

Multiple Dopamine Functions at Different Time Courses

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Abstract

Many lesion studies report an amazing variety of deficits in behavioral functions that cannot possibly be encoded in great detail by the relatively small number of midbrain dopamine neurons. Although hoping to unravel a single dopamine function underlying these phenomena, electrophysiological and neurochemical studies still give a confusing, mutually exclusive, and partly contradictory account of dopamine's role in behavior. However, the speed of observed phasic dopamine changes varies several thousand fold, which offers a means to differentiate the behavioral relationships according to their time courses. Thus dopamine is involved in mediating the reactivity of the organism to the environment at different time scales, from fast impulse responses related to reward via slower changes with uncertainty, punishment, and possibly movement to the tonic enabling of postsynaptic motor, cognitive, and motivational systems deficient in Parkinson's disease.

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INTRODUCTION

Imagine that you are away at a conference on a Caribbean island. It is December and cold at home, but here the sun shines, and there is a smell and a softness in the air that only a subtropical island can provide. You have just given a presentation on dopamine and reward in a darkened, air-conditioned room. Here comes the highly respected senior scientist, who takes you politely aside, asking whether he might have missed something. He wants to know whether from now on one should consider Parkinson's disease a disorder of reward processes. You may have heard this question before, but given the prominence of the questioner, you consider again whether you might have gotten something wrong.

Switch the scene slightly. You are about to enter the United States, and the immigration officer at Hartsfield airport in Atlanta asks you about your profession. You tell him that you

are in neuroscience, working for a British university and interested in reward. He seizes the occasion and exclaims, "oh, you must be working on dopamine!" Who is right: the eminent senior scientist or the immigration officer? And what do you think about your own position in between these mutually incompatible statements?

Our knowledge of mammalian brain function in behavior is strongly influenced by the well-advanced understanding of primary sensory systems, extending from peripheral receptors to the primary sensory cortical areas. We know their physiology: how they transform environmental energies into action potentials and deliver these neural signals to brain structures the functions of which we can describe accurately. The somatosensory cortex receives information from touch, vibration, and other forms of mechanical, and sometimes chemical, stimuli. It is obviously involved in a single, well-defined function, the

coding of somatosensory information. The same reasoning applies for the functions of the visual and auditory systems. We may have become used to thinking that every brain system subserves exactly one, and only one, physiological function. We apply this belief to other brain systems and ask what their one single function might be, and then we may run into problems when considering systems outside the primary sensory and motor domains. When we use the classic lesioning approach for assessing the function of a brain system, we find severe movement disorders in hundreds of thousands of human Parkinsonian patients worldwide, and we conclude that motor control must be the one function of the midbrain dopamine system. But what should we do with an alleged dopamine function in reward?

This review attempts to solve the riddle of potentially contradictory multiple dopamine functions. We postulate that single brain systems can indeed have multiple functions that might only be somewhat related to each other. On the basis of the large range of available data on dopamine functions, we argue that the midbrain dopamine system has many functions, and we may be able to define several specific dopamine functions if we can relate them to dissociable behavioral processes occurring at different time courses.

MULTIPLE DOPAMINE FUNCTIONS INFERRED FROM BEHAVIORAL DEFICITS

Movement Deficits

The classic view of dopamine motor functions derives from the clinical neurologist examining a human Parkinsonian patient who suffers from severe problems with ocular, facial, and skeletal movements, resting tremor, and muscular rigidity. Although initial attempts to link these disorders to a hypothetical nigrospinal motor pathway (Hassler 1978) failed, pathophysiological studies quantified the deficits in the preparation, initiation, and execution of

REWARD SIGNALS WITHOUT REWARD RECEPTORS

Public perception associates rewards primarily with happiness and special gratification, but behavioral research suggests wider functions. A reward is any object or event that generates approach behavior and consumption, produces learning of such behavior, and is an outcome of decision making. Rewards are crucially important for individual and gene survival, and they support such elementary processes as drinking, eating, and reproduction. Dysfunctional reward mechanisms are associated with obesity and drug addiction. Rewards are polysensory and do not engage specialized reward receptors; the brain extracts the reward information from visual, auditory, somatosensory, olfactory, and other sensory information. Thus rewards are not defined by the physics and chemistry of their inputs but by the behavioral reactions they induce.

The lack of dedicated receptors makes the neural processing of reward more difficult to understand than the function of sensory systems. A helpful first step would be to identify an explicit neuronal reward signal, just as visual stimuli produce retinal responses as starting points for further neuronal processing. The search for a retina of the reward system has located brain signals related to reward value irrespective of sensory and motor attributes in midbrain dopamine neurons and in select neurons of orbitofrontal cortex, dorsal and ventral striatum, and possibly amygdala. The dopamine reward signal is a rapid, subsecond response that differs from slower dopamine responses associated with uncertainty, punishment, movement, and other events and contrasts with the tonic enabling function of dopamine evident from lesion effects. Reward signals influence movement processes in cortical structures and striatum to produce economic decision making.

skeletal, facial, and ocular movements (Hallett & Khoshbin 1980, Stelmach et al. 1986), which become more severe as task complexity increases (Stern et al. 1983). Experimental dopamine depletions by lesions or drugs, or dopamine receptor blockade, result in severe behavioral deficits of movement initiation and execution and in associated changes in neuronal activity in striatum, globus pallidus, and motor cortex of monkeys and rats (Carlsson et al. 1958, Burns et al. 1983, Filion et al. 1988, Schultz et al. 1989, Doudet et al. 1990).

Cognitive Deficits

Parkinsonian patients and experimentally dopamine-depleted monkeys and rats have numerous and substantial cognitive deficits impairing working memory (Brozoski et al. 1979), decision making (Rogers et al. 1999), timing behavior (Artieda et al. 1992), movement imagery (Cunnington et al. 1997), strategy generation (Taylor et al. 1986), attention (Brown & Marsden 1988, Downes et al. 1989), and mental flexibility (Cools et al. 1984). Impulsivity, gambling, attention deficit hyperactivity disorder (ADHD), and restless leg syndrome are based on altered dopamine function or dopamine receptor polymorphism (Perez-de-Castro et al. 1997, Stiasny et al. 2000, Sagvolden et al. 2005). By contrast, some behavioral functions are less affected, including externally (as opposed to internally) driven behavior, recognition memory, mirror reading, and paired-associate learning (Brown & Marsden 1990, Harrington et al. 1990). Lesions or local injections of dopamine receptor antagonists in monkeys result in changes to working memory and movement preparation together with associated prefrontal and striatal activities (Taylor et al. 1990, Sawaguchi & Goldman-Rakic 1991, Williams & Goldman-Rakic 1995, Inase et al. 1997).

Motivational and Learning Deficits

Parkinsonian patients demonstrate deficits in procedural learning tasks (Saint-Cyr et al. 1988) and show reductions in emotional responses to affective and approach-generating stimuli (Canavan et al. 1989, Linden et al. 1990, Vriezen & Moscovitch 1990, Sprengelmeyer et al. 1995, Knowlton et al. 1996), which may be more pronounced for positive than negative reinforcers (Frank et al. 2004). Rats show deficits in approach behavior and appetitive learning after dopamine depletion or systemic or local administration of dopamine receptor antagonists, even when motor factors are ruled out (Di Ciano et al. 2001, Parkinson et al. 2002, Faure et al.

2005), and some lesions produce deficits in aversive reactions (McCullough et al. 1993). However, some studies failed altogether to find dopamine-related reward approach or learning deficits (Horvitz & Ettenberg 1991, Berridge & Robinson 1998, Cannon & Palmiter 2003).

Interference with dopamine neurotransmission disrupts cellular learning mechanisms in dopamine-innervated postsynaptic brain structures. Lesions of the nigrostriatal dopamine system, applications of D1 or D2 dopamine receptor antagonists, or differential knockouts of dopamine receptors impair long-term depression in striatum and prefrontal cortex (Calabresi et al. 1992, 1997; Wang et al. 2006) and long-term potentiation in striatum and cortex (Gurden et al. 1999, Kerr & Wickens 2001, Tang et al. 2001). D1 receptor agonist administration or adenylyl cyclase activation enhances long-term potentiation in prefrontal cortex (Gurden et al. 2000) and hippocampus (Otmakhova & Lisman 1996). Changes in dopamine neurotransmission affect the maintenance of hippocampal plasticity and memory consolidation (Packard & White 1991, Huang et al. 2004). Interference with dopamine transmission by lesions, receptor antagonists, and receptor-targeted antisense DNA reduced learned differential neuronal responses in striatum, amygdala, and rhinal cortex to liquid reward-predicting visual and auditory stimuli and foot shock-predicting odors (Aosaki et al. 1994, Rosenkranz & Grace 2002, Liu et al. 2004).

Functional Interpretations

Interpretations of lesion deficits are complicated by a variety of powerful compensatory processes. Parkinsonian deficits occur only with more than 80% lesions of the nigrostriatal dopamine system. Adaptive mechanisms occur while dopamine depletions are subthreshold, and overt symptoms appear only after compensation fails (Schultz 1982). Dopamine concentrations remain normal

despite considerable neuronal loss because of reduced feedback inhibition and reduced reuptake by the few dopamine varicosities (Agid et al. 1973). More substantial dopamine depletions lead to postsynaptic receptor supersensitivity (Creese et al. 1977). The depletion thresholds for overt deficits vary between the different motor, cognitive, and learning functions. Some functions become deficient with just moderate dopamine depletions, whereas other functions show impairments only with more severe depletions. Behavioral tests after global dopamine depletions can result primarily in deficits of less well-compensated functions, whereas better-compensated functions remain long undetected. For example aphagia and adipisia occur only with >99% dopamine depletion (Creese & Iversen 1975), at which point motor functions have already become deficient. In addition, intense stimuli can induce temporary recovery (paradoxical kinesia; Schwab 1972, Marshall et al. 1976). Thus the different depletion thresholds and the functional adaptations make it difficult to assess a particular function in isolation and may explain false negative results.

Although inactivation studies using lesions and drugs are important for showing the involvement of brain systems in specific behaviors, including the dopamine system, they do not allow researchers to investigate the direct relationships to time-specific processes lasting a few seconds or minutes. The effects of lesions are usually stable for hours or days, and drug effects last mostly for several tens of minutes or hours. These methods have limited value for discriminating among dopamine functions on the basis of time courses.

TIME COURSES OF BEHAVIORAL PROCESSES

Behavioral processes have adaptively evolved to match the rate of changes in the physical and biological worlds. To understand how the brain controls behavioral processes, we need to relate the function of specific brain systems

to the speed of the behavioral processes controlled by the system.

Imagine you type on a computer keyboard, trying to compose a coherent sentence while remembering what you just typed, planning a few keystrokes in advance and trying to avoid mistakes. Although the sentence itself may take several seconds, each correctly sequenced keystroke takes less than a hundred ms, indicating that different cognitive and motor processes have different, overlapping time courses. In sequential movement tasks, monkeys see different subsecond-long cues at 1-s intervals and remember their sequence over several seconds until they are allowed to touch the cues in the remembered sequence (**Figure 1**) (Ninokura et al. 2003). More simple behavioral actions occur over even shorter time spans, such as Pavlovian conditioning of reward-predicting stimuli with optimal stimulus-reward intervals of 1.5–3.0 s (**Figure 2**) (Waelti et al. 2001). Monkeys performing in reaction time tasks show ocular saccadic latencies of 80–180 ms (Fischer 1987), electromyographic latencies of 180–250 ms, arm movement reaction times of ~300 ms, and movement durations of 150–500 ms (Schultz et al. 1989). Typical prefrontal spatial-delayed response tasks involve mnemonic and movement preparatory delays of 2–20 s (Fuster 1973, Funahashi et al. 1989), decisions evolving during sensory discriminations and comparisons take 350–1000 ms (Roitman & Shadlen 2002, Reddi et al. 2003, Romo et al. 2004), and simple T-mazes take 2–3 s (Jog et al. 1999). Thus reward prediction, stimulus presentation, working memory, spatial decisions, muscle contractions, and overt arm and eye movements all span millisecond to second intervals.

A system involved in the initial stages of learning must be able to follow the millisecond time courses of the fastest stimuli and actions to be conditioned. The learning of Pavlovian reward predictions or instrumental lever pressing requires subjects to identify the exact stimulus or action responsible for the reward and keep a neural “eligibility trace” of

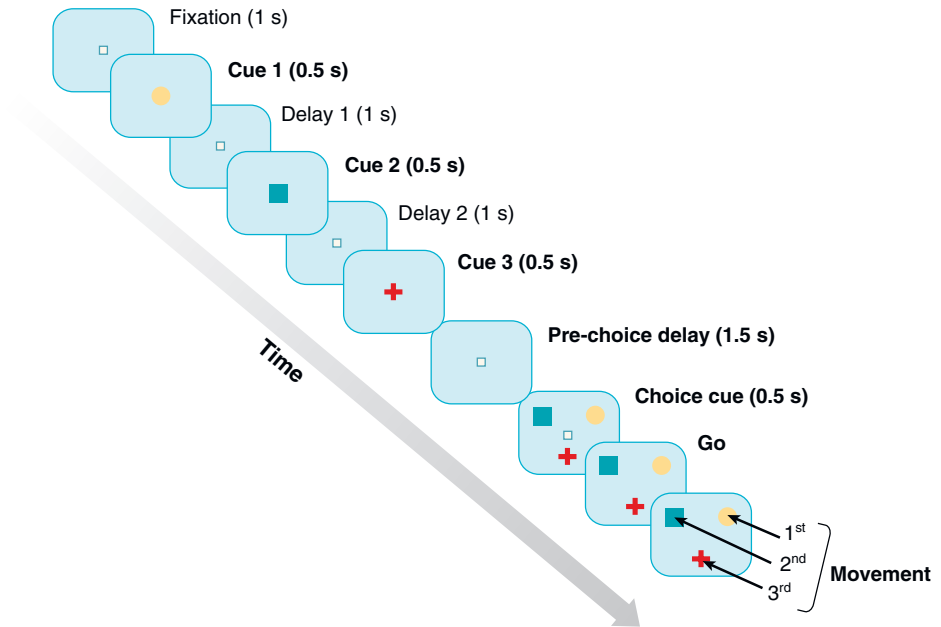


Figure 1

Time courses of events in a behavioral task testing the processing of the temporal order of objects in the prefrontal cortex of monkeys. The animal receives the reward only if it repeats correctly at the response phase the previously seen sequence of stimuli without being able to make simple spatial associations. The task contains multiple visual stimuli, working memory, visual-spatial transformations, decision making, multiple arm movements, reward prediction, and reward delivery, all of which need to be discriminated neuronally within a time span of a few seconds. Reward is associated not with a single stimulus but with the memorized sequence. After Ninokura et al. (2003). Copyright by The American Physiological Society.

the event onto which the subsequent reward can exert its reinforcing effect (“credit assignment”; Sutton & Barto 1981). The eligibility trace must follow the same time course of a few seconds as the event-reward intervals over which the assigned credit is being maintained. By contrast, subsequent learning mechanisms such as the incremental increase in associative strength over successive trials and subsequent memory consolidation occurs in the second, minute, and even hour ranges. Changes in appetite, hunger, and satiation occur over several minutes and even hours. Similar slow time courses are typical for many basic positive and negative emotions and mood changes, opponent motivational processes following termination of rewards and punishers, aggression and fatigue. Brain mechanisms involved in these processes would occur accordingly

at a much slower time course than those contributing to sensorimotor reactions and learning.

TIME COURSES OF NONDOPAMINE, BEHAVIOR-RELATED NEURONAL MECHANISMS

Sensory and motor neurophysiology postulates that individual neurons change their activity in close temporal relation to the observable behavior in which they play an important role (**Figure 3**). Neurons in the primary visual cortex increase their impulse activity 40–60 ms after the visual stimulus is presented and encode information about specific stimulus parameters, such as form, position, intensity, or color (Thorpe et al. 2001). Latencies do

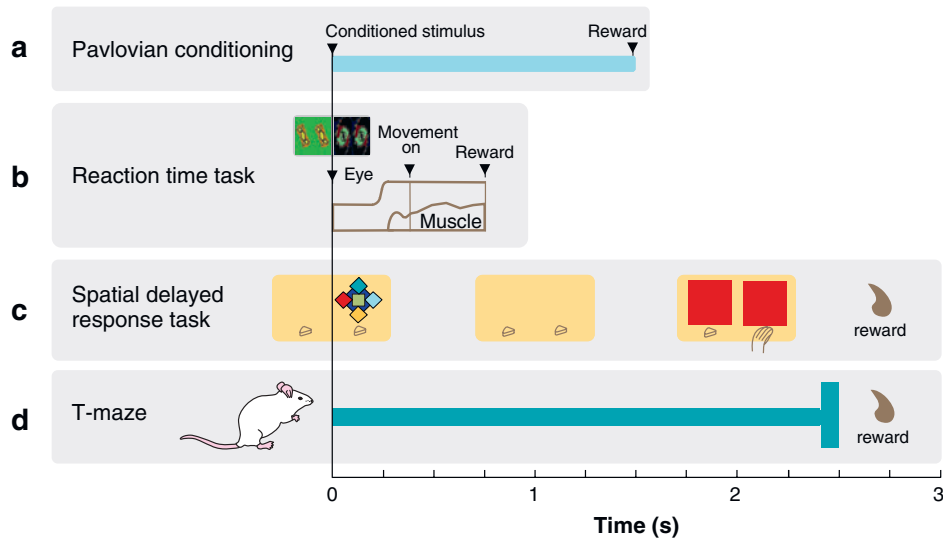


Figure 2

Time courses of principal sensorimotor tasks. *a*: Pavlovian reward prediction with stimulus-reward interval of 1.5 s typically used in rats and monkeys. *b*: Ocular, arm muscle, and arm movement reactions in a simple reaction time task typically used in humans and monkeys. *c*: Spatial delayed response task with mnemonic delay of 2.0 s typically used in monkey electrophysiological experiments. *d*: T-maze typically used in rodents. All tasks contain visual stimuli; working memory; decision making; eye, arm, leg, or body movements; reward prediction; and reward delivery occurring within 2 s.

not usually exceed 100 ms even in the highest temporal visual areas, and category-specific responses to visual stimuli in the dorsolateral prefrontal cortex have latencies of 100–130 ms in monkeys (Freedman et al. 2001) and ~150 ms in humans (Treisman & Kanwisher 1998).

Movement-related activity in primary motor cortex starts ~100 ms before the movement and lasts for a few hundred milliseconds during the movement (Georgopoulos et al. 1982). During sequential movement tasks of the kind shown in **Figure 1**, neuronal activity in prefrontal cortex, supplementary motor cortex, and striatum lasts less than one second and occurs during a very specific part of a particular sequence in exact temporal relation to that part (Ninokura et al. 2003).

During more cognitive delay tasks, primate prefrontal neurons change their working memory and movement preparation-related activity in close temporal relation to the time course of the delay in the seconds range (Fuster 1973, Funahashi et al. 1989),

and neurons show choice-predicting activity during sensory decisions in the millisecond range (Roitman & Shadlen 2002, Romo et al. 2004). Striatal and orbitofrontal neurons show sustained activations over a few seconds during the expectation of reward (Hikosaka et al. 1989b, Schultz et al. 1992, Tremblay & Schultz 1999). Expected rewards differentially influence the specific stimulus, movement, and delay-related changes in the millisecond and second range in prefrontal, parietal, and striatal neurons (Watanabe 1996, Hollerman et al. 1998, Platt & Glimcher 1999), suggesting that influences of rewards on task-specific neuronal processes have subsecond precision.

MECHANISMS OF DOPAMINE RELEASE

Impulse-Dependent Release

After sending a single electric shock to the axons of dopamine neurons, extracellular

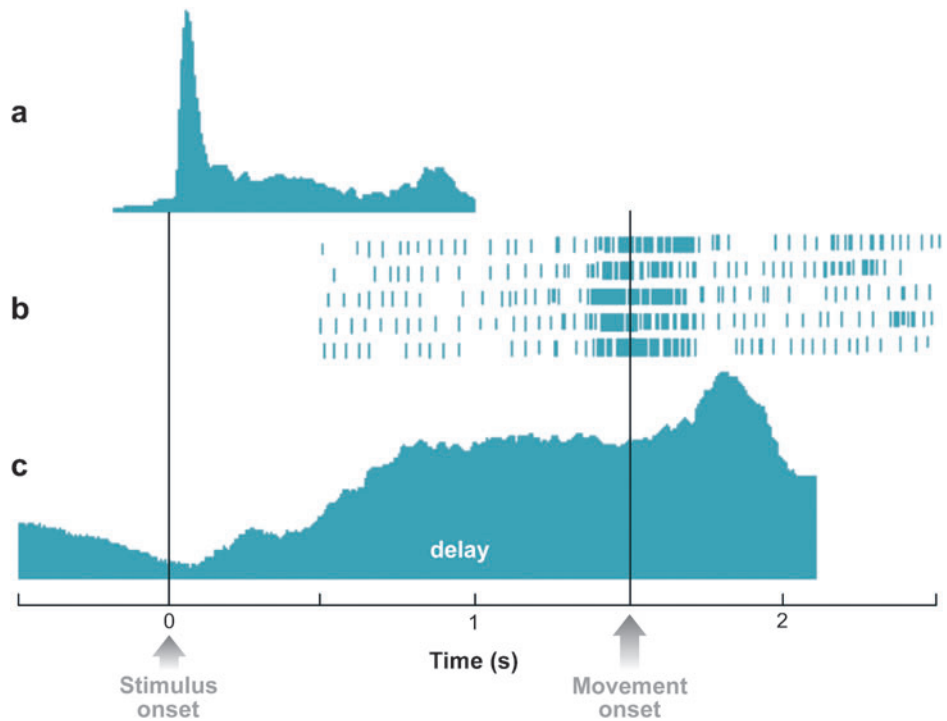


Figure 3

Time courses of neuronal responses in principal brain structures during performance of sensorimotor tasks. *a*: Responses in primary visual cortex to visual stimulation to the retina. Data from Roelfsema et al. 1998. Copyright by Nature Macmillan Ltd. *b*: Activity increases above background discharges in primary motor cortex preceding and accompanying an arm movement in a monkey. Data from Georgopoulos et al. 1982. Copyright by Society for Neuroscience. *c*: Delay activity in prefrontal cortex during a delayed response task in monkey. Data from Freedman et al. 2001. Copyright by American Association for the Advancement of Science.

dopamine concentration in the dorsal and ventral striatum rises within 1.3–10.0 ms from baselines of 5–10 nM via intrasynaptic peaks of 500–3000 nM to extrasynaptic concentrations of 250–500 nM in rats and guinea pigs and 500–1600 nM in monkeys (Kawagoe et al. 1992, Dugast et al. 1994, Garris et al. 1994, Cragg et al. 2000). Concentrations quickly become homogeneous at ~80 nM within a sphere of 3.5–4 micrometers in diameter (Gonon 1997, Cragg & Rice 2004), which is the average distance between the dopamine-releasing varicosities (Doucet et al. 1986). Maximal diffusion is reached within 75 ms after release onset and extends to 7–12 micrometers, even with intact reuptake transport. Multiple electrical shocks at inter-

vals of 16.66 to 500 ms (2–60 Hz) induce peaks exceeding 4000 nM after 200–300 ms, which are higher than those obtained with the same number of more widely spaced impulses (Garris & Wightman 1994, Gonon 1988, 1997). Owing to the action of the extrasynaptic dopamine reuptake transporter, concentrations come back to baseline within 200 ms after single pulses and within 500–600 ms after multiple pulses. Thus synaptically released dopamine diffuses rapidly into the immediate juxtasympatic area and reaches short peaks of regionally homogenous extracellular concentrations. The peak concentrations of hundreds of nanomoles would be sufficient to activate D1 receptors transiently in their low-affinity state, whereas the background

dopamine concentrations in the low nanomolar range produce a tonic activation of D2 receptors (Richfield et al. 1989). Taken together, the impulse-dependent dopamine release from axonal varicosities in striatum and frontal cortex constitutes moderate volume transmission rather than precise point-to-point transmission (Agnati et al. 2006) and occurs in the same subsecond time range as the fastest behavioral reactions and the neuronal activity underlying them.

Presynaptic Interactions

Dopamine concentrations are finely regulated in dopamine terminal areas by a number of cellular mechanisms. Glutamate released from corticostriatal and nucleus accumbens axons has a facilitating influence on dopamine release via presynaptic receptors located on dopamine terminals (Chesselet 1984). This presynaptic dopamine influence is independent of dopamine impulse activity (Giorguieff et al. 1977, Nieoullon et al. 1978, Romo et al. 1986, Krebs et al. 1991). Thus behavior-related activity in corticostriatal axons can lead to changes in striatal dopamine concentration through local presynaptic mechanisms without accompanying changes in dopamine impulse activity. The same corticostriatal inputs inducing the local dopamine release may also affect the impulse activity in striatal neurons. Therefore, the characteristics of task-related striatal impulse activity may indicate particular behavioral situations to which the striatal dopamine released through presynaptic interactions may be related.

DIFFERENT TIME COURSES OF DOPAMINE FUNCTIONS

Bursting Background Activity

Basic phenomenon. Under chloral hydrate anesthesia or without anesthesia, dopamine neurons discharge action potentials in the absence of specific stimulation in two patterns: short bursts of 3–4 impulses with mean

inter-spike intervals of 50–73 ms, and periods with more regularly spaced impulses (Grace & Bunney 1984, Hyland et al. 2002). About 25% of dopamine neurons discharge 60% of their action potentials in such bursts, and 55% of dopamine neurons discharge 29% of their action potentials in bursts. The remaining neurons show more regularly spaced impulses (Grace & Bunney 1984, Floresco et al. 2003). The 50–73-ms burst intervals in dopamine neurons exceed the typical 3–10-ms intervals in bursting neurons of other systems such as cerebellum, hippocampus, and thalamus (Grace & Bunney 1984). Burst firing of dopamine neurons depends on NMDA receptors (Johnson et al. 1992) and excitatory inputs from nucleus pedunculopontinus (Scarnati et al. 1984, Kelland et al. 1993, Floresco et al. 2003, Lodge & Grace 2006a) and the laterodorsal tegmental nucleus (Lodge & Grace 2006b). The burst mode would be suited particularly for transmitting time-specific, phasic information via impulse-dependent dopamine release, whereas the tonic background activity might provide an enabling influence on postsynaptic mechanisms (Grace 1991).

Relationship to dopamine release. The bursts in dopamine neurons are adapted particularly to the temporal aspects of impulse-dependent dopamine release, as the burst inter-spike intervals (50–73 ms) are within the range of nonlinearly increasing dopamine release shown with electrical stimulation (16.66–500 ms), which would result in transient >100 nM dopamine concentrations sufficient to stimulate D1 receptors (Gonon 1988). Although the burst-induced transient dopamine changes should be measurable by voltammetry, they are not detectable by *in vivo* microdialysis (Floresco et al. 2003).

Modulatory events. Increased bursting activity may occur in dopamine neurons during vibrissa movements, orienting behavior, and locomotion (Freeman & Bunney 1987, Diana et al. 1989). However, whether

the bursts constitute responses of dopamine neurons to novel or reward-related stimuli during these behaviors or reflect true changes in background bursting pattern unrelated in time to specific events is not clear. No information is available about the time courses of such changes, although they are likely to occur within seconds and minutes of the behavioral changes.

Electrophysiological Reward Signal

Effective events. Most dopamine neurons (60%–80%) in the substantia nigra and ventral tegmental area respond to visual and auditory reward-predicting stimuli, primary food rewards, and liquid rewards and to physically salient visual and auditory stimuli.

The response to reward appears to code the discrepancy between the reward and its prediction (“prediction error”) such that an unpredicted reward elicits an activation (positive prediction error), a fully predicted reward elicits no response, and reward omission induces a depression at the time of the predicted reward (“negative error”; Schultz et al. 1993, 1997; Waelti et al. 2001). The positive and negative prediction error responses are graded, such that partial prediction errors induce smaller error responses (Fiorillo et al. 2003, Morris et al. 2004) and reward omissions after invariant predictions produce constant depressions (Bayer & Glimcher 2005). The prediction error responses reflect the normalized expected values of the probability distributions of reward magnitudes relative to their prediction (Sato et al. 2003, Tobler et al. 2005). The prediction error is sensitive to both the occurrence and the time of reward because delayed rewards induce depressions at the habitual reward time and activations at the new time (Hollerman & Schultz 1998). Inedible objects do not produce dopamine responses (Romo & Schultz 1990).

The response to conditioned stimuli (CS) consists of an activation (Miller et al. 1981, Pan et al. 2005) and reflects the prediction of reward irrespective of spatial position, sensory

stimulus attributes, and arm, mouth, and eye movements (Schultz & Romo 1990, Waelti et al. 2001). It covaries with reward probability (Fiorillo et al. 2003, Morris et al. 2004) and the expected value of the reward distribution (Tobler et al. 2005) and is modulated by the motivation of the animal (Sato et al. 2003), the time course of predictions (Nakahara et al. 2004), and the animal’s choice among rewards (Morris et al. 2006). Activations do not occur when the CS are predicted by another stimulus in time ranges of seconds (Schultz et al. 1993). These responses conform to temporal difference learning models that conceptualize prediction errors irrespective of primary or conditioned reinforcers and view a CS response as reflecting an error in the prediction of the CS (Sutton & Barto 1981, Suri & Schultz 1999). Although discriminating between reward-predicting CS and neutral stimuli, dopamine activations tend toward generalization (Schultz & Romo 1990, Mirenowicz & Schultz 1996, Waelti et al. 2001).

Physically intense stimuli can induce substantial activations in dopamine neurons (Steinfels et al. 1981, Horvitz et al. 1997), which are enhanced by stimulus novelty (Ljungberg et al. 1992). However, visual stimuli that become effective for driving dopamine neurons after pairing with reward do not induce saliency or novelty responses before conditioning (Waelti et al. 2001, Tobler et al. 2003), suggesting that novelty per se is not sufficient to activate dopamine neurons. Because other attention-inducing stimuli such as aversive events, reward omission, and conditioned inhibitors do not induce major activations (Mirenowicz & Schultz 1996, Tobler et al. 2003), the responses to intense-novel stimuli may reflect sensitivity either to a specific but unknown form of attention attached commonly to rewards and intense-novel stimuli but not to punishers, or to the rewarding, approach-generating functions of such stimuli.

Time courses. The dopamine response to predominantly reward-related events consists

of a single activation (appetitive CS and positive reward prediction error), a single depression (aversive CS, inhibitory CS, and negative reward prediction error), or a single sequence of activation followed by depression (aversive CS, inhibitory CS, and generalized CS response). The activations to novel stimuli, primary rewards, and reward-predicting stimuli show latencies of 60–100 ms and endure for less than 200 ms (**Figure 4a**) (Steinfels et al. 1981, Ljungberg et al. 1992, Horvitz et al. 1997). Activations consist of a single impulse or a burst of impulses with

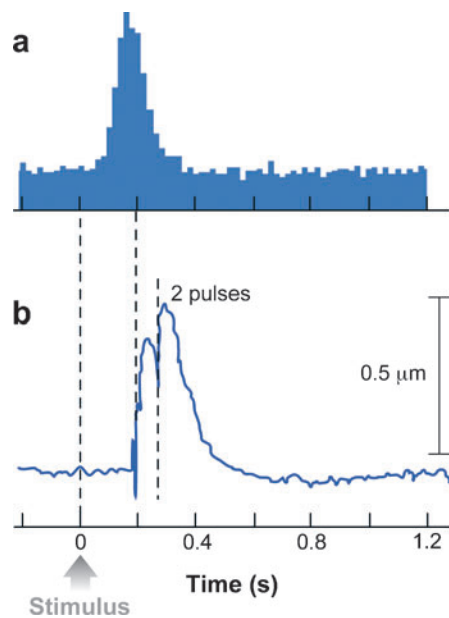


Figure 4

Time courses of dopamine responses to reward-predicting stimuli. *a*: activating impulse response of single midbrain dopamine neuron to reward-predicting visual stimulus. *b*: increase in voltammetrically recorded dopamine concentration following two electrical stimuli to dopamine axons in the medial forebrain bundle of the anesthetized rat. Two impulses correspond to the average dopamine response (Hyland et al. 2002). The time course of voltammetric response is positioned at the corresponding position of the impulse response shown in (*a*) to obtain a graphic estimate of the total time course of stimulus-evoked dopamine release. Voltammetry data from Gonon 1997. Copyright by Society for Neuroscience.

intervals of 10–50 ms. The depressions with negative reward prediction errors are slightly slower, with latencies of 100–200 ms and durations of usually 200–300 ms without exceeding 500 ms (Schultz et al. 1993, Hollerman & Schultz 1998, Waelti et al. 2001). Sequences of activation followed by depression after conditioned stimuli do not last longer than 400–500 ms (Schultz & Romo 1990, Tobler et al. 2005). The predominantly reward-related activations and depressions constitute the fastest reactions of dopamine neurons to behaviorally significant events known so far.

Comparison with spontaneous bursts.

The instantaneous frequencies during the reward-related activations are on the order of 10–50, and occasionally exceeding 100, impulses/s and thus are in a similar range but slightly higher compared with the bursts in background activity (Hyland et al. 2002).

Relationship to dopamine release.

Electrical stimulation of dopamine axons with two consecutive shocks at a 67-ms interval (15 Hz) corresponds to the average activation of dopamine neurons in awake animals following reward-related stimuli (Hyland et al. 2002) and produces striatal dopamine increase lasting ~200 ms (Gonon 1997). Adding this duration to the time course of electrophysiological responses, the dopamine increase following a reward-related stimulus would last <500 ms (**Figure 4b**). Depressions in activity lasting >100 ms, as seen with negative prediction errors, would transiently reduce the basal dopamine release.

Comparisons with behavior and neuronal activities.

The activating and depressant dopamine reward responses are faster than most movement reactions and shorter than stimulus-reward intervals or delays in delayed response tasks (**Figure 2**). They are well suited to distinguish between stimuli and behavioral reactions. The dopamine responses have time courses comparable to visual cortical responses and movement-related

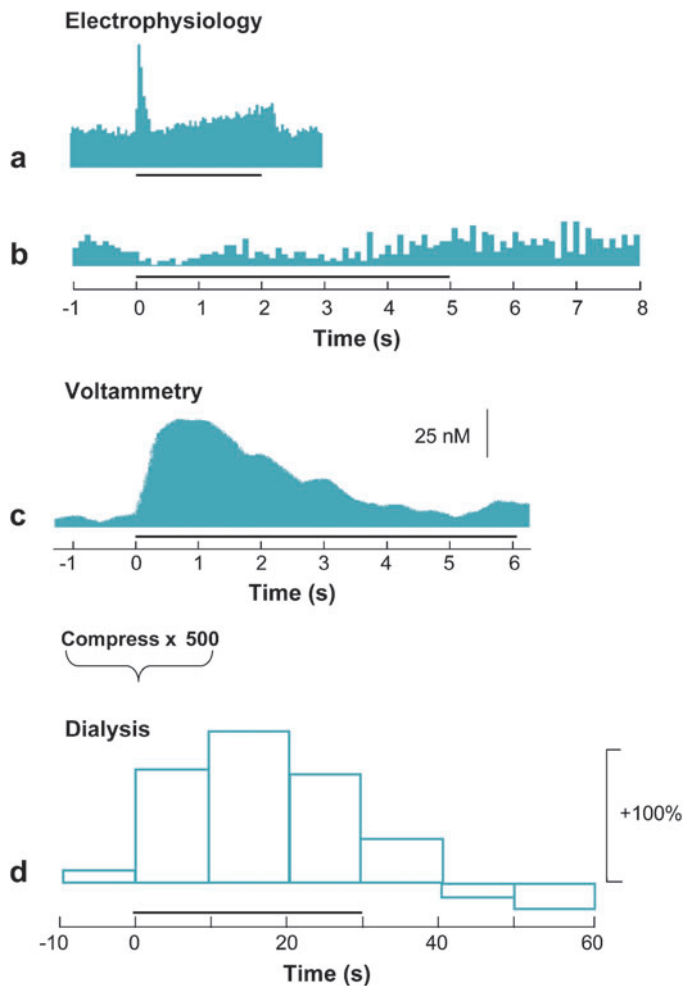


Figure 5

Time courses of dopamine responses measured by different methods and related to different kinds of information. *a*: Combined reward value–predicting response (*short peak to the left*) and uncertainty-related response (*ramp*). Uncertainty is measured by statistical variance. Data from Fiorillo et al. 2003. *b*: Depression with pain pinch. Data from Schultz & Romo 1987. *c*: Voltammetry of dopamine concentration change following reward-predicting visual-auditory compound stimulus. Redrawn from Roitman et al. 2004. Copyright by Society for Neuroscience. *d*: Time course of dopamine concentration change following reward-predicting visual stimuli, as measured by in vivo microdialysis. Redrawn from data by Young et al. 1992, Datla et al. 2002, Cheng et al. 2003. Some microdialysis responses to foot shock–predicting visual stimuli have shorter time courses on the order of minutes (Young et al. 1993, Young 2004). Lines below graphs in *a–d* indicate periods of effective stimuli. CORRECTION: Time base in *d* should be minutes, not seconds.

activations in motor cortex and are faster than delay-related activity in delayed response tasks (**Figure 3**). The temporal characteristics of such dopamine signals are appropriate for influencing neural mechanisms in striatum and frontal cortex related to behavioral actions occurring with intervals of 1–2 s. Indeed, the temporal difference model of reinforcement learning, whose teaching signal largely matches the dopamine response, is efficient particularly for learning movement sequences (Suri & Schultz 1998). The temporal precision of dopamine responses would be sufficient to influence specific neuronal eligibility traces of events that have led to reward, thus providing a neuronal solution to the credit assignment problem of associative learning.

Electrophysiological Uncertainty Signal

Rewards usually occur with some degree of uncertainty. The use of different probability distributions of fixed magnitudes separates expected reward value (linearly increasing from $p = 0$ to $p = 1$) from uncertainty expressed as a variance of the distributions (inverted U function peaking at $p = 0.5$). More than one third of dopamine neurons show a slower, sustained activation between the reward-predicting stimuli and the reward that covaries with variance, whereas CS and reward-prediction error responses covary with expected value and are uncorrelated with the uncertainty-related response (**Figure 5a**) (Fiorillo et al. 2003). Such activations are not seen with brief cues in operant situations, possibly because of fractionation of the CS–reward interval, nor with stimuli predicting nonrewarding visual images. The distinct neural coding of reward value and uncertainty is consistent with the separation of expected utility into these two components by financial decision theory (Huang & Litztenberger 1988) but contrasts with the combined coding as scalar utility in expected utility theory (von Neumann & Morgenstern 1944).

Comparison with other neuronal activities. Whereas the value signal lasts ~200 ms, the uncertainty signal is at least 5–10 times slower during the 2-s stimulus-reward interval and may be even slower with longer intervals. This time course makes the uncertainty signal considerably slower than do the behavioral reactions in simple sensorimotor behaviors and their underlying neuronal activity. As it increases toward the reward, it may play a role in modifying the neuronal processing of the reward prediction error, in keeping with the role of uncertainty in attentional learning theories (Pearce & Hall 1980).

Relationship to dopamine release. The impulse rate during the uncertainty response is about twice as high as the background activity and would produce dopamine concentrations of ~10–30 nM, which would be sufficient to activate D2 receptors but not the low-affinity D1 receptors presumably activated by dopamine released through the phasic value signal. The difference in receptor activation may be one way for postsynaptic neurons to distinguish between the two signals.

Electrophysiological Responses to Aversive Events

Effective events. In awake monkeys, aversive air puffs to body parts, hypertonic saline to the mouth, and conditioned visual and auditory stimuli in air puff or saline avoidance trials induce in only 10%–15% of midbrain dopamine neurons the short-latency, phasic activation that is typical for reward-related events (Mirenowicz & Schultz 1996). Visual and auditory stimuli predicting inescapable electric shock to the ear induced similar phasic activations in 18%–29% of dopamine neurons of awake cats (Guarraci & Kapp 1999). By contrast, the aversive stimuli led to depressions of activity in 31% and 10% of dopamine neurons in the two studies, respectively.

In anesthetized rats, aversive pinch stimulation to the tail or other body parts induces

mostly depressions of activity in dopamine neurons in a number of studies (Tsai et al. 1980, Maeda & Mogenson 1982, Ungless et al. 2004), although some studies report frequent activations (Chiodo et al. 1979). Mesocortical dopamine neurons appear to be predominantly activated by tail pinch, whereas mesoaccumbens neurons are more frequently depressed (Mantz et al. 1989). Pain pinch in anesthetized monkeys leads predominantly to depressions in nigrostriatal neurons, and activations are about as rare as with air puff and saline in awake monkeys (17%) (**Figure 5b**) (Schultz & Romo 1987). Neurons showing depressant, but not activating, responses to pain pinch stain immunopositive for the dopamine marker tyrosine hydroxylase, indicating that neurons activated by aversive stimuli under anesthesia may not be dopaminergic (Ungless et al. 2004).

Electrical stimulation of peripheral nerves (usually the sciatic nerve) produces mostly depressions of dopamine impulse activity (Tsai et al. 1980, Kelland et al. 1993). The response may be due to excitation of nonnoxious A fibers or noxious C fibers, and stimulation with appropriate currents for C fiber excitation leads to depressions (Hommer & Bunney 1980).

Aversive stimuli may induce additional, slower activations, which often outlast the stimulation period and thus have a disproportionately strong effect on overall impulse activity (Maeda & Mogenson 1982, Schultz & Romo 1987, Mantz et al. 1989). Furthermore, depressions can be followed by rebound activations, which are rare after pain pinch (Maeda & Mogenson 1982, Schultz & Romo 1987) but frequent after sciatic nerve stimulation (Hommer & Bunney 1980, Kelland et al. 1993) and may influence average dopamine firing more than the depressions.

Time courses. The timing of mechanical pain pinch stimulation is often difficult to monitor precisely. The activating and depressant neuronal responses start more than 100–300 ms after stimulus onset and last for

several seconds (Schultz & Romo 1987, Mantz et al. 1989, Ungless et al. 2004). This contrasts with the rapid depressions following sciatic nerve stimulation (latencies of 35–60 ms, durations of 100–220 ms), whereas the frequent rebound activations following the depressions are slower (latencies of 200–300 ms, durations of 50 ms–5 s; Hommer & Bunney 1980, Tsai et al. 1980, Kelland et al. 1993). Thus the initial depressant response to electrical nerve stimulation is very phasic and resembles the depressant response to natural aversive stimuli in awake monkeys and cats and the depressions with negative prediction errors. By contrast, the fewer activations to aversive stimuli are 5–10 times slower than the phasic activations following reward-related stimuli.

Relationship to dopamine release. The few direct activations of impulse activity would produce dopamine release in the time range of seconds and thus be weaker and slower compared with the millisecond release following reward-related stimuli. The rebound activations of impulse activity following depressions in some aversive situations would produce an overall net increase rather than a decrease of dopamine release in the second-to-minute range (Ungless 2004), whereas pure depressant responses would decrease dopamine release.

Comparison with dopamine reward responses. In responding to few direct activations, some rebound activations, and predominant depressions to aversive stimuli, dopamine impulse activity distinguishes quite clearly between aversive and reward-related stimuli. In particular, the phasic, unidirectional, activating impulse response typical for rewards occurs only rarely after aversive stimuli in both awake and anesthetized animals. These differences are in the subsecond time range. They should be easily detectable by postsynaptic striatal and cortical neurons operating with tens of milliseconds precision but

are unlikely to be picked up by dopamine release measured over minutes.

Comparison with behavior and neuronal activities. Although slower than the reward-related responses, the aversive responses are within the time range of slower sensorimotor reactions and their underlying neuronal activity. The dopamine activation rebounds following aversive-induced depressions occur in the subsecond-to-second time range and are faster than the subjective “rewarding” rebound conceptualized by the opponent-process theory of motivation (Solomon & Corbit 1974). Rebound activations following inhibitory responses are not uncommon in cortical and subcortical sensory structures and likely play a role in dampening or counteracting the initial neuronal depressions without necessarily being associated with a specific opponent behavioral action.

Behavior-Related Dopamine Changes Measured by Voltammetry

Electrochemical methods permit the detection of rapid changes in dopamine concentrations in submillimeter-to-micrometer spheres at the tips of microelectrodes inserted into specific brain structures containing dopamine release sites, such as the nucleus accumbens, striatum, and frontal cortex, mostly of rats.

Effective events. Regional dopamine concentrations increase in relation to several behaviorally relevant events, including novel visual environments (Rebec et al. 1997); unpredicted primary food rewards (Mitchell & Gratton 1992); presentation to male rats of sexually relevant odors and bedding from female rats (Mitchell & Gratton 1991, 1992); introduction to male rats of sexually receptive as opposed to nonreceptive females (Loulot et al. 1991) even separate from copulation (Robinson et al. 2002); conditioned visual and olfactory stimuli predicting liquid, food, or drug rewards (Phillips et al. 1993, Richardson & Gratton 1996, Di Ciano et al. 1998a,

Jeanblanc et al. 2002, Roitman et al. 2004), primary and conditioned aversive stimuli such as tail pinch, ice bath, restraint stress, restraining objects, and same sex intruders (Keller et al. 1983, Louilot et al. 1986, Doherty & Gratton 1992); and lever approach and lever-pressing movements (Kiyatkin & Gratton 1994, Richardson & Gratton 1996, Di Ciano et al. 1998b, Phillips et al. 2003, Stuber et al. 2005). Dopamine concentrations decrease following fully predicted compared with unpredicted rewards (Kiyatkin & Gratton 1994, Richardson & Gratton 1996), suggesting prediction-dependent reward coding.

Time courses. The earliest voltammetric studies report increases of dopamine concentrations lasting several minutes that may fail to return to baseline. These slow dopamine changes occur with sexually relevant stimuli (Louilot et al. 1991, Mitchell & Gratton 1991), reward-predicting stimuli (Phillips et al. 1993, Di Ciano et al. 1998a, Jeanblanc et al. 2002), aversive events (Keller et al. 1983, Doherty & Gratton 1992), and motor activity (Di Ciano et al. 1998b). However, the changes are difficult to attribute specifically to individual behavioral events because many sensory and motor events occur together over such long periods.

Recent measurements use time scales closer to those of simple sensorimotor behavior and allow better attribution of dopamine changes to behaviorally relevant events. Dopamine increases with novel environments (dopamine increase for a duration of 8 s; Rebec et al. 1997), primary liquid reward (duration of 15–30 s; Richardson & Gratton 1996), sexual stimuli (duration of 600 ms; Robinson et al. 2002), food and drug reward-predicting visual stimuli (latency of 5 s and duration of 60 s; Richardson & Gratton 1996; onset latency of 200 ms, peak latency of 700 ms for concentrations of 50–100 nM, duration of 2.4–3.3 s; Roitman et al. 2004), and approach behavior during reward expectation preceding lever pressing for food or drug reward (from 30 s before lever press until press onset: Kiyatkin

& Gratton 1994; preceding single lever press by 1–3 s and outlasting for 5–10 s: Richardson & Gratton 1996, Phillips et al. 2003, Stuber et al. 2005). These faster dopamine measurements reveal more restricted relationships to primary rewards, reward-predicting stimuli, approach behavior, and novel stimuli. By contrast aversive events and unrewarded motor activity have not yet been tested with rapid voltammetry.

Possible dopamine release mechanisms.

The fastest voltammetric dopamine changes within seconds are only slightly slower than sensorimotor reactions and behavior-related neuronal activity in striatum and frontal cortex. These changes occur with similar behavioral events as the electrophysiological responses of dopamine neurons, namely rewards and novel stimuli, and at approximately comparable time courses. They may well be due to impulse-dependent dopamine release. The shortest dopamine increases of 2–3 s following reward-predicting stimuli are still longer than the added durations of about 0.5 s of electrophysiological responses and electrically induced dopamine release (**Figure 5c** versus **Figure 4b**). Possible reasons may be the 20–100-ms jitters of natural dopamine responses compared with the likely more effective synchronicity with electrical stimulation, technical difficulties in bringing down the voltammetric signal after an increase, and differences in behavioral situations.

Some of the behavior-related changes measured by dopamine voltammetry are rarely seen with dopamine impulse activity, in particular the increases following aversive events and during movements in earlier voltammetry studies (Romo & Schultz 1990). A possible explanation for these discrepancies could be an insufficient specificity for measuring dopamine as opposed to other molecules in the earlier voltammetry studies. Because the recent voltammetry methods provide better specificity for dopamine, the measured dopamine concentrations during movements should derive primarily from physiological

factors. A possible source for the release could be the presynaptic influences of glutamatergic cortical inputs on striatal dopamine release (Chesselet 1984). The same cortical inputs might mediate the movement-related changes in striatal neurons. The reduced lever press-related dopamine release after extinction of cocaine-seeking behavior (Stuber et al. 2005) may correspond with the reward dependency of striatal and prefrontal movement-related activity (Watanabe 1996, Hollerman et al. 1998). The dopamine increase preceding lever pressing (Phillips et al. 2003, Stuber et al. 2005) resembles the striatal and frontal activity preceding spontaneous movements (Romo & Schultz 1992, Schultz & Romo 1992), and the lack of its disappearance with reward omission may correspond with reward expectation activity in striatal and orbitofrontal neurons during initial unrewarded learning trials (Tremblay et al. 1998, Tremblay & Schultz 2000b). A delay of reward by several seconds induces a prolongation of both prefrontal dopamine release (Richardson & Gratton 1998) and reward expectation-related activity in orbitofrontal and striatal neurons (Apicella et al. 1992, Tremblay & Schultz 2000a).

Behavior-Related Dopamine Changes Measured by Microdialysis

Submillimeter-thin tubes with semipermeable membranes are inserted into specific brain structures, such as the nucleus accumbens, striatum, and frontal cortex, mostly of rats, and are perfused with artificial cerebrospinal fluid into which molecules from the surrounding tissue diffuse. The perfusate is analyzed for dopamine using sensitive biochemical and electrochemical methods.

Effective events. Dopamine concentrations in nucleus accumbens, striatum, and frontal cortex increase by 20%–100%, occasionally up to 200%, above baselines of 5–10 nM in relation to novel environments (Feenstra et al. 2000); primary food and liquid rewards

(Young et al. 1992, Bassareo & Di Chiara 1999) modulated by drive state (Wilson et al. 1995); visual and auditory stimuli predicting food, liquid, or drug rewards (Bassareo & Di Chiara 1999, Ito et al. 2000, Datla et al. 2002, Cheng et al. 2003); female and male sexual activity (Meisel et al. 1993), aversive electric foot shock, tail shock, handling, and restraint stress (Abercrombie et al. 1989, Imperato et al. 1992, Young et al. 1993, 1998, Kalivas & Duffy 1995, Young 2004); visual, auditory, and taste stimuli associated with foot shock or lithium-induced malaise (Mark et al. 1991, Young et al. 1993, Saulskaya & Marsden 1995, Wilkinson et al. 1998, Pezze et al. 2001, Young 2004); lever pressing for food (Hernandez & Hoebel 1988, McCullough & Salamone 1992), and active electric foot shock avoidance (McCullough et al. 1993). Dopamine increase correlates better with lever pressing than does the amount of food pellets consumed (Cousins et al. 1999). Dopamine release by conditioned stimuli is reduced by preexposure inducing behavioral latent inhibition (Young et al. 1993) and occurs with sensory preconditioning without explicit stimulus-reinforcer pairing (Young et al. 1998). Dopamine concentrations increase in the human amygdala during reading and paired-associate learning (Fried et al. 2001). However, some studies report the absence of changes with food or aversive events (Bassareo & Di Chiara 1999, Levita et al. 2002; for review see Joseph et al. 2003, Young et al. 2005).

Behavior-related dopamine increases show regional differences. Delayed alternation task performance in monkeys increases dopamine only in dorsolateral but not ventrolateral prefrontal cortex; whereas a sensorimotor control task without working memory increases dopamine only in premotor cortex (Watanabe et al. 1997). Rewards increase dopamine in the shell of rat nucleus accumbens, whereas visual reward-predicting stimuli increase dopamine in the core (Bassareo & Di Chiara 1999), although no such core-shell difference occurs with auditory reward-predicting stimuli (Cheng et al. 2003). Aversive footshock

and auditory shock–predicting stimuli increase dopamine in the shell but not the core, whereas environmental shock conditioning increases dopamine in the core (Kalivas & Duffy 1995, Pezze et al. 2001).

Time courses. Time-limiting factors are the speed of perfusion through the microdialysis cannula and the minimum amount of collected molecules necessary for analysis. Microdialysis-measured behavior-related changes in dopamine concentration are measured with sampling periods of 10 min and occur with 10–60 min of presentation of novel environments, primary rewards and reward-predicting stimuli, sexual activity, primary and conditioned aversive stimuli, lever pressing for food, active avoidance behavior, and cognitive tasks (Figure 5*d*). Dopamine increases often outlast the studied behavior by at least one 10-min sample period. With sampling periods of 1 min, aversive stimuli induce dopamine increases within one sample and terminate in the next sample with stimulus offset (Young 2004).

Comparison with other dopamine changes. Owing to technical limitations the microdialysis-measured dopamine changes are on the order of 10–60 min and thus are ~200–1800 times slower compared with the fastest behavior-related voltammetric changes of 2–3 s and are 3000–18,000 times slower compared with electrophysiological responses to reward-related stimuli lasting 200 ms. Dopamine changes occurring within a single 1-min sample are still 300 times slower than the 200-ms dopamine reward signal. Whereas fast-scan voltammetry can detect rapid transients in dopamine concentration, the microdialysis dopamine signal may partly reflect temporal integration of transients. Thus the temporal differences between microdialysis and other measures of dopamine activity are substantial and may suggest different underlying behavioral processes.

Comparison with behavior and neuronal activities. A single microdialysis measure of dopamine covering one or several minutes is difficult to relate to the multiple sensory, motor, motivational, and cognitive events changing within seconds or fractions of seconds to which the slower temporal resolution of microdialysis is not matched (Figures 1 and 2). However, the observed dopamine changes may be derived more from slower underlying behavioral processes, including changes in appetite, hunger, satiation, behavioral excitation, aggression, mood, fatigue, despair, sleepiness, maintenance of hippocampal plasticity, or memory consolidation to which the speed of microdialysis is better matched (Packard & White 1991, Huang et al. 2004).

Possible dopamine release mechanisms. Presentation of one reward-related stimulus every 10 s would elicit an average of 2 stimulus-induced impulses (Hyland et al. 2002). Compared with background activity of 2–3 impulses/s, the change would be <10%. Although the two extra impulses would produce a time-specific dopamine release detectable by voltammetry (Gonon 1997), the 10% change is below the usual 20%–100% dopamine change measured by time-integrating microdialysis and may not be discriminable from noise. Thus, owing to technical limitations, dopamine microdialysis is unlikely to detect the rapid, subsecond dopamine release produced by impulse responses, and microdialysis changes following reward-related stimuli may not derive from phasic impulse activity.

The effects of punishers and movements on dopamine microdialysis changes do not correspond to the general inefficacy of these events in driving electrophysiological responses. Because dopamine microdialysis provides good specificity for dopamine as opposed to other molecules, a microdialysis signal could derive from physiological processes such as the electrophysiological rebound activation following aversive-induced depressions (Hommer & Bunney 1980, Kelland et al.

1993, Daw et al. 2002, Ungless 2004). Although release of restraint stress produces substantial dopamine increase (Imperato et al. 1992), the aversive-induced dopamine release during, rather than after, 1-min stimulation suggests that dopamine microdialysis changes do not require opponent rebound (Young 2004).

Corticostriatal fibers from different origins carrying activities related to movement, reward, and punishment could induce dopamine release through local presynaptic influences on dopamine varicosities without involving changes in dopamine impulse activity, which could explain the divergent changes between microdialysis and electrophysiology. Indeed accumbens dopamine release following aversive stimuli diminishes after differential blockade of striatal glutamate receptors (Saulskaya & Marsden 1995), although another study emphasizes the necessary role of dopamine impulses (Keefe et al. 1993). Presynaptic dopamine release mechanisms might also explain the regional differences in primary and conditioned punisher-induced dopamine release in nucleus accumbens and frontal cortex (Kalivas & Duffy 1995, Watanabe et al. 1997, Bassareo & Di Chiara 1999, Pezze et al. 2001, Cheng et al. 2003).

Steady-State Dopamine Function

Clinical and experimental lesion studies demonstrate that externally administered dopamine receptor stimulating agents help to reconstitute many motor, cognitive, and motivational functions, although some deficits remain in discrimination, learning, and appetitive behavior (Ahlenius 1974, Canavan et al. 1989, Vriezen & Moscovitch 1990, Sprengelmeyer et al. 1995, Knowlton et al. 1996). Owing to the physical destruction of dopamine neurons and axons, dopamine receptor agonist treatment cannot restore dopamine impulse activity, impulse-dependent dopamine release, or presynaptic glutamate-dopamine interactions. Without these processes being restored, behavior-

specific temporal changes in dopamine receptor stimulation cannot occur. Thus dopamine neurotransmission is crucially involved in a number of behavioral processes for which it does not appear to show temporal changes. The mere presence of dopamine receptor stimulation without temporal changes assures the proper functioning of the many behavioral processes deficient after dopamine depletion.

Dopamine depletion in Parkinson's disease produces severe movement and cognitive deficits, and monkeys with impaired prefrontal dopamine transmission have difficulties in performing eye movements towards remembered spatial positions (Williams & Goldman-Rakic 1995). However, dopamine neurons do not show major changes in impulse activity with arm and eye movements (Romo & Schultz 1990). The striatal and prefrontal neurons, rather than the dopamine neurons, encode this information (Funahashi et al. 1989, Hikosaka et al. 1989a, Schultz et al. 1992). Apparently, the large variety of behavior-related changes in postsynaptic neurons depends on the tonic activation of dopamine receptors, and dopamine may play a predominantly enabling, modulatory role on these functions.

Increases and not just decreases of prefrontal dopamine induce behavioral impairments (Murphy et al. 1996). Dopamine concentration is regulated locally within a narrow range by synaptic overflow, extrasynaptic release, reuptake transport, negative feedback control of synthesis and release, and presynaptic influences from other neurotransmitters. The postsynaptic neurons need to receive an appropriate level of tonic dopamine receptor stimulation to function properly, and this stimulation should be neither too low nor too high to assure optimal functioning.

The tonic enabling function of dopamine may be based on spontaneous discharges that maintain an ambient, sustained, extracellular dopamine concentration, as if the dopamine projection system functions as a unitary, dopamine-releasing pellet. The basal striatal dopamine concentration of 5–10 nM is

part of the extracellular “soup of neurotransmitters” and can tonically stimulate the D2-type dopamine receptors in their mostly high-affinity state (Richfield et al. 1989). Thus, the tonic-enabling dopamine concentration may be derived from the same impulse-dependent or presynaptically controlled dopamine release that changes phasically in relation to behavior-related events.

TOWARD A COMPREHENSIVE ACCOUNT OF DOPAMINE FUNCTIONS

Who is right: the Parkinson’s researcher arguing for an exclusive role of dopamine in movements, or the airport immigration officer probably favoring a primary role for dopamine in reward? Is there more to dopamine than reward (and probably more to reward than dopamine, given the involvement of orbitofrontal, striatal, and amygdalar systems)? Scholars have numerous and mutually exclusive views on dopamine function based on the fallacy that there should be only one major role for every brain system. Results from individual experiments using different methods suggest a role in movement, reward, punishment, salience, learning, cognition, and many other processes. Certainly these functions contribute to the individual’s unlearned and learned reactions to the environment, but such a function would be too general to be meaningful. Given the active and often crucial role of dopamine in these behavioral processes, it might be worth considering that dopamine indeed plays important but differing roles in several brain functions and that these roles are related to the different time courses at which these functions occur.

The study of time courses provides a phenomenological account of the functional involvement in behavioral and neural processes (**Figure 5**). At the fastest time course, dopamine neurons play a preferential role in reward and the valuation of predicted outcomes of behavior. At the slowest time course,

dopamine has a steady-state function without changes in impulse rate akin to slow hormones. This function is required for a large variety of specific behaviors and amounts to an enabling dopamine influence on specific behavior-related neurons in postsynaptic structures such as striatum and frontal cortex. Between these very fast and very slow functions are a number of processes that include, with increasing durations, the uncertainty signal in the second range; the aversive-related impulse increases and decreases in the ranges of seconds and fractions of seconds; the reward- and movement-related changes in voltammetrically measured dopamine release in the second range; and the changes accompanying reward, punishment, stress, and movement measured by voltammetry and microdialysis in the minute to tens-of-minutes range.

There are only ~7000 dopamine neurons in rats and 200,000 in rhesus monkeys and humans on each side of the brain (Stark & Pakkenberg 2004), and their axons project to ~1000 times more postsynaptic neurons in the striatum, cortex, amygdala, and other structures. We have learned from the neuropsychology of cortical lesions that the deficits reveal the negative image of the active, information-processing function of the area under study. However, this reasoning may not be applicable to dopamine functions. Despite being necessary for many behavioral processes, the limited numbers of dopamine neurons may not be numerous enough to encode actively in full detail the information necessary for controlling every single component of the large range of functions that become deficient following dopamine depletions. For most functions other than reward, the dopamine cell bodies may simply provide the synthesis and release machinery for a steady-state concentration of dopamine that is finely regulated by local mechanisms in the terminal areas and that plays a permissive role without encoding information in time.

One helpful descriptor of some dopamine functions may be its long-debated role as

neuromodulator devoid of carrying specific information. This mechanism corresponds to the enabling influence of ambient dopamine without its own behavior-related changes underlying the large variety of behavioral deficits after dopamine depletion. By contrast, the dopamine reward-prediction error signal carries information about reward value and time and may serve in a three-factor Hebbian learning model of striatal and cortical plasticity (the other two factors are presynaptic input and postsynaptic activity) (Schultz 1998). Thus the role of dopamine neurotransmission can be described as both modulatory and informational.

Taken together dopamine function is characterized by a multitude of processes involved in mediating the reactivity of the organism to the environment to assure the survival of the animal. Dopamine makes essential contributions to reward, approach behavior, economic decision making, and adaptive behavior. The monitoring of uncertainty, the prediction and detection of punishers, and the necessary involvement in movement and cognition are important components of basic reactivity and survival functions, and these components are easily discriminable on the basis of their different time courses by postsynaptic mechanisms operating with subsecond precision.

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Errata

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