can increase firing of GABAergic projection neurons of the NAc, which, in turn, inhibits neural activity in the ventral pallidum, leading to disinhibition of DA neurons in the VTA (Fig. 10B Left) (Floresco et al., 2001). Accordingly, the observed increase in DA efflux in the NAc would be dependent on the firing rate of neurons in the VTA. A separate but complementary mechanism may involve direct presynaptic modulation of DA release by the action of glutamate on DA varicosities in the NAc (Floresco et al., 2001). In the light of these data, we propose that activity within neural circuits linking the ventral hippocampus to the mPFC and NAc can engage the mesocorticolimbic DA projection and thereby influence the motivational state of the organism. Increased dopaminergic tone, in turn, could modulate

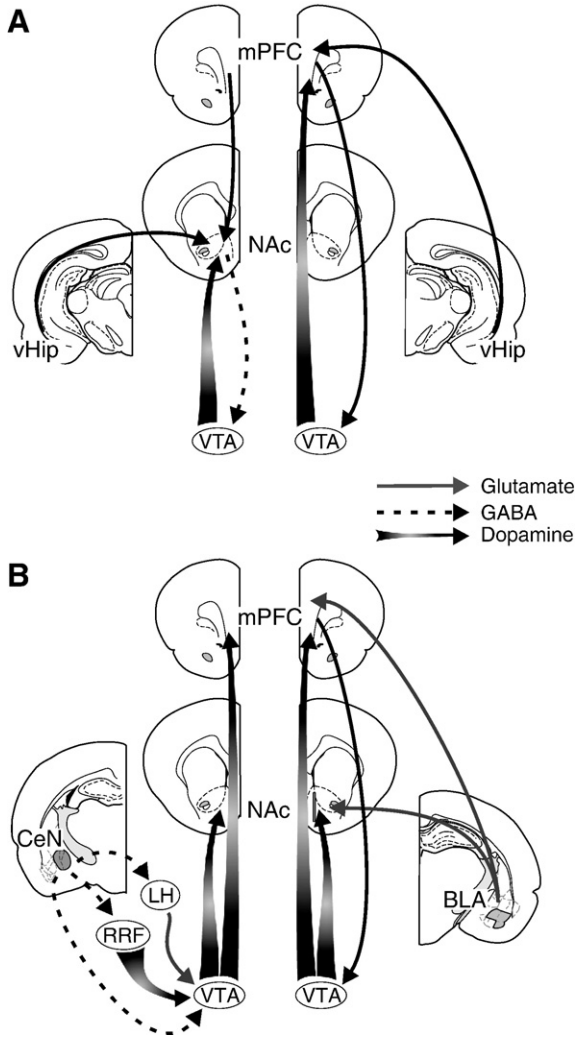


Fig. 10. Schematic diagram of putative hippocampal and amygdalar interactions with the mesocorticolimbic dopamine system. *Shaded arrows* represent dopaminergic pathways from the VTA to the mPFC and NAc. Also depicted are glutamatergic (*solid black arrows*) and GABAergic (*dashed arrows*) projections from corticolimbic areas to the cell body and terminal levels of the DA system. A Left, Glutamatergic projections from the mPFC and vHip to the NAc provide presynaptic modulation of DA release in the NAc. Feedback, via GABAergic projections from the NAc to the VTA may also indirectly influence DA transmission. A Right, Glutamatergic inputs from the vHip to the mPFC and glutamatergic afferents from the mPFC to the VTA, directly and indirectly, modulate DA release in the mPFC. B Left, CeN provides direct and indirect (via the RRF and LH) GABAergic inputs to the VTA. B Right, Glutamatergic inputs arising from the BLA provide presynaptic modulation of DA release in the mPFC and NAc. Glutamatergic afferents from the mPFC to the VTA serves as a feedback loop.

working memory function across short and long delays. Collectively, these processes would ensure coordination between the cognitive processes that assess current opportunities in the environment and the motivational systems that select and engage the appropriate patterns of motor behavior required to access reward stimuli and ensure survival.

We have also championed a similar hypothesis for the influence exerted by CeN and BLA nuclei of the amygdala on DA efflux in the NAc of the rat. Specifically, we proposed that the CeN maintains control, via an indirect pathway, of the tonic activity of a population of ventral tegmental DA neurons that specifically regulate basal DA efflux in the NAc. In contrast, we suggested that activation of the BLA can evoke transient increases in DA efflux in the NAc and mPFC and may also stabilize the activity of dopaminergic neurons projecting to the mPFC. In keeping with the theme of this review, it was proposed that rapid transient regulation of DA efflux in the NAc by the BLA might influence the selection and co-ordination of specific sequences of behaviors appropriate to incentive stimuli present in the environment (Phillips et al., 2003).

The anatomical bases of this differential influence on DA efflux in the NAc and the mPFC most likely involve amygdalar projections to different levels of the DA system. Modulation of tonic levels of DA efflux in the NAc may involve a GABAergic projection from the CeN to the midbrain, including the VTA, the substantia nigra, and the retrorubral field (Fig. 10B left) (Phillipson, 1979; Sun and Cassell, 1993; Wallace et al., 1992). On the other hand, phasic changes in DA efflux may require excitatory inputs from the BLA, which have been shown to terminate in close proximity to DA varicosities in the NAc (Fig. 10B Right) (Johnson et al., 1994). This anatomical arrangement in the NAc may provide a presynaptic mechanism for modulation of DA efflux by the BLA. A similar arrangement of BLA and DA inputs to the mPFC has yet to be demonstrated.

## 8. Summary

Rather than linking DA efflux in terminal regions of the mesocorticolimbic DA pathways to the presence or absence of primary reward stimuli, we propose that it serves as a neurochemical correlate of incentive motivation, a state in which behavior is selected and initiated by external incentive stimuli signal that predict the availability and location of primary rewards. The brain dialysis data reviewed here show clearly that dynamic changes in extracellular concentration of DA, operating on a timescale of many minutes can have functional significance by representing the current state of incentive motivation as it changes from vigorous initiation of responding to eventual satiation. This emphasis on the functional importance to goal-directed behavior of phasic sustained changes in DA activity stands in contrast to a recent attempt to provide a comprehensive account of DA function across vastly different timescales (Schultz, 2007). Shultz argues that aside from brief periods of phasic activity required to encode reward function and prediction errors, DA neurons ensure steady-state concentrations of extracellular DA that play a permissive role which is incompatible with encoding information in time. On the contrary, our brain dialysis data show clearly that extrasynaptic levels of DA can reflect in a meaningful way the current motivational state of the organism. As noted above, a computational model exists that reconciles the encoding of temporal difference learning and reward prediction with incentive salience (McClure et al., 2003). Furthermore by incorporating intermediate states and rules for transitioning between states based on error signals and probability of initiating appropriate action, this model can account for action over extended periods of time. Sustained phasic release of DA as observed in most brain dialysis studies may provide a complimentary mechanism for achieving the same ends.

In the context of working memory, a phasic increase in DA efflux in the mPFC during recall would ensure an appropriate level of DA $D_1$ receptor activation essential for the retrieval of trial-unique information by working memory processes which, in turn, can guide response selection during delayed response tasks (Robbins, 2000; Sawaguchi and Goldman-Rakic, 1994; Seamans et al., 1998; Williams and Goldman–Rakic, 1995). Despite differences in time scale, the significant correlation between the magnitude of DA efflux and the accuracy of correct choices during recall parallels findings in electrophysiological studies of single unit activity in the mPFC during delayed memory tasks. In these experiments, robust increases in neural activity during either the delay period or responding are associated with accurate memory, whereas low levels of firing are accompanied by erroneous responses (Goldman-Rakic, 1995; Pratt and Mizumori, 2001). It has also been suggested that D1 receptors may mediate the tonic effects of DA in the mPFC, whereas phasic effects involve activity at D2 receptors. Cohen et al. (2002) postulate that tonic $D_1$ activity contributes to stability of memory engrams in the mPFC, by increased signal to noise ratios of background activity at the expense of evoked activity. Encoding and maintenance of salient new inputs is linked to phasic activity at D2 receptors. These authors emphasize the value of multilevel approaches (from biophysics to neural connections) to the development of viable neural models and suggest that they may be helpful in predicting the effects of specific drugs on selective aspects of behavior.

Collectively, the behavioral, neurochemical and anatomical data reviewed above support a very different vision of the sequence of events responsible for activation of the mesocorticolimbic DA compared to that provided by a consideration of how this system is activated by hedonic stimuli. A growing body of data suggest an important role for DA in the modulation of working memory function and a top-down perspective could explain the coordination between cognitive processes responsible for assessment of current opportunities and the motivational systems that select and engage patterns of approach behavior that bring organisms into contact with the essentials for survival.

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